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Translating Genotypes into Phenotypes – Past, Present, Future

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Chapter 7

Cellular Control of Time, Size, and Shape in Development and Evolution

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7.1 A BRIEF HISTORY OF TIME, SIZE, AND SHAPE

The rules by which anatomical size and shape are generated have intrigued scientists for centuries. In 1638, Galileo suggested a mathematical relationship between proportional changes in the shape of bones as animals increase in size, which he argued was a functional necessity for weight bearing (1914). The formalism of Galileo, whereby, physical forces and mathematical laws became integrated with studies of size and shape in biology, was most conspicuously encapsulated over a hundred years ago in the 1917 monumental tome by D'Arcy Thompson entitled, *On Growth and Form* (Thompson 1917). In a breathtakingly comprehensive manner, Thompson synthesized the observations of numerous predecessors and contemporaries, and through countless examples built a theoretical and experimental framework for describing changes in morphology that persists to this day (Stern and Emlen 1999; Arthur 2006).

An essential component of Thompson's treatise was his system of Cartesian coordinates he employed to map the geometrical transformation of organs and organisms. Many other biologists in the 1920s and 1930s were motivated to address similar questions on size and shape in both the scholarly and popular literature (Gayon 2000). In 1926, John Haldane wrote a topical essay entitled, *On Being the Right Size*, in which he stated that, "The most obvious differences between different animals are differences of size, but for some reason, the zoologists have paid singularly little attention to them.…For every type of animal, there is a most convenient size, and a large change in size inevitably carries with it a change of form" (p. 1) (Haldane 1926). This was just one of many topics during Haldane's career for which he showed remarkable prescience; by pointing out how little attention had been given to size and shape previously, he in effect anticipated a whole discipline.

A Huxley and Allometry

Soon thereafter, Haldane's close friend Julian Huxley in his *Problems of Relative Growth* (which he dedicated to Thompson) expanded the discussion of size and shape to include mathematical representations of morphological transformations that arise over time, specifically during ontogeny and phylogeny (Huxley 1932). Along with Georges Teissier, Huxley symbolized relative growth with an algebraic power formula and introduced the term allometry to explain how changes in shape relate to changes in size (Huxley and Teissier 1936; Gayon 2000). A major motivation of Huxley, as well as many others who followed was to gain insight into the developmental (e.g., genetic and cellular) mechanisms generating allometric changes in proportion during evolution (Hersh 1934; von Bonin 1937; Lumer 1940; Needham and Lerner 1940; Anderson and Busch 1941; Lumer et al. 1942; Clark and Medawar 1945; Rensch 1948; Huxley 1950; Reeve 1950; Kermack and Haldane 1950; Bertalanffy and Pirozynski 1952; Gould 1966, 1971; Lande 1979; Alberch et al. 1979; Atchley 1981; Gould 1981; Coppinger and Coppinger 1982; Shea 1983; Atchley et al. 1984; Riska and Atchley 1985; Shea 1985; Coppinger et al. 1987; Deacon 1990; Godfrey and Sutherland 1995a; Coppinger and Schneider 1995; Stern and Emlen 1999; Smith et al. 2015).

Haldane and Huxley viewed size and shape predominantly through the prism of genetics, which during that period was surpassing embryology as the arbiter of acceptable explanations for mechanisms controlling the evolution of morphology. This grew from the seeding of Mendel alongside Darwin, and the paradigm being cultivated vis-à-vis genes, mechanisms of inheritance, and mutations that affect morphology from geneticists such as William Bateson, Richard Goldschmidt, and others (Bateson 1894; Bateson and Mendel 1902; Robb 1935; Goldschmidt 1938, 1940). Ten years after *Problems of Relative Growth*, Huxley published *Evolution, the Modern Synthesis* (Huxley 1942) in which he somewhat unintentionally helped push embryology out of the field of evolution for almost thirty years. This does not mean that embryologists were not thinking about evolution at the time or thereafter, but genetics ruled the roost due primarily to the robust and highly visible efforts of some former embryologists like Thomas Hunt Morgan (Morgan et al. 1915; Morgan 1919) and mathematical geneticists such as Ronald Fisher, Haldane, Sewall Wright, and Theodosius Dobzhansky (Fisher 1930; Wright 1931; Sinnott and Dunn 1932; Haldane 1932; Dobzhansky 1937).

Huxley was well-versed in embryology and evolution, given that his close colleague, Gavin de Beer had written *Embryology and Evolution* in 1930, and Huxley coauthored *Elements of Experimental Embryology* with de Beer in 1934 (de Beer 1930; Huxley and de Beer 1934). Even though Huxley's *Modern Synthesis* has been viewed as a nail in the coffin for evolutionary embryology, Huxley left some openings for development to play a role. He stated, "The course of Darwinian evolution is thus seen as determined (in varying degrees in different forms) not only by the type of selection, not only by the frequency of mutation, not only by the past history of the species, but also by the nature of the developmental effects of genes and of the ontogenetic process in general" (p. 555) (Huxley 1942). Likely, this inclusion of developmental growth was influenced by his own earlier studies (Huxley 1924, 1932) and by those who continued to work contemporaneously on allometry (Hersh 1934; Gregory 1934; Lumer 1940; Anderson and Busch 1941; Lumer and Schultz 1941; von Bonin 1937; Needham and Lerner 1940; Lumer et al. 1942), as well as other mechanisms of evolutionary embryology, especially those advanced by Walter Garstang (1922) and de Beer (1930).

B de Beer and Heterochrony

Gavin de Beer not only recognized the importance of allometry but also devised a series of definitions and schemas relating time to size and shape that is arguably one of the most important contributions in the history of the field of evolutionary developmental biology. First and foremost, de Beer was an evolutionary embryologist (Ridley 1985; Hall 2000a; Brigandt 2006). His work emphasized the significance of changes in the timing of developmental events, or heterochrony, in transforming the morphology of a descendant relative to an ancestor. Heterochrony was initially conceived by Ernst Haeckel and has been applied in various scenarios to link development and evolution (Kollmann 1885; Russell 1916; Bolk 1926; Garstang 1928; de Beer 1930; Dechambre 1949; Gould 1977; Hall 1984; McKinney 1988b; Klingenberg 1998; Smith 2003; Keyte and Smith 2014). de Beer classified eight modes of evolution through

which ancestral and descendant ontogenies can differ (de Beer 1930). He provided examples for each type of heterochrony but argued that *neoteny*, defined as the retention of juvenile features in the adult form, was the one that truly allowed for large, rapid phenotypic change and morphological diversification. Other significant evolutionary concepts that de Beer advanced in the context of embryology include clandestine evolution, homology, and evolutionary plasticity. Notably, de Beer dropped the word *Evolution* that was in his first edition book title and instead adopted *Embryos and Ancestors* for the 1940 and subsequent editions (de Beer 1940, 1954, 1958), which can be seen as a reflection of how much the field of population genetics, and not embryology, laid claim to the study of evolution during that era.

C The Holy Trinity of Time, Size, and Shape

Nonetheless, the theory that changes to the rate of growth and/or timing of events during ontogeny could alter the course of phylogeny continued as a subplot to the main story of evolution until becoming more generally accepted during the rebirth of *evo-devo* in the 1970s. Even Darwin in his *Origin of Species* was vexed and tantalized by the correlations of growth observed in embryos, which he acknowledged were a potential source of evolutionary variation (Darwin 1859). In *Chapter I, Variation Under Domestication*, Darwin wrote, "There are many laws regulating variation, some few of which can be dimly seen…I will here only allude to what may be called correlation of growth. Any change in the embryo or larva will almost certainly entail changes in the mature animal" (p. 11). He also stated: "If man goes on selecting, and thus augmenting, any peculiarity, he will almost certainly unconsciously modify other parts of the structure, owing to the mysterious laws of the correlation of growth. The result of the various, quite unknown, or dimly seen laws of variation is infinitely complex and diversified" (p. 12). Then again in *Chapter V, Laws of Variation*, Darwin explained that: "Changes of structure at an early age will generally affect parts subsequently developed; and there are very many other correlations of growth, the nature of which we are utterly unable to understand" (p. 168). Clearly, such *correlations of growth* were exactly on what Thompson focused, and his efforts helped lay the groundwork for a broad range of studies comparing changes in size and shape during development.

All the more so, about a decade before Thompson's seminal work, Charles Minot provided a complimentary and in many ways equally important embryological perspective that connected the size of animals and/or their organs with the regulation of cell number, differentiation, and rates of growth as a function of age (Minot 1908). Borrowing from this idea, In Chapter III, *The Rate of Growth*, Thompson equated age with time and stated that "the *form* of an organism is determined by its rate of *growth* in various directions; hence rate of growth deserves to be studied as a necessary preliminary to the theoretical study of form, and organic form itself is found, mathematically speaking, to be a *function of time*" (p. 79) (Thompson 1952). Similarly, Huxley latched on to the importance of time when contemplating evolutionary changes in relative size. He proposed potential genetic mechanisms involving "(a) mutations affecting the primary gradient of the early embryo, on which the time-relations of antero-posterior differentiation depend; (b) mutations affecting specific

rate-genes; (c) mutations affecting specific 'time-genes'—genes controlling time of onset and not rate of processes" (p. 242) (Huxley 1932). Accordingly, changes to these *rate-genes* and *time-genes* can affect growth gradients and alter morphology at multiple levels in a coordinated way. Such theories were supported by Goldschmidt's discovery of genes that alter rates of development (Goldschmidt 1938, 1940; Dietrich 2000), something which was also integrated into evolutionary embryology, and more specifically heterochrony, by de Beer (Hall 2000a). On this point, de Beer stated, "By acting at different rates, the genes can alter the time at which certain structures appear" (p. 20) (de Beer 1954).

Therefore, primarily through the critical contributions of Minot, Thompson, Huxley, and de Beer during the first half of the twentieth century, the three parameters of time, size, and shape became unified in essence as the *holy trinity* of evolutionary morphology. But while some of these authors and others strived to integrate findings from the emerging field of developmental genetics led by classically trained embryologists and morphologists such as Goldschmidt (1938, 1940, 1953); Conrad Waddington (1939, 1940, 1957b, 1962) and Ivan Schmalhausen (1949), a deeper understanding of the molecular and cellular mechanisms that unite time, size, and shape during ontogeny and phylogeny would have to wait for almost fifty years. Moreover, the neo-Darwinians remained very skeptical that developmental genetics could contribute to evolutionary theory, and thought-leaders such as Dobzhansky (1937, 1951) and Ernst Mayr (1963, 1983) argued most vociferously that all evolution was microevolution arising from "the continuous adjustment of an integrated gene complex to a changing environment" (p. 332) (Mayr 1963). In other words, this was the prevailing synthetic theory that embraced natural selection and survival of the fittest, distribution of alleles at the level of populations, and gradual adaptive evolution as the sole agent of change. In this regard, the neo-Darwinians thoroughly rejected and even mocked the ideas of Goldschmidt (Gould 1982b), especially that small genetic changes affecting developmental time or rates could rapidly generate large phenotypic transformations in size and shape.

So, by the 1950s, evolutionary studies predicated on allometry and heterochrony were either vastly overshadowed by the neo-Darwinian paradigm, or more pointedly they were viewed as gross oversimplifications of embryonic growth by developmental biologists. Waddington, for example in a paper discussing how to measure size and shape in a meaningful and biologically relevant way stated that, "The validity of any biological conclusions which may be drawn from measurements of size and form depends far more on the adequacy of the physiological insight on which they are based than on the precision of the mathematical techniques used to summarize and compare them" (p. 515) (Waddington 1950). This sentiment begged the question of what governs growth over time and demanded a more in-depth probing of developmental mechanisms regulating size and shape.

7.2 TIME, SIZE, AND SHAPE REDUX

Despite Waddington's emphasis on acquiring a deeper understanding of developmental processes and his admonishment of expending too much energy on generating more sophisticated and precise methods for measuring size and shape (Waddington 1950),

studies on allometry continued unabated for decades (Stern and Emlen 1999; Gayon 2000). Moreover, a whole field of morphometrics burgeoned based on multivariate methods and ultimately computer-based algorithms for quantifying and visualizing complex changes in size and shape (Bookstein 1978, 1990; Benson et al. 1982; Siegel and Benson 1982; Marcus 1996; Zelditch 2004; Hallgrimsson et al. 2015). Granted, the technical ability to analyze size and shape became more refined over time, but results generally remained phenomenological. Therefore, many morphometricians endeavored to frame their studies within the context of quantitative genetics and/or heterochrony, in order to make predictions about mechanisms through which size and shape can change during ontogeny and phylogeny (Gould 1966, 1981; Lande 1979; Alberch et al. 1979; Atchley 1981; Cheverud 1982; Benson et al. 1982; Riska 1986; McKinney 1988a; Atchley and Hall 1991; Coppinger and Schneider 1995; Klingenberg 1998; Roth and Mercer 2000; Drake 2011; Smith et al. 2015; Lord et al. 2016).

A Clocks for Time, Size, and Shape

Some of the most prominent work, applying numerical methods to characterize growth-related changes in size and shape came at the end of the 1960s and in the 1970s from Stephen Jay Gould, who almost single-handedly made allometry and heterochrony fashionable again and also acceptable as alternatives to the adaptationist program for studying evolution offered by the neo-Darwinians (Gould 1966, 1971, 1977; Gould and Lewontin 1979; Gould 1981, 1982a; Gayon 2000; De Renzi 2009).

Through a series of monographs and major papers on evolutionary allometry, Gould began to put developmental mechanisms front and center. Then, in a landmark book, *Ontogeny, and Phylogeny*, Gould (1977) traced the history of conceptual advances in understanding the relationship of development to evolution. Gould opened with the *Great Chain of Being* from the Greeks; continued to theories that ontogeny parallels or recapitulates phylogeny from various French and German transcendentalists such as Johann Meckel, Etienne Serres, Lorenz Oken, Louis Agassiz, and Ernst Haeckel; and finally described the outright rejection of recapitulation by Karl Ernst von Baer, Garstang, de Beer, and others. In the second half of his book, Gould revisited and expanded upon de Beer's schema for heterochrony and presented his own semi-quantitative *clock model* in which the hands for size and shape depicted the morphology of a species relative to its ancestor. Each clock allowed for size, shape, and age (i.e., time) to be altered separately during evolution and accordingly could be adjusted to represent the many manifestations of heterochrony such as neoteny, progenesis, pedomorphosis, proportional dwarfism, and proportional gigantism.

In his impressive treatise and throughout his career, Gould confronted the neo-Darwinian view of morphological evolution head-on and argued forcefully for the role of development in macroevolutionary change (Gould 1966, 1971, 1977, 1982a, 2002; Eldredge and Gould 1972; Gould and Lewontin 1979; Gould and Vrba 1982). But Gould was a paleontologist, not an embryologist, and one critical issue was that his clock model was essentially qualitative and static (like the models of de Beer), and defined simple evolutionary patterns or end states rather than capture the

complex and dynamic nature of developmental processes (Etxeberria and De la Rosa 2009). Shortly thereafter, the embryologist David Wake and his 24-year-old graduate student Pere Alberch invited Gould to collaborate on what was to become an especially celebrated paper that effectively launched the modern field of evolutionary developmental biology (Wake 1998; De Renzi 2009).

B Quantitative Methods for Time, Size, and Shape

Alberch thought Gould's clock models were a good start in theory but insufficient in actuality (Reiss et al. 2008), and so in a paper entitled *Size and shape in ontogeny and phylogeny*, Alberch, Gould, Oster, and Wake (1979) presented a tangible quantitative method to describe the relationship between heterochrony and evolution. Their intention was to "clothe" Gould's clock model in mathematics (Wake 1998) and in so doing build a better graphical framework for integrating changes in time with changes in size and shape during development and evolution. They formulated differential equations as a way to encapsulate a more dynamic view of heterochrony, which they described as shifts in the onset, cessation, or rate of growth, rather than as an end result (Etxeberria and De la Rosa 2009).

This highly cited work became an instant classic that helped spawn a decade of conferences and books on how to measure size, shape, and time in the context of heterochrony (Bonner 1982; Maderson et al. 1982; Raff and Kaufman 1983; McKinney 1988b; Wake and Roth 1989; De Renzi et al. 1999; Reiss et al. 2008). Moreover, as part of the re-birth of evo-devo as a discipline, heterochrony became the lens through which all kinds of biology was viewed (Alberch 1980a; Alberch and Alberch 1981; Balon 1981; Coppinger and Coppinger 1982; Gould 1982a; Haluska and Alberch 1983; Shea 1983; Bemis 1984; Hanken and Hall 1984; Roth 1984; Coppinger et al. 1987; Geist 1987; Hoberg 1987; Slatkin 1987; Foster and Kaesler 1988; Hafner and Hafner 1988; Coppinger and Smith 1989; Roth and Wake 1989; Shea 1989; Coppinger and Feinstein 1991; Blanco and Alberch 1992; Zelditch et al. 1992; Blackstone and Buss 1993; Klingenberg and Spence 1993; Allmon 1994; Duboule 1994; Coppinger and Schneider 1995; Godfrey and Sutherland 1995a, b; Richardson 1995; Gilbert et al. 1996; Maunz and German 1996; Richardson et al. 1997; Smith 1997; Nunn and Smith 1998; MacDonald and Hall 2001; Vaglia and Smith 2003; Crumly and Sanchez-Villagra 2004; Tokita et al. 2007; Drake 2011; Nagai et al. 2011; Mitgutsch et al. 2011).

C Construction Rules for Time, Size, and Shape

While such morphometric approaches helped elucidate critical developmental stages and events whereby changes in size and shape occur, by necessity they often reduced the complex dynamic nature of development into something much more simplistic and static, their framework was typically applied globally at the level of organisms rather than in relation to individual systems or structures, they tended to divide continuous development into artificially discrete steps in order to compare ontogenetic trajectories, and also, they largely left much to be understood in terms of underlying molecular and cellular mechanisms.

Seemingly anticipating these points and echoing Waddington's sentiments, Alberch and his colleagues (1979) challenged the field when they expressed that: "We hope that our attempts to construct a quantitative theory will stimulate others to delve more deeply below the level of pure phenomenology and come to grips with the central issue underlying evolutionary diversification of size and shape—that is, the morphogenetic unfolding of genetic programs in ontogeny and their alteration in the course of phyletic evolution" (p. 297).

Such an emphasis on the mechanistic and more dynamic aspects of development grew directly out of Waddington's epigenetic landscapes and concepts like canalization, which basically served as metaphors for how gene regulation could alter the course of ontogeny and phylogeny (Waddington 1957a), and guided the remainder of Alberch's remarkably influential but tragically foreshortened career (De Renzi et al. 1999; Wake 1998; Reiss et al. 2008). To this very point, in his elegant first solo paper on the role of ontogeny in morphological diversification, Alberch (1980b) argued that "epigenetic interactions drastically constrain the universe of possible morphological novelties and impose directionality in morphological transformations through phylogeny" (p. 654). In other words, even if a genetic mutation is random, the morphological outcome is not. Why? Because developmental systems are highly integrated, iterative, accommodative, hierarchical, and ultimately defined by an "internal structure" that limits "the realm of possible morphologies" (Alberch 1982a:319).

In his subsequent and quite a formidable body of work, Alberch addressed the role of development in the evolution of size, shape, and other aspects of morphology on multiple levels in a wide range of organisms and organs. A critical concept that he advanced pertained to *construction rules* through which developmental systems are built and become altered from one morphological state to another during evolution (Alberch 1982a, 1985; Oster and Alberch 1982; Oster et al. 1988). Accordingly, development consists of interwoven "dynamical systems, where a small set of simple rules of cellular and physicochemical interactions" lead to complex morphology (Oster and Alberch 1982:455). Evolutionary changes in organ size, for example, can be achieved by varying the quantitative parameters of cells, including the number of progenitors, the rate of proliferation, length of the cell cycle, and timing of differentiation. Other parameter values that can potentially be modulated pertain to "biochemical, cell–cell, or tissue interactions" (Alberch 1985:50), which, in turn, can affect developmental processes such as "rates of diffusion, mitotic rate, cell adhesion, etc." (Alberch 1989:27).

Throughout his research program, Alberch combined insights from comparative morphology, experimental embryology, and teratology, to generate models and other mathematical tools that helped define morphogenesis as an emergent property of physical and biochemical interactions, as well as cyclical, multidimensional, and nonlinear feedback schemes operating at the level of molecules, genes, and proteins, and extending up through tissues. In stark contrast to the neo-Darwinian view of the relationship between genotype and phenotype, Alberch argued that "genes are just one step in the chain of interactions; gene expression is both the cause and the effect of a morphogenetic process" (Alberch 1991:6). Using amphibian limb buds as a model system for studying the relationship between construction rules and morphological outcomes, Alberch and his colleagues experimentally manipulated

parameters such as cell number (using the mitotic inhibitor colchicine, for example) and showed that changes in size and shape of the limb, and number of the digits became altered in a non-random way once a critical threshold was reached (Alberch and Gale 1983, 1985; Shubin and Alberch 1986).

While these studies predated the technical ability to link such outcomes with molecular biology (specifically, underlying changes in gene expression), their results were completely consistent with predictions made in their mathematical models and pattern-generating algorithms (Oster et al. 1988), and showed that the phenotypes arising from perturbations to developmental programs were not stochastic. Because of such findings, Alberch argued that "even if the parameters of the system are randomly perturbed, by either genetic mutation or environmental variance or experimental manipulation during development, the system will generate a limited and discrete subset of phenotypes. Thus the realm of possible forms is a property of the internal structure of the system" (Alberch 1989:27). Analyses of genetic mutations and experimental manipulations in a range of model organisms by many subsequent workers in the field provided critical information on the internal structure of developmental systems. In particular, these types of approaches have been especially productive with regard to understanding how parameter changes in construction rules on the molecular and cellular levels have likely played a generative role during the evolution of size and shape in the vertebrate skull.

7.3 TIME, SIZE, AND SHAPE IN THE VERTEBRATE SKULL

For numerous reasons, including its inimitable paleontological record, its measurable geometry, its evolutionary adaptability, its functional significance, and its easily visualized embryogenesis, the vertebrate skull has long been the subject of intensive research on size and shape (de Beer 1937; Hanken and Hall 1993). This has occurred chiefly with regard to; (a) genes that affect skeletal element identity (Balling et al. 1989; Lufkin et al. 1992; Gendron-Maguire et al. 1993; Rijli et al. 1993; Schilling 1997; Qiu et al. 1997; Hunt et al. 1998; Smith and Schneider 1998; Pasqualetti et al. 2000; Grammatopoulos et al. 2000; Depew et al. 2002; Creuzet et al. 2002; Kimmel et al. 2005); (b) tissue interactions required for mesenchymal differentiation into cartilage and bone (Schowing 1968; Tyler 1978; Bee and Thorogood 1980; Hall 1980, 1982b; Tyler 1983; Thorogood et al. 1986; Thorogood 1987; Hall 1987; Richman and Tickle 1989, 1992; Dunlop and Hall 1995; Shigetani et al. 2000; Ferguson et al. 2000; Couly et al. 2002; Francis-West et al. 2003; Merrill et al. 2008); (c) secreted molecules that regulate axial polarity and skeletal outgrowth (Barlow and Francis-West 1997; Francis-West et al. 1998; Schneider et al. 2001; Hu et al. 2003; Abzhanov and Tabin 2004; Crump et al. 2004; Wilson and Tucker 2004; Wu et al. 2004; Abzhanov et al. 2004; Liu et al. 2005; Marcucio et al. 2005; Wu et al. 2006); and (d) mesenchymal control of species-specific pattern (Andres 1949; Wagner 1959; Noden 1983; Schneider and Helms 2003; Tucker and Lumsden 2004; Mitsiadis et al. 2006).

The special ability of mesenchyme to transmit species-specific information on size and shape has been recognized primarily through interspecific grafting experiments of mesenchymal cells destined to form the jaw skeleton (Noden and Schneider 2006; Lwigale and Schneider 2008). The exact molecular mechanisms through

which mesenchyme performs this complicated function appear to involve the ability of mesenchyme to determine the timing of its own gene expression and differentiation, as well as that of adjacent tissues such as epithelia (Schneider and Helms 2003; Eames and Schneider 2005; Schneider 2005; Merrill et al. 2008). Taken together, results from genetic, molecular, and cellular studies lead to the conclusion that the regulation of skeletal size and shape by mesenchyme involves multiple gene regulatory networks, reciprocal signaling interactions with adjacent tissues, and hierarchical levels of control.

A Bird Beaks

Studies on the beaks of birds have been particularly helpful in identifying factors that influence skeletal size and shape (Helms and Schneider 2003; Schneider 2005, 2007; Fish and Schneider 2014c; Schneider 2015). For example, differential domains of *Bmp4* expression in beak progenitor cells underlie variation in beak depth and width among birds including Darwin's finches, cockatiels, chicks, and ducks (Abzhanov et al. 2004; Wu et al. 2004, 2006).

Beak length seems to be managed separately through a calmodulin-dependent pathway (Abzhanov et al. 2006; Schneider 2007). Similarly, factors including SHH, FGFs, WNTs, and BMPs, which are secreted from adjacent epithelial tissues also appear to affect the shape and outgrowth of the beak skeleton (MacDonald et al. 2004; Young et al. 2014; Hu and Marcucio 2009; Foppiano et al. 2007; Hu et al. 2015a, b; Hu and Marcucio 2012; Brugmann et al. 2007; Brugmann et al. 2010; Abzhanov and Tabin 2004; Bhullar et al. 2015; Grant et al. 2006; Wu et al. 2006; Ashique et al. 2002a; Richman et al. 1997; Rowe et al. 1992; Szabo-Rogers et al. 2008; Mina et al. 2002; Doufexi and Mina 2008; Havens et al. 2008; Schneider et al. 1999, 2001). A clearer picture of how these signaling pathways are regulated and how changes to their regulation affect skeletal size and shape has begun to emerge.

B Quail–Duck Chimeras

In particular, additional details on molecular and cellular mechanisms through which the craniofacial skeleton acquires its proper size and shape have come from our studies, using a unique avian chimeric transplantation system that exploits species-specific differences between Japanese quail and white Pekin duck (Schneider and Helms 2003, 2005, 2007; Lwigale and Schneider 2008; Jheon and Schneider 2009; Ealba and Schneider 2013; Fish and Schneider 2014b).

As a proxy for studying the orchestration of morphogenesis more generally, we have been posing the question of how do skeletal elements in the jaw skeleton of quail and duck achieve their distinct size and shape? Quail have short and narrow jaws in comparison to those of duck, which are relatively long and broad (Figure 7.1a, b). We have focused on the lower jaw (Figure 7.1c), which forms embryonically within the paired mandibular primordia. Neural crest mesenchyme (NCM) that migrates from the caudal midbrain and rostral hindbrain is the only source of precursor cells that give rise to cartilage and bone within the skeleton of the face and jaws (Figure 7.1d)

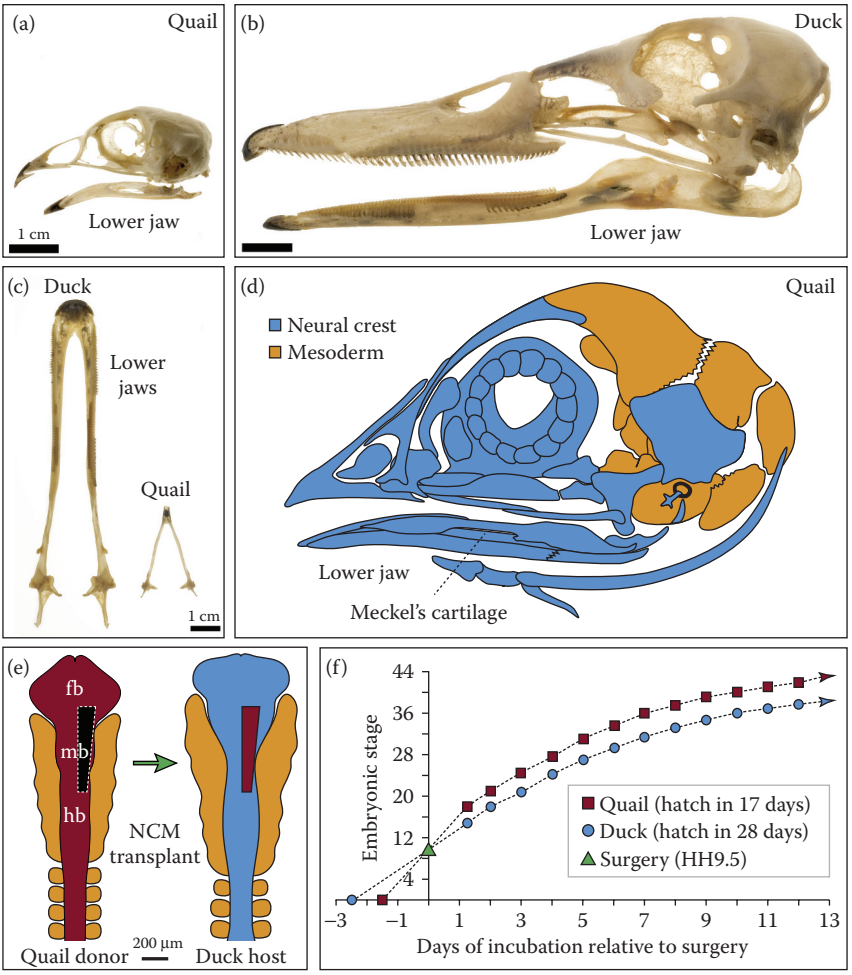

FIGURE 7.1 The quail–duck chimeric system for studying time, size, and shape in the head skeleton. (a) Head skeletons of adult Japanese quail (*Coturnix coturnix japonica*) and (b) white Pekin duck (*Anas platyrhyncos*) showing species-specific differences in size and shape. (c) Lower jaws of adult duck and quail. (d) Neural crest cells generate the facial and jaw skeletons (blue) whereas mesoderm forms the caudal cranial vault and skull base (orange). (e) Schematic of an embryonic rostral neural tube (dorsal view) depicting the origin of neural crest mesenchyme (NCM) from the forebrain (fb), midbrain (mb), and hindbrain (hb). NCM destined for the jaw primordia are grafted (green arrow) from a quail donor (red) to a duck host (blue). (f) Embryonic quail (red squares) and duck (blue circles) have distinct rates of maturation but can be stage-matched for surgery (green triangle on Y-axis) by setting eggs in the incubator at separate times. Approximately three embryonic stages distinguish faster-developing quail from duck embryos within two days following surgery, and this three-stage difference remains relatively constant during the period of jaw morphogenesis. (Panels [a, b] modified from Fish, J.L. et al., *Development*, 141, 674–684, 2014; Panels [c, e, f] modified from Eames, B.F., and Schneider, R.A., *Development*, 135, 3947–3958, 2008; Panel [d] modified from Schneider, R.A., *J. Anat.*, 207, 563–573, 2005, and based on a drawing from D. Noden.)

(Le Lièvre and Le Douarin 1975; Noden 1978; Couly et al. 1993; Köntges and Lumsden 1996; Helms and Schneider 2003; Noden and Schneider 2006).

Our experimental strategy involves transplanting pre-migratory NCM between quail and duck embryos (Figure 7.1e). We transplant NCM either bilaterally, so that donor cells fill both sides of the host jaw skeleton, or unilaterally, which allows the nonsurgical side of the host to serve as an internal control. Unilateral transplants enable us to compare donor- and host-derived tissues in the same chimeric embryo (Tucker and Lumsden 2004; Eames and Schneider 2005, 2008; Lwigale and Schneider 2008; Fish and Schneider 2014b; Solem et al. 2011; Tokita and Schneider 2009). A powerful and serendipitous feature of this chimeric system is the fact that quail embryos develop at a quicker rate than duck embryos (17 vs. 28 days from fertilization to hatching), which causes faster-developing quail cells and relatively slower-maturing duck cells to interact with one another over time while they become progressively asynchronous (Figure 7.1f). Having such divergent developmental trajectories conveniently offers a way to screen for the effects of donor cells on the host by looking for species-specific changes to the timing of gene expression, cell differentiation, and tissue formation. Consequently, and especially in the context of the aforementioned holy trinity of evolutionary developmental morphology, this system also affords us with the unique opportunity to evaluate directly and in the same embryo, the effects of changes in growth rates and the timing of developmental events on size and shape. We can use an anti-quail antibody, which does not recognize duck cells, to distinguish the contributions of donor versus host and we can quantify the proportion of quail versus duck cells at the molecular level, using a PCR-based strategy (Schneider 1999; Lwigale and Schneider 2008; Ealba and Schneider 2013; Fish and Schneider 2014b; Fish et al. 2014; Hall et al. 2014; Ealba et al. 2015).

Once quail and duck cells become mixed within chimeras, they become challenged to assimilate two separate morphogenetic programs controlling species-specific size and shape. Chimeric "*quck*" contain quail donor NCM inside of a duck host whereas "*duail*" have duck NCM in a quail host. As a result, we can discover mechanisms directing jaw patterning by (1) characterizing donor-mediated changes to jaw size and shape; (2) assaying for temporal and spatial shifts in developmental events underlying cartilage and bone formation such as mesenchymal condensation and differentiation; (3) analyzing the effects of donor NCM on non-NCM host derivatives that participate in skeletal patterning and growth such as epithelia, muscles, blood vessels, and osteoclasts; (4) looking for genes that become differentially expressed in chimeras; and (5) modulating the expression of these genes to test if they account for the chimeric phenotype and affect skeletal size and shape (Eames and Schneider 2005, 2008; Noden and Schneider 2006; Merrill et al. 2008; Tokita and Schneider 2009; Solem et al. 2011; Hall et al. 2014; Ealba et al. 2015).

An important point to emphasize is that this chimeric system can reveal in a more or less "normal" developmental context those molecular and cellular interactions between the donor and host that are divergent and ultimately generative of species-specific size and shape. In this context, the quail–duck chimeric system offers a unique opportunity to observe what Alberch et al. (1979) called "the morphogenetic unfolding of genetic programs in ontogeny and their alteration in the course of

phyletic evolution" (p. 297). We can also probe for construction rules and identify those parameter changes that may account for evolutionary differences between each species. Along similar lines, Shubin and Alberch (1986) argued that while the basic morphogenetic rules have remained the same; what have changed during vertebrate evolution are the parameters through which these interactions occur (Etxeberria and De la Rosa 2009).

By combining a classical comparative method (Sanford et al. 2002) with experimental embryology (i.e., the quail–duck chimeric transplant system), we have found that NCM relies upon multiple mechanisms to exert cellular control over time, size, and shape, primarily through three phases of development:

- At the onset of NCM migration, quail and duck embryos allocate different numbers of progenitors to the presumptive jaw region, with duck having significantly more cells (Fish et al. 2014).
- Thereafter, when these populations of NCM expand, there is species-specific regulation of, and response to, critical signaling pathways in a manner that is dependent on their own rates of maturation (Eames and Schneider 2008; Merrill et al. 2008; Hall et al. 2014).
- Lastly, as these progenitors start to form cartilage and bone, they execute autonomous molecular and cellular programs for matrix deposition and resorption through patterns and processes that are inherent to each species and deeply rooted in the timing of developmental events (Eames and Schneider 2008; Merrill et al. 2008; Mitgutsch et al. 2011; Hall et al. 2014; Ealba et al. 2015; Schneider 2015).

Moreover, on the molecular level, the SHH, FGF, BMP, and TGFβ signaling pathways all seem to be clearly but not unexpectedly involved since many members and targets show species-specific expression and they become altered in quail–duck chimeras.

Thus, the ability of NCM to regulate the timing, levels, and spatial patterns of gene expression and to do so in a species-specific manner, likely modulates the proliferation, differentiation, and growth of skeletal progenitors, and determines the size and shape of cartilage and bone. Such work offers insight into the many ways NCM exerts its regulatory abilities during ontogeny and phylogeny, which has been a long-standing question in the field (Gans and Northcutt 1983; Noden 1983; Maderson 1987; Hall and Hörstadius 1988; Hanken 1989; Baker and Bronner-Fraser 1997; Hall 1999, 2000b; Graham 2003; Santagati and Rijli 2003; Trainor et al. 2003; Graham et al. 2004; Le Douarin et al. 2004; Noden and Schneider 2006; Jheon and Schneider 2009; Fish and Schneider 2014c; Sanchez-Villagra et al. 2016). Specific examples of the multiple ways NCM exercises control over skeletal size and shape, especially by keeping track of time, are detailed in the sections below.

7.4 EARLY CELLULAR DETERMINANTS OF JAW SIZE AND SHAPE

The genesis of NCM involves several sequential embryonic events, including induction at the boundary between neural and non-neural ectoderm, specification and regionalization along the dorsal margins of the neural folds, regulation of cell cycle

and maintenance of multipotency, transition from epithelium to mesenchyme, and migration throughout the head and trunk (Betancur et al. 2010; Nikitina et al. 2008). NCM that arises from the midbrain through the first and second rhombomeres of the hindbrain migrates into the mandibular primordia (Le Lièvre and Le Douarin 1975; Noden 1978; Couly et al. 1993; Köntges and Lumsden 1996; Schneider et al. 2001). While the gene regulatory networks and developmental programs that govern these morphogenetic events are extremely conserved across vertebrates (Nikitina et al. 2008; Depew and Olsson 2008; Bronner-Fraser 2008; Northcutt 2005), much remains to be understood about when and where changes can lead to the evolution of species-specific morphology.

A Quantifying Jaw Precursor Cells

For this reason, we have been concentrating on exactly when and where ducks assemble their long bills, compared to quail, who make relatively short beaks. Using a simple analogy that constructing a taller building might involve adding more bricks, as opposed to bigger bricks (Fish and Schneider 2014a), and following the spirit of Alberch and his construction rules, we set out to determine the number of jaw precursors that migrate into the mandibular primordia in duck versus quail (Figure 7.2a, b). We started by counting NCM at key embryonic stages (Fish et al. 2014).

At an initial embryonic stage, when NCM is specified along the neural folds, duck and quail appear to have the same total amount of cranial NCM. But soon afterwards, when NCM coalesces on the dorsal margins of the neural tube, duck has about 15% more NCM at the midbrain and rostral hindbrain levels, which is where the population that migrates into the presumptive jaw region originates. Remarkably only several stages later, the mandibular primordia of duck contain twice as many cells as do those of quail (Figure 7.2c). To understand how a 15% difference could quickly lead to a doubling in size, we looked for species-specific variation in cell proliferation and cell cycle length. Our results show that although duck has a longer cell cycle (13.5 versus 11 hours in quail), if the total duration of each embryonic stage during this period is taken into account in terms of absolute time (45 versus 32 hours), then duck cells, in fact, proliferate more than those of quail. By maintaining their intrinsic rates of maturation, duck deploy a cellular mechanism that increases jaw size progressively throughout development (Fish and Schneider 2014c; Fish et al. 2014; Schneider 2015). In so doing, they directly link developmental time with size.

B Genes and Brain Regionalization

But how might duck initially generate more midbrain NCM that can then migrate into the presumptive jaw region? To address this question, we assayed for species-specific variation in the expression of genes known to affect brain regionalization. We examined the expression of *Pax6* in the forebrain, *Otx2* in the forebrain and midbrain, *Fgf8* at the midbrain–hindbrain boundary, and *Krox20* in rhombomeres 3 and 5 of the hindbrain (Figure 7.2d). Landmark-based morphometrics was used to compare brain shape in duck and quail embryos after neurulation, and we pinpointed species-specific differences that were correlated with changes in domains

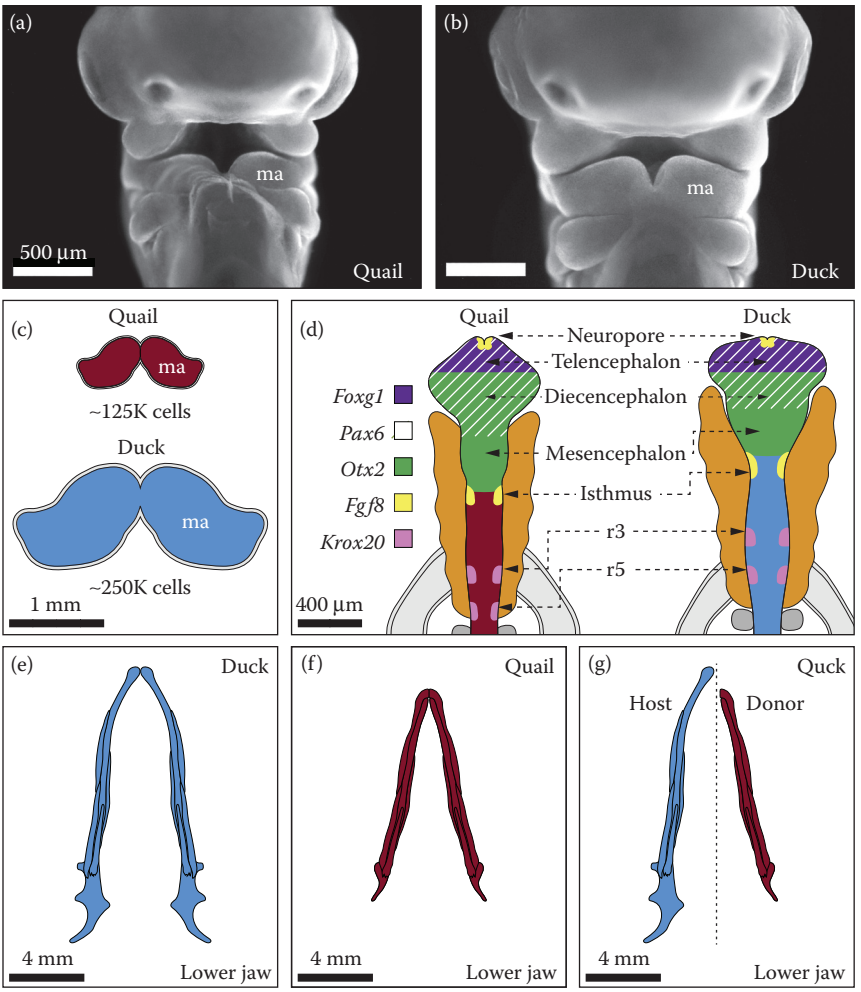

FIGURE 7.2 Molecular and cellular control of species-specific size and shape. (a, b) Frontal views of the heads of quail and duck embryos showing differences in the size of the mandibular primordia (ma), from which the lower jaw skeleton develops. (c) At this stage, the mandibular primordia (ma) in quail embryos (red) is approximately half the size of that of duck (blue) in terms of total number of cells. (d) Quail and duck embryos have distinct shapes and regionalization of the rostral neural tube. The duck midbrain (mesencephalon) is foreshortened and broader mediolaterally. Genes including *Foxg1*, *Pax6*, *Otx2*, *Fgf8*, and *Krox20* are expressed in specific domains, each domain being shifted more anteriorly in duck than in quail. The lower jaw skeletons of duck (e) and (f) quail show stage-specific and species-specific differences in size and shape with duck being longer and more curved. (g) In quck mandibles, the quail donor-derived jaw skeleton (red) is shorter and straighter than the contralateral duck host-derived jaw skeleton (blue), which is longer and curved. (Panels [a, b, e, f, g] modified from Fish, J.L. et al., *Development*, 141, 674–684, 2014; Panel c modified from Merrill, A.E. et al., *Development*, 135, 1223–1234, 2008; Panel [d] modified from Schneider, R.A., *Curr. Top Dev. Biol*., 115, 271–298, 2015.)

of gene expression. Most strikingly, we found that the duck midbrain is shorter and broader and has a correspondingly restricted domain of *Otx2* expression along the anterior to posterior axis. Presumably, a broader midbrain in duck allows more NCM to accumulate and migrate into the mandibular primordia. Importantly, we observed these differences in *Otx2* expression even before neural tube formation or the genesis of NCM, demonstrating that species-specific patterning mechanisms affecting jaw size may function at the earliest stages of development. Thus, this work reveals how small spatial and temporal modifications to aspects of developmental programs controlling the allocation and proliferation of NCM have likely influenced the course of jaw size evolution.

C Regulation of Jaw Length

In addition to discovering that the total amount of NCM present in the mandibular primordia is a determinant of species-specific jaw size, we also paradoxically found that reducing or augmenting NCM by up to 25% does not significantly alter jaw length (Fish et al. 2014). This is consistent with other experiments showing that the jaw can return to its normal size after extirpation of precursor cells at the level of the neural folds, a process often referred to as *regulation* (Scherson et al. 1993; Hunt et al. 1995; Sechrist et al. 1995; Couly et al. 1996). In these previous investigations, however, normal jaw length was thought to arise from regeneration of NCM along the neural tube, either by a re-specification of remaining dorsal neuroepithelium (Sechrist et al. 1995; Hunt et al. 1995), or by an expansion of NCM generated by adjoining neural folds (Scherson et al. 1993; Couly et al. 1996). Instead, we conclude that NCM does not regenerate at the level of the neural tube and therefore, the restoration of normal jaw length depends upon another compensatory mechanism possibly involving signaling interactions with surrounding epithelia. That is to say, normal jaw length may also be affected by local regulation of proliferation within the postmigratory environment of the mandibular primordia.

This type of regulative development in the local environment would allow for compensation of deficiencies in NCM up to some intrinsic species-specific population size. Such findings are consistent with prior tissue regeneration and transplantation experiments revealing that individual organs possess autonomous determinants of size and can regulate growth appropriately in various contexts (Stern and Emlen 1999; Leevers and McNeill 2005). Moreover, that a strong correlation exists between innate rates of growth and overall size is well established in birds (Starck 1989; Ricklefs and Starck 1998; Starck and Ricklefs 1998).

7.5 CELLULAR CONTROL OF JAW SIZE AND SHAPE DURING SKELETAL DIFFERENTIATION

Once appropriate amounts of NCM are allocated to the mandibular primordia of quail versus duck, the next question is how these differences are integrated into the programs for skeletal differentiation that eventually produces species-specific size and shape? To answer this question, we examined the formation of Meckel's cartilage in the lower jaw skeleton (Eames and Schneider 2008).

A Meckel's Cartilage and Species-Specific Size and Shape

Meckel's cartilage is more-or-less a cylindrical rod that is derived exclusively from NCM (Helms and Schneider 2003; Noden and Schneider 2006; Noden 1978, 1982; Noden and Trainor 2005) and rarely goes on to ossify (Kavumpurath and Hall 1990; Ekanayake and Hall 1994; Eames et al. 2004; de Beer 1937). To identify molecular and cellular mechanisms through which Meckel's cartilage acquires its species-specific size and shape, we unilaterally transplanted NCM from quail embryos into a stage-matched duck. These quail donor NCM filled the right half of the duck host mandible, which allowed for an unambiguous comparison of donor quail-derived versus host duck-derived Meckel's cartilage development in the same chimeric mandible.

During normal growth of Meckel's cartilage, conspicuous stage-specific and species-specific differences in size and shape emerge in quail and duck. At early embryonic stages in both quail and duck, Meckel's cartilage goes from being slightly curved to more S-shaped. Shortly afterward, however, Meckel's cartilage in duck remains curved (Figure 7.2e), whereas Meckel's cartilage in quail becomes straightened (Figure 7.2f). Meckel's cartilage grows in each successive stage thereafter, but steadily gets larger in duck. In quck chimeras, quail donor NCM maintained its faster rate of growth within the relatively slower duck host environment, and Meckel's cartilage on the donor side was always accelerated by approximately three stages. Moreover, the size and shape of the donor side was consistently more quail-like compared to that observed on the contralateral duck host side (Figure 7.2g). Using landmark-based morphometrics and a Procrustes analysis (Chapman 1990; Rohlf and Bookstein 1990; Coppinger and Schneider 1995; Marcus 1996; Roth and Mercer 2000; Schneider and Helms 2003; Zelditch 2004), we quantified changes in Meckel's cartilage and found that NCM controls both stage-specific and species-specific size and shape.

To clarify the molecular and cellular mechanisms through which NCM accomplishes this complex task, we assayed for changes in the program of cartilage differentiation that might presage the genesis of size and shape. Cartilage differentiation involves the condensation of pre-chondrogenic mesenchyme, followed by overt chondrification where an abundant extracellular matrix is secreted by chondrocytes (Eames et al. 2003; Hall 2005). In quck chimeras, NCM on the donor side differentiated into chondrocytes and formed cartilage, following the timeframe of quail. Donor-dependent acceleration to the timing of cartilage differentiation was evident from the beginning of mesenchymal condensation. The transcription factor *Sox9*, which is the earliest known molecular marker of chondrogenic condensations (Healy et al. 1996; Zhao et al. 1997; Eames et al. 2003, 2004), and *Col2a1*, which is directly regulated by *Sox9* (Bell et al. 1997), were expressed prematurely by quail donor NCM relative to the duck host. We also observed that FGF signaling, which operates upstream of *Sox9* and chondrogenesis (Bobick et al. 2007; Govindarajan and Overbeek 2006; Murakami et al. 2000; Petiot et al. 2002; Healy et al. 1999; de Crombrugghe et al. 2000; Eames et al. 2004) was similarly regulated by donor NCM in temporal and spatial patterns like those observed in quail. For example, while the secreted ligands *Fgf4* and *Fgf8* were expressed continuously by duck

host epithelium prior to and during formation of Meckel's cartilage, the receptor *Fgfr2* was prematurely expressed just by quail donor NCM. When we inhibited FGF signaling during this discrete temporal window of receptor activation, we blocked chondrogenesis. Thus by exerting control over the timing of FGF signaling and the expression of downstream targets such as *Sox9* and *Col2a1*, NCM likely transmits information establishing stage-specific and species-specific size and shape to Meckel's cartilage.

B Epithelia and Cartilage Patterning

While these experiments demonstrate that NCM dictates the size and shape of cartilage, other studies have shown that adjacent epithelia also play essential roles during cartilage pattern formation. For instance, in the 1980s Peter Thorogood advanced a "*flypaper model*" in which he proposed that interactions between epithelia and mesenchyme drive the production of extracellular matrix, which adhesively "traps" migrating NCM at their site of differentiation and leads to the induction of cartilage (Garrod 1986; Thorogood 1988, 1993). In the head, such epithelia are associated with the surface ectoderm and pharyngeal endoderm around the facial primordia, as well as the brain and sensory capsules, all of which are known to initiate and maintain chondrogenesis at one stage or another (Thorogood et al. 1986; Hall 1980, 1981).

While some data suggest that epithelia can play an inhibitory role during chondrogenesis (Mina et al. 1994), additional studies demonstrate that epithelia impart axial polarity and regional identity to the underlying NCM-derived skeletal tissues. More specifically, epithelia around the developing jaws and face (e.g., frontonasal, maxillary, mandibular primordia) seem to provide positional cues and maintenance factors necessary for patterned outgrowth of individual skeletal elements along the proximodistal, mediolateral, and dorsoventral axes (Hu et al. 2003; Foppiano et al. 2007; Hu and Marcucio 2009; Schneider et al. 1999; Young et al. 2000; Cordero et al. 2002; Helms and Schneider 2003; Young et al. 2010; Chong et al. 2012; Hu et al. 2015a). Experiments that rotate epithelium in the mid- and upper face, for example, cause mirror image duplications of distal upper beak structures along the dorsoventral axis (Hu et al. 2003; Marcucio et al. 2005). Similarly, transplantation studies and genetic analyses demonstrate that endodermal epithelium lining the pharynx transmits region-specific polarity and segmental identity to NCM, which is critical for the proper growth and orientation of bone and cartilage in the jaw skeleton (Couly et al. 2002; Haworth et al. 2007; Kikuchi et al. 2001; Kimmel et al. 1998; Veitch et al. 1999; Piotrowski and Nusslein-Volhard 2000; Miller et al. 2000; David et al. 2002; Crump et al. 2004). When either ectodermal or endodermal epithelia are rotated surgically, the underlying NCM-derived skeleton follows accordingly. Taken together, such studies indicate that the primary role for epithelia is to contribute local signals for generalized anatomical pattern, which in turn induce and/or maintain programmatic responses from underlying NCM (Richman and Tickle 1989; Langille and Hall 1993; Tucker et al. 1999; Ferguson et al. 2000; Mitsiadis et al. 2003; Santagati and Rijli 2003; Le Douarin et al. 2004; Wilson and Tucker 2004; Fish and Schneider 2014c; Foppiano et al. 2007; Hu and Marcucio 2009, 2012; Marcucio et al. 2011;

Hu et al. 2015b). Importantly, the timing of expression of these epithelial signals is under the regulatory control of NCM (Schneider and Helms 2003; Eames and Schneider 2005; Merrill et al. 2008).

The finding that NCM executes autonomous molecular and histological programs for cartilage size and shape can be combined with other experimental results about the role of epithelia in the following way. If the steps of skeletal patterning involve mesenchymal migration, proliferation, condensation, overt chondrocyte differentiation, and ultimately the morphogenesis of cartilage as a three-dimensional structure, then the interactions with pharyngeal endoderm and facial ectoderm, for example, would dictate cartilage orientation and regional identity along the oral cavity. Such interactions could happen before mesenchymal condensation and promote and align the spatial distribution of pre-chondrogenic mesenchyme. In this context, these epithelia would be acting instructively initially but then assume a more permissive role that facilitates the execution of NCM-dependent programs and enables chondrogenesis to proceed in a time-independent manner.

So, while epithelia derived from ectoderm and endoderm may define where chondrogenic condensations occur along an axis, which is presumably quite similar between quail and duck, our transplants reveal that NCM consequently responds via intrinsic, stage-specific and species-specific programs that determine cartilage size and shape. Equivalent roles have also been postulated for epithelia during osteogenesis of the mandible and other bones (Tyler and Hall 1977; Hall 1978, 1987; Bradamante and Hall 1980; Hall 1980, 1981, 1982a, b; Hall and Van Exan 1982; Hall et al. 1983; Van Exan and Hall 1984; Merrill et al. 2008). Further support is lent by the finding that several chondrogenic signaling pathways including FGFs and BMPs are expressed continuously by epithelia prior to and during the arrival of NCM in the mandible (Francis-West et al. 1994; Wall and Hogan 1995; Shigetani et al. 2000; Mina et al. 2002; Ashique et al. 2002b; Havens et al. 2006; Eames and Schneider 2008; Merrill et al. 2008). By controlling the timing of receptor activation, in this case, for *Fgfr2*, NCM allows the signal transduction required for chondrogenesis to proceed, and by doing so, initiates the program for cartilage size and shape.

Overall, this integrated perspective on the roles of mesenchyme and epithelium in the establishment of size and shape is also consistent with classic embryological work from the lab of Hans Spemann who first discovered the origins of species-specific pattern in the 1920s and 1930s through interspecific grafting experiments and especially by exchanging mouth-forming tissues between frogs and newts (Spemann and Mangold 1924; Spemann and Schotté 1932; Spemann 1938; Fassler 1996; Noden and Schneider 2006). These remarkable experiments showed that general anatomical features of the mouth are guided by local signals, but that species-specific pattern is dictated by information in the responding cells. Evidently, Spemann interpreted his finding to mean that, "The ectoderm says to the inducer, 'you tell me to make a mouth; all right, I'll do so, but I can't make your kind of mouth; I can make my own, and I'll do that'" (Harrison 1933). Ensuing transplant experiments between salamanders and frogs, between mice and chicks (in this instance for jaws and teeth), as well as divergent species of birds, including quail, chick, duck, and emu have also supported the conclusion that species-specific pattern is largely driven by NCM (Andres 1949; Wagner 1959; Lumsden 1988; Mitsiadis et al. 2003;

Lwigale and Schneider 2008; Sohal 1976; Yamashita and Sohal 1986; Schneider and Helms 2003; Tucker and Lumsden 2004; Eames and Schneider 2005; Schneider 2005; Noden and Schneider 2006; Eames and Schneider 2008; Jheon and Schneider 2009; Tokita and Schneider 2009; Fish and Schneider 2014c; Fish et al. 2014; Hall et al. 2014; Ealba et al. 2015; Schneider 2015).

C Time as a Developmental Module for Chondrogenesis

Our results suggest that the program for chondrogenesis through which NCM implements species-specific size and shape is integrated at multiple levels and through time as a developmental module. This is equivalent to the identification of developmental modules and the role proposed for mesenchyme in other embryonic systems such as epidermal appendages (Eames and Schneider 2005; Schneider 2005).

In a similar vein as that described by Alberch (Alberch 1982a), modularity is predicated on the observation that many developmental programs appear to function as semi-autonomous, self-directing, and hierarchical units that can be continuously iterated during development and rapidly diversified during evolution as a consequence of the inductive relationships among their constituent parts (Raff 1996; Bolker 2000; West-Eberhard 2003; Schlosser and Wagner 2004). The notion that NCM engineers size and shape by presiding over a highly integrated developmental module is supported by the fact that NCM executes autonomous molecular and cellular programs for both the formation of cartilage as a tissue and as a three-dimensional organ. Importantly, these programs include many of the same gene regulatory networks and signaling molecules that operate during NCM specification, proliferation, and differentiation such as members and targets of the BMP and FGF pathways, and that affect the size and shape of cartilage in the avian jaw and facial skeletons (Francis-West et al. 1994; Wall and Hogan 1995; Mina et al. 1995; Ekanayake and Hall 1997; Barlow and Francis-West 1997; Richman et al. 1997; Wang et al. 1999; Tucker et al. 1999; Barlow et al. 1999; Shigetani et al. 2000; Mina et al. 2002; Ashique et al. 2002b; Abzhanov et al. 2004; Wilson and Tucker 2004; Havens et al. 2006; Schneider 2007; Abzhanov and Tabin 2004; Wu et al. 2004, 2006; Foppiano et al. 2007).

Further evidence for modularity as a principal mechanism through which NCM exerts control over skeletal size and shape relates to the way NCM accounts for time. In fact, this is one of the most striking revelations to emerge from the quail–duck chimeric system: NCM keeps track of stage-specific and species-specific size and shape concurrently. In other words, as quail donor NCM shifts the timing of cartilage differentiation and morphogenesis in the duck to something like that found in the quail, these cells generate stage-appropriate and species-appropriate size and shape simultaneously. This result offers a novel mechanism that connects skeletal development with skeletal evolution vis-à-vis a single population of cells, the cranial NCM. Moreover, this melding of time links ontogeny with phylogeny in a manner completely consistent with previous theories of heterochrony as a means to understand transformations in size and shape.

While historically, heterochrony has been used to describe changes in the timing of developmental events between ancestors and descendants (Russell 1916;

de Beer 1930), the concept can also concern comparisons of closely related taxa (such as quail and duck) and be employed to assess the effects of changes in rates of growth on size and shape (Gould 1977; Alberch et al. 1979; Hall 1984; Roth 1984; McKinney 1988a; Foster and Kaesler 1988; Klingenberg and Spence 1993; Raff 1996). This type of growth heterochrony is probably one of many variables introduced by the faster-developing quail donor NCM in the relatively slower-growing duck host. While such an effect would largely arise from intrinsic species-specific differences in maturation rates, another variable could be any experimentally induced shifts in relative onsets, cessations, and/or durations of molecular and cellular events during chondrogenesis. Under normal circumstances, these types of changes would be considered instances of sequence heterochrony, which is another way changes in time can relate to changes in size and shape (Smith 2001, 2002, 2003), particularly with regard to reciprocal epithelial–mesenchymal interactions underlying skeletal evolution (Smith and Hall 1990).

The predisposition of quail NCM to follow its endogenous rate and time for cartilage development likely arises from cell-autonomous mechanisms that limit the cycling and proliferation of cells to a quail-specific timetable. As a result, chondrogenesis advances three embryonic stages ahead of schedule, and Meckel's cartilage attains species-specific size and shape. To be clear, this scenario was not the only theoretically possible outcome of our transplant experiments. Quail donor NCM could have acted naively, followed the timetable of the duck host, and made cartilage that was duck-like in morphology; or they could have become confused and created some novel anatomy that was either a combination of, or unlike what is normally observed in quail or duck. But instead, within a duck host environment and all that entails in terms of duck-specific signaling, quail donor NCM altered the relative timing and rates of differentiation, executed an innate program of cartilage morphogenesis that replaced and/or superseded the duck program, and in so doing, made something like that normally observed in quail. Thus, not only does NCM coordinate the developmental timing of its own derivatives, but host epithelium also responds to this premature induction and expresses secreted molecules on the donor timetable as well (Schneider and Helms 2003; Eames and Schneider 2005; Merrill et al. 2008).

Overall, our work supports the conclusion that heterochrony can underlie the species-specific evolution of size and shape, but in the case of the quail–duck chimeric system, such heterochrony does so with at least two important caveats. First, since quail donor NCM followed their own timetable and acted as they would normally do, the heterochrony we created is not heterochrony in the true sense of the word. In this chimeric system, absolute time remained the same, and the heterochrony we constructed can only be contemplated in terms of relative timing of developmental events (i.e., to that of the duck host). Second, timing is not the only thing that was altered in these transplants. Once inside the duck host, quail NCM seemingly and progressively implemented a quail-specific genome. Likely, donor NCM does so in response to shared common signals present in duck host epithelium (e.g., FGF and BMP) that appear to be expressed continuously during a broad developmental window, and which might be able to accommodate any difference in stage between the donor and the host. Even transplants in avian species with much wider disparities in

maturation rates like quail and emu (i.e., 17 vs. 58 days from fertilization to hatching), which are separated by approximately seven embryonic stages during chondrogenesis, demonstrate that apparently there are few limits in the ability of the host to support the deployment of NCM-mediated programs for cartilage and bone at any given time during development (Hall et al. 2014). Similarly, duail chimeras, in which slower-growing duck NCM act out their programs on a delayed timetable relative to faster-developing quail host and consequently make duck-like structures, reveal that the same phenomenon is true in reverse (Schneider and Helms 2003; Eames and Schneider 2005; Merrill et al. 2008).

D Time as a Developmental Module for Osteogenesis

In a similar manner to what we have observed for cartilage, NCM also appears to provide species-specific information on size and shape to the bone in the craniofacial skeleton by setting the timing of key events during osteogenesis. Following transplants of NCM destined to form the lower jaw, quail NCM maintains its faster timetable for development and autonomously executes molecular and cellular programs that initiate and synchronize each discrete step of osteogenesis including induction, proliferation, differentiation, osteoid deposition, mineralization, and matrix remodeling (Merrill et al. 2008; Hall et al. 2014; Ealba et al. 2015).

Again, this role as a developmental timekeeper holds true both in reverse and in the extreme, as evidenced by transplants of duck NCM into quail (i.e., *duail*) and quail NCM into emu (i.e., *qumu*), respectively. In accordance with one of Alberch's theoretical predictions concerning parameter changes to a construction rule, we find that NCM determines the timing of bone formation in the jaw skeleton by controlling cell cycle progression. In particular, we observed that NCM regulates the cell cycle through stage- and species-specific expression of cyclin and cyclin-dependent kinase inhibitors (CKI), including p27 (*Cdkn1b*), which is a CKI that decreases proliferation in cell types such as differentiating osteoblasts; cyclin E (*Ccne1*), which is required for G1/S phase transition; and cyclin B1 (*Ccnb1*), which is required for G2/M phase transition (Zavitz and Zipursky 1997; Coats et al. 1996; Drissi et al. 1999). Our data suggest that differences in the expression or post-translational processing of these cell cycle regulators may enable species such as quail to lessen mesenchymal proliferation and form a faster-developing and smaller beak. For example, in quail and quck we observed an up-regulation of p27 relative to that observed in duck. Previous studies have shown that p27 is correlated with size, including p27-deficient mice, which are substantially larger than wild-type littermates and have no apparent defects in skeletal development (Drissi et al. 1999). Additionally, the developing duck frontonasal process has a lower p27 level than in chick (Powder et al. 2012), and also the mandibular primordia shows tissue-specific post-translational regulation of p27, like what has been reported in other systems (Hirano et al. 2001; Zhang et al. 2005). Thus, modulating p27 may be a means to influence tissue- and species-specific size and/or overall growth. Ultimately, such a direct mechanistic link between the regulation of cell cycle progression and the sequence of developmental events during osteogenesis likely endows NCM with the capacity to generate changes in skeletal size and shape during evolution.

Another mechanism through which NCM appears to determine the size and shape of bones in the jaw skeleton is through members and targets of TGFβ and BMP pathways, especially, osteogenic transcription factors such as *Runx2*, which become expressed prematurely and at higher levels in quck chimeras (Merrill et al. 2008; Ealba and Schneider 2013; Hall et al. 2014; Ealba et al. 2015). *Runx2* is a master regulator of bone formation since its expression is sufficient to direct osteoblast differentiation, initiate the timing of mineralization, and affect skeletal size (Eames et al. 2004; Maeno et al. 2011; Ducy et al. 1997; Komori et al. 1997; Otto et al. 1997; Ducy et al. 1999; Pratap et al. 2003; Galindo et al. 2005; Thomas et al. 2004). Moreover, we observe premature expression of bone matrix-producing genes such as *Col1a1*.

Consistent with what we observed in our cartilage studies, the systemic environment of the duck host seems to be more or less permissive and supports osteogenesis independently by supplying circulating minerals and blood vessels. NCM controls precisely where and when bone forms by dictating the timing of cell cycle progression and by mediating the transition from cell proliferation to cell differentiation. If we experimentally induce premature cell cycle exit, we can mimic chimeras by accelerating and elevating expression of *Runx2* and *Col1a1* (Hall et al. 2014). Experimentally increasing and accelerating the timing of *Runx2* expression leads to a decrease in the size of the beak skeleton like that observed in quail. In effect, this mirrors the relationship between endogenous *Runx2* levels and species-specific beak size, since we also observed higher endogenous expression of *Runx2* in quail concomitant with their smaller beak skeletons. In fact, by the time the jaw becomes mineralized, *Runx2* levels in quail are more than double those of duck. This supports other studies, which have predicted a mechanistic connection between expected *Runx2* expression levels (based on ratios of tandem repeats in DNA) and facial length in dogs and other mammals (Fondon and Garner 2004; Sears et al. 2007; Pointer et al. 2012).

That the timing and levels of *Runx2* directly affect the size of the craniofacial skeleton, is a finding fulfilling predictions made around 75 years earlier by Huxley, Goldschmidt, and de Beer concerning genes that alter the time and rate of development (Huxley 1932; Goldschmidt 1938, 1940; de Beer 1954). Insight into how *Runx2* might play this role comes from *in vitro* studies in which *Runx2* both responds to and modulates cell cycle progression through direct and indirect mechanisms, including repressing rRNA synthesis, and up-regulating p27 expression (Young et al. 2007; Galindo et al. 2005; Thomas et al. 2004; Pratap et al. 2003).

These studies suggest that NCM controls jaw size by maintaining precise species-specific levels of essential transcription factors such as *Runx2* and by regulating the timing of skeletal cell differentiation. Duck NCM seemingly proliferates more slowly and expands in size for longer periods of time before differentiating, which then leads to larger skeletal elements. In contrast, quail embryos suppress proliferative signals more quickly, exit the cell cycle sooner, and achieve a smaller overall beak size. This scenario invokes possible changes to the balance between mesenchymal proliferation and differentiation during a critical phase of osteogenesis, which is condensation (Ettinger and Doljanski 1992; Hall 1980; Hall and Miyake 1992, 1995). Such changes would likely affect the size, shape, and location of these condensations, which can generate morphological variation in development and evolution (Atchley and Hall 1991; Dunlop and Hall 1995; Smith and Hall 1990; Hall

and Miyake 2000; Smith and Schneider 1998). So, in terms of absolute time, earlier osteogenic condensations can lead to smaller skeletal elements and ultimately affect their shape through allometric growth. With regard to the differentiation of both cartilage and bone, the astonishing ability of NCM to transmit information on size and shape across embryonic stages and between species in parallel, lends strong support to the notion that development has played a generative role during the course of skeletal evolution (Alberch 1982b; Maderson et al. 1982).

7.6 CELLULAR CONTROL OF JAW SIZE AND SHAPE DURING LATE-STAGE GROWTH

Whereas most of our studies reveal that NCM imparts species-specific size and shape to the jaw skeleton by controlling the molecular and cellular programs that underlie the induction and deposition of cartilage and bone, we have also found that a previously unrecognized but perhaps equally important mechanism affecting size and shape is the ability of NCM to mediate the process of bone resorption (Ealba et al. 2015). Bone resorption is typically associated with bone deposition and as a metabolic process helps maintain homeostasis in the adult skeleton (Filvaroff and Derynck 1998; Buckwalter et al. 1996; Hall 2005; Teitelbaum 2000; Teitelbaum et al. 1997; Nguyen et al. 2013; O'Brien et al. 2008). The extent to which bone resorption affects the embryonic skeleton has not been studied extensively except for some hypotheses proposing differential fields of resorption to account for changes in size and shape that arise during the development of the human jaw skeleton (Enlow et al. 1975; Moore 1981; Radlanski et al. 2004; Radlanski and Klarkowski 2001).

A Bone Resorption

Bone resorption relies on the activities of two cell types, which can be distinguished by their distinct embryological lineages and morphology:

- *Osteoclasts*, which come from the mesodermal hematopoietic lineage (Jotereau and Le Douarin 1978; Kahn et al. 2009), have traditionally been thought of as the principal population of bone-resorbing cells (Hancox 1949; Martin and Ng 1994; Teitelbaum et al. 1997; Filvaroff and Derynck 1998; Teitelbaum 2000; Boyle et al. 2003). In our quail–duck chimeric system, all osteoclasts arise entirely from host mesoderm.
- *Osteocytes* are the second cell type that resorb bone (Belanger 1969; Qing et al. 2012; Tang et al. 2012; Xiong et al. 2014; O'Brien et al. 2008; Xiong and O'Brien 2012; Akil et al. 2014; Fowler et al. 2017; Jauregui et al. 2016), and in the skeleton of the jaws and face form solely from NCM (Helms and Schneider 2003; Noden 1978; Le Lièvre 1978). Hence in quail–duck chimeras, osteocytes are derived exclusively from donor NCM.

Both osteoclasts and osteocytes secrete an enzyme called tartrate-resistant acid phosphatase (TRAP) when they resorb bone (Minkin 1982; Qing et al. 2012; Tang et al. 2012). Also, osteoclasts and osteocytes express different molecular markers such

as *Mmp9*, which is found in osteoclasts (Reponen et al. 1994; Engsig et al. 2000), and *Mmp13*, which is detected in osteocytes (Johansson et al. 1997; Behonick et al. 2007; Sasano et al. 2002). Therefore, following the transplant of NCM into the lower jaw of chimeric quck, *Mmp9* expression would be coming from duck host-derived osteoclasts whereas *Mmp13* would be expressed by quail donor-derived osteocytes.

When we examine the initiation of bone resorption in short-beaked quail versus long-billed duck we detect significantly higher levels and different spatial domains of TRAP, *Mmp9*, and *Mmp13* in quail, signifying that quail undergo more bone resorption than duck, and indicating that elevated resorption may relate to their shorter beaks. Correspondingly, chimeric quck have elevated quail-like levels of TRAP, *Mmp9*, and *Mmp13* coincident with their quail-like jaw skeletons. This means that in chimeric quck, quail donor NCM executes an autonomous species-specific program for bone resorption by way of higher *Mmp13* expression and TRAP activity, and also through upregulation of *Mmp9* expression in duck host osteoclasts. This reveals an unexpected NCM-mediated mechanism that potentially contributes to the shorter jaws of quail and chimeric quck. In other words, levels of bone resorption in bird beaks seem to be inversely proportional to jaw size.

To test if bone resorption is a determinant of jaw size, we used a biochemical approach to activate or inhibit resorption by osteocytes and osteoclasts. We administered treatments systemically when bone deposition is just starting and resorption has not yet begun. Inhibiting resorption causes the quail lower jaw to elongate, whereas activating resorption significantly shortens the jaw (Ealba et al. 2015). Thus, quail and duck express species-specific developmental programs for bone resorption that are distinct in terms of levels and spatial domains, these programs are governed by NCM, and bone resorption appears to be a contributing mechanism establishing beak length. Such experiments point to a novel function for NCM-mediated bone resorption, which is to help control species-specific jaw size, and they extend previous studies on Darwin's finches and other species, which argue that an important regulator of beak length is the calcium binding protein, *calmodulin* (Abzhanov et al. 2006; Schneider 2007; Gunter et al. 2014).

This connection is particularly intriguing because *calmodulin* has been shown to regulate osteocytes and osteoclasts in the local environment (Seales et al. 2006; Zayzafoon 2006; Choi et al. 2013a, b). Since calcium signaling is known to affect bone resorption (Hwang and Putney 2011; Kajiya 2012; Xia and Ferrier 1996; Xiong et al. 2014), NCM-mediated bone resorption may serve as another developmental mechanism that drives the evolvability of the avian beak more generally (Kirschner and Gerhart 1998), and determines jaw size more specifically (Gunter et al. 2014; Parsons and Albertson 2009). Additionally, this work suggests that bone resorption may act like a rheostat during jaw size evolution and one that is particularly sensitive to the availability of dietary calcium in the environment, the endocrine effects of calcium-dependent hormones, and gradients of calcium signaling within the jaw primordia (Schneider 2007).

The spatial and temporal regulation by the NCM of expression domains for genes including *Mmp9* and *Mmp13* are likely to affect shape as well, by establishing local zones of resorption that in effect sculpt the bone and promote or inhibit directional growth. Genetic disruptions to these genes and others that affect bone

resorption are known to alter the morphology of the craniofacial skeleton. For example, mice with mutations in *Mmp2* have abnormal snouts (Egeblad et al. 2007), and defects in jaw morphology are observed in humans with clinical conditions such as Spondyloepimetaphyseal dysplasia (i.e., *Mmp13*), Juvenile Paget's disease (i.e., *Opg*), and following treatments with high doses of bisphosphonates, such as zoledronic acid, which inhibit bone resorption (Gorlin et al. 1990; Lezot et al. 2014).

Therefore, the remarkable ability of NCM to exert spatiotemporal control over not only the induction, differentiation, deposition, and mineralization of bone (Eames and Schneider 2008; Hall et al. 2014; Merrill et al. 2008; Schneider and Helms 2003), but also the resorption of bone, seamlessly integrates the molecular and cellular determinants of jaw size and shape, and confers NCM with its unique capacity to generate species-specific variation during development and evolution.

7.7 CONCLUSIONS

In the beginning of his collected works, Waddington (1975) expressed his "deeply ingrained conviction that the evolution of organisms must really be regarded as the evolution of developmental systems" (p. 7). A long line of evolutionary developmental biologists would certainly concur with Waddington's viewpoint particularly those researchers who have focused on allometry and/or heterochrony as mechanisms to explain species-specific transformations in size and shape. A major factor behind such transformations clearly involves modifications to the fundamental parameter of time, mainly in terms of total developmental time, differential rates of growth, and/or the timing of developmental events. Thus as in good comedy, timing is everything.

While in many respects Minot, Thompson, Huxley, de Beer, Goldschmidt, Waddington, Gould, and Alberch were way ahead of their own time, over the past 25 years, technological and conceptual advances in genetics, genomics, and molecular biology have revolutionized the study of pattern formation during development. Many of the genes that regulate basic developmental phenomena have been identified, and the processes they guide have been redefined in mechanistic terms. Notably, we have come to recognize that the construction rules of embryonic development and the genetic and epigenetic architecture required to enforce those rules are shared broadly across disparate taxa. This has led to the spread of a common language for evolutionary developmental biologists studying the embryos of seemingly diverse organisms, including but certainly not limited to mice, chicks, frogs, fish, flies, and worms. As a direct result, the pace of research in the field has greatly accelerated because discoveries in one species swiftly lead to progress in understanding the development of other species. This progress has transformed developmental biology from a descriptive science into one that can now explain the complexities of organ and tissue development as consequences of known signal transduction pathways and transcriptional programs.

Whether changes to the temporal and spatial programs for development become propagated at the level of genomic organization, at the *cis*-regulatory level of individual genes, at the transcriptional and post-transcriptional level through the epigenetic activities of non-coding RNA, at the level of nodes within gene regulatory networks, at the level of biochemical interactions among gene products such as enzymes and

other proteins, at the level of post-translation modification of proteins, at the level of diffusion-reaction gradients and thresholds that establish the inductive abilities of cells, at the level of cell properties and cell movements, or at the level of physical and signaling interactions between tissues, the downstream effects on morphological phenotypes can range from subtle to profound. Internal modifications to developmental programs at any of these hierarchical levels of organization can generate the variation necessary for evolution, but they would also be buffered by the robustness and stability of the internal networks and nested interactions that ultimately work together to generate individual morphological units and ensure fidelity for structural and functional integration.

This feature of developmental systems has allowed the vertebrate craniofacial complex to be both highly conserved in its basic anatomical organization and extraordinarily diversified in its size and shape. Individual morphological units within the craniofacial complex can become modified rapidly over time, yet still, maintain connections and keep relationships that are required for meeting structural and functional demands. By focusing on the molecular and cellular regulation of species-specific pattern in the craniofacial complex we hope our work has helped pinpoint precisely where and when changes to developmental programs can affect the course of morphological evolution. Our experiments in quail and duck embryos reveal that NCM plays a special role in generating species-specific pattern in the craniofacial complex, by dominating its own signaling interactions with surrounding tissues and by way of autonomous morphogenetic programs that can span and accommodate fluctuations in time. Simply because of these virtues, cranial NCM has likely endured as a key effectuator of skeletal size and shape during development and evolution.

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REFERENCES

Abzhanov, A., Kuo, W. P., Hartmann, C., Grant, B. R., Grant, P. R., and Tabin, C. J. 2006. The calmodulin pathway and evolution of elongated beak morphology in Darwin's finches. *Nature* 442: 563–567.

Abzhanov, A., Protas, M., Grant, B. R., Grant, P. R., and Tabin, C. J. 2004. Bmp4 and morphological variation of beaks in Darwin's finches. *Science* 305: 1462–465.

Abzhanov, A. and Tabin, C. J. 2004. Shh and Fgf8 act synergistically to drive cartilage outgrowth during cranial development. *Dev Biol* 273: 134–148.

Akil, O., Hall-Glenn, F., Chang, J., Li, A., Chang, W., Lustig, L. R., Alliston, T., and Hsiao, E. C. 2014. Disrupted bone remodeling leads to cochlear overgrowth and hearing loss in a mouse model of fibrous dysplasia. *PLoS One* 9: e94989.

Alberch, P. 1980a. Adaptation and heterochrony in the evolution of Bolitoglossa (Amphibia: Plethodontidae). PhD thesis, University of California, Berkeley, CA.

Alberch, P. 1980b. Ontogenesis and morphological diversification. *Amer Zool* 20: 653–667.

Alberch, P. 1982a. Developmental constraints in evolutionary processes. In *Evolution and Development* (Ed.) Bonner, J. T., pp. 313–332. Berlin, Germany: Springer-Verlag.

Alberch, P. 1982b. The generative and regulatory roles of development in evolution. In *Environmental Adaptation and Evolution: A Theoretical and Empirical Approach* (Eds.) Mossakowski, D. and Roth, G., pp. 19–36. Stuttgart, Germany: G. Fischer-Verlag.

Alberch, P. 1985. Problems with the interpretation of developmental sequences. *Syst Zool* 34: 46–58.

Alberch, P. 1989. The logic of monsters: Evidence for internal constraint in development and evolution. *Geobios* 22 (Suppl 2): 21–57.

Alberch, P. 1991. From genes to phenotype: Dynamical systems and evolvability. *Genetica* 84: 5–11.

Alberch, P. and Alberch, J. 1981. Heterochronic mechanisms of morphological diversification and evolutionary change in the neotropical salamander, *Bolitoglossa occidentalis* (Amphibia: Plethodontidae). *J Morphol* 167: 249–264.

Alberch, P. and Gale, E. 1983. Size dependence during the development of the amphibian foot. Colchicine induced digital loss and reduction. *J Embryol Exp Morphol* 76: 177–197.

Alberch, P. and Gale, E. 1985. A developmental analysis of an evolutionary trend: Digital reduction in Amphibians. *Evolution* 39: 8–23.

Alberch, P., Gould, S. J., Oster, G. F., and Wake, D. B. 1979. Size and shape in ontogeny and phylogeny. *Paleobiology* 5: 296–317.

Allmon, W. D. 1994. Patterns and processes of heterochrony in lower tertiary turritelline gastropods U.S. Gulf and Atlantic Coastal Plains. *J Paleont* 68: 80–95.

Anderson, B. G. and Busch, H. L. 1941. Allometry in normal and regenerating antennal segments in daphnia. *Biol Bull* 81: 119–126.

Andres, G. 1949. Untersuchungen an Chimären von *Triton* und *Bombinator. Genetica* 24: 387–534.

Arthur, W. 2006. D'Arcy Thompson and the theory of transformations. *Nat Rev Genet* 7: 401–406.

Ashique, A. M., Fu, K., and Richman, J. M. 2002a. Endogenous bone morphogenetic proteins regulate outgrowth and epithelial survival during avian lip fusion. *Development* 129: 4647–4660.

Ashique, A. M., Fu, K., and Richman, J. M. 2002b. Signalling via type IA and type IB bone morphogenetic protein receptors (BMPR) regulates intramembranous bone formation, chondrogenesis and feather formation in the chicken embryo. *Int J Dev Biol* 46: 243–253.

Atchley, W. R. 1981. Genetic components of size and shape. II. Multivariate covariance patterns in the rat and mouse skull. *Evolution* 35: 1037–1055.

Atchley, W. R. and Hall, B. K. 1991. A model for development and evolution of complex morphological structures. *Biol Rev Camb Philos Soc* 66: 101–157.

Atchley, W. R., Riska, B., Kohn, L. A. P., Plummer, A. A., and Rutledge, J. J. 1984. A quantitative genetic analysis of brain and body size associations, their origin and ontogeny: Data from mice. *Evolution* 38: 1165–1179.

Baker, C. V. and Bronner-Fraser, M. 1997. The origins of the neural crest. Part II: An evolutionary perspective. *Mech Dev* 69: 13–29.

Balling, R., Mutter, G., Gruss, P., and Kessel, M. 1989. Craniofacial abnormalities induced by ectopic expression of the homeobox gene Hox-1.1 in transgenic mice. *Cell* 58: 337–347.

Balon, E. K. 1981. Saltatory processes and altricial to precocial forms in the ontogeny of fishes. *Amer Zool* 21: 573–596.

Barlow, A. J., Bogardi, J. P., Ladher, R., and Francis-West, P. H. 1999. Expression of chick *Barx-1* and its differential regulation by FGF-8 and BMP signaling in the maxillary primordia. *Dev Dyn* 214: 291–302.

Barlow, A. J. and Francis-West, P. H. 1997. Ectopic application of recombinant BMP-2 and BMP-4 can change patterning of developing chick facial primordia. *Development* 124: 391–398.

Bateson, W. 1894. *Materials for the Study of Variation, Treated With Especial Regard to the Discontinuity in the Origin of Species*. New York: Macmillan Publishers.

Bateson, W. and Mendel, G. 1902. *Mendel's Principles of Heredity; A Defence*. Cambridge, UK: Cambridge University Press.

Bee, J. and Thorogood, P. 1980. The role of tissue interactions in the skeletogenic differentiation of avian neural crest cells. *Dev Biol* 78: 47–66.

Behonick, D. J., Xing, Z., Lieu, S., Buckley, J. M., Lotz, J. C., Marcucio, R. S., Werb, Z., Miclau, T., and Colnot, C. 2007. Role of matrix metalloproteinase 13 in both endochondral and intramembranous ossification during skeletal regeneration. *PLoS One* 2 (11): e1150.

Belanger, L. F. 1969. Osteocytic osteolysis. *Calcif Tissue Res* 4: 1–12.

Bell, D. M., Leung, K. K., Wheatley, S. C., Ng, L. J., Zhou, S., Ling, K. W., Sham, M. H., Koopman, P., Tam, P. P., and Cheah, K. S. 1997. SOX9 directly regulates the type-II collagen gene. *Nat Genet* 16: 174–178.

Bemis, W. E. 1984. Paedomorphosis and the evolution of the Dipnoi. *Paleobiology* 10: 293–307.

Benson, R. H., Chapman, R. E., and Siegel, A. F. 1982. On the measurement of morphology and its change. *Paleobiology* 8: 328–339.

Bertalanffy, L. and Pirozynski, W. J. 1952. Ontogenetic and evolutionary allometry. *Evolution* 6: 387–392.

Betancur, P., Bronner-Fraser, M., and Sauka-Spengler, T. 2010. Assembling neural crest regulatory circuits into a gene regulatory network. *Ann Rev Cell Devel Biol* 26: 581–603.

Bhullar, B. A., Morris, Z. S., Sefton, E. M., Tok, A., Tokita, M., Namkoong, B., Camacho, J., Burnham, D. A., and Abzhanov, A. 2015. A molecular mechanism for the origin of a key evolutionary innovation, the bird beak and palate, revealed by an integrative approach to major transitions in vertebrate history. *Evolution* 69: 1665–1677.

Blackstone, N. W. and Buss, L. W. 1993. Experimental heterochrony in Hydractiniid Hydroids: Why mechanisms matter. *J Evol Biol* 6: 307–327.

Blanco, M. J. and Alberch, P. 1992. Caenogenesis, developmental variability, and evolution in the carpus and tarsus of the marbled newt *Triturus marmoratus*. *Evolution* 46: 677–687.

Bobick, B. E., Thornhill, T. M., and Kulyk, W. M. 2007. Fibroblast growth factors 2, 4, and 8 exert both negative and positive effects on limb, frontonasal, and mandibular chondrogenesis via MEK-ERK activation. *J Cell Physiol* 211: 233–243.

Bolk, L. 1926. *Das problem der Menschwerdung*. Jena, Germany: Gustav Fischer.

Bolker, J. A. 2000. Modularity in development and why it matters to Evo-Devo. *Amer Zool* 40: 770–776.

Bonner, J. T. (Ed.). 1982. *Evolution and Development*. Berlin, Germany: Springer-Verlag.

Bookstein, F. L. 1978. *The Measurement of Biological Shape and Shape Change*. New York: Springer-Verlag.

Bookstein, F. L. 1990. Multivariate methods. In *Proceedings of the Michgan Morphometrics Workshop* (Eds.). Rohlf, F. J. and Bookstein, F. L., pp. 75–76. Ann Arbor, MI: University of Michigan Museum of Zoology.

Boyle, W. J., Simonet, W. S., and Lacey, D. L. 2003. Osteoclast differentiation and activation. *Nature* 423: 337–342.

Bradamante, Z. and Hall, B. K. 1980. The role of epithelial collagen and proteoglycan in the initiation of osteogenesis by avian neural crest cells. *Anat Rec* 197: 305–315.

Brigandt, I. 2006. Homology and heterochrony: The evolutionary embryologist Gavin Rylands de Beer (1899–1972). *J Exp Zool B Mol Dev Evol* 306: 317–328.

Bronner-Fraser, M. 2008. On the trail of the 'new head' in Les Treilles. *Development* 135: 2995–2999.

Brugmann, S. A., Goodnough, L. H., Gregorieff, A., Leucht, P., ten Berge, D., Fuerer, C., Clevers, H., Nusse, R., and Helms, J. A. 2007. Wnt signaling mediates regional specification in the vertebrate face. *Development* 134: 3283–3295.

Brugmann, S. A., Powder, K. E., Young, N. M., Goodnough, L. H., Hahn, S. M., James, A. W., Helms, J. A., and Lovett, M. 2010. Comparative gene expression analysis of avian embryonic facial structures reveals new candidates for human craniofacial disorders. *Hum Mol Genet* 19: 920–930.

Buckwalter, J. A., Glimcher, M. J., Cooper, R. R., and Recker, R. 1996. Bone biology. II: Formation, form, modeling, remodeling, and regulation of cell function. *Instr Course Lect* 45: 387–399.

Chapman, R. E. 1990. Conventional procrustes approaches. *Proceedings of the Michigan Morphometrics Workshop*, Ann Arbor, MI.

Cheverud, J. M. 1982. Phenotypic, genetic, and environmental morphological integration in the cranium. *Evolution* 36: 499–516.

Choi, Y. H., Ann, E. J., Yoon, J. H., Mo, J. S., Kim, M. Y., and Park, H. S. 2013a. Calcium/calmodulin-dependent protein kinase IV (CaMKIV) enhances osteoclast differentiation via the up-regulation of Notch1 protein stability. *Biochim Biophys Acta* 1833: 69–79.

Choi, Y. H., Choi, J. H., Oh, J. W., and Lee, K. Y. 2013b. Calmodulin-dependent kinase II regulates osteoblast differentiation through regulation of Osterix. *Biochem Biophys Res Commun* 432: 248–255.

Chong, H. J., Young, N. M., Hu, D., Jeong, J., McMahon, A. P., Hallgrimsson, B., and Marcucio, R. S. 2012. Signaling by SHH rescues facial defects following blockade in the brain. *Dev Dyn* 241: 247–256.

Clark, W. E. L. G. and Medawar, P. B. (Eds.). 1945. *Essays on Growth and Form Presented to D'Arcy Wentworth Thompson*. Oxford, UK: Clarendon Press.

Coats, S., Flanagan, W. M., Nourse, J., and Roberts, J. M. 1996. Requirement of p27Kip1 for restriction point control of the fibroblast cell cycle. *Science* 272: 877–880.

Coppinger, L. and Coppinger, R. P. 1982. Livestock–guarding dogs that wear sheep's clothing. *Smithsonian* 13: 64–73.

Coppinger, R. P. and Feinstein, M. 1991. Why dogs bark. *Smithsonian* January: 119–129.

Coppinger, R. P., Glendinning, J., Torop, E., Matthay, C., Sutherland, M., and Smith, C. K. 1987. Degree of behavioral neoteny differentiates canid polymorphs. *Ethology* 75: 89–108.

Coppinger, R. P. and Schneider, R. A. 1995. Evolution of working dogs. In *The Domestic Dog* (Ed.) Serpell, J., pp. 21–47. Cambridge, UK: Cambridge University Press.

Coppinger, R. P. and Smith, C. K. 1989. A model for understanding the evolution of mammalian behavior. In *Current Mammalogy* (Ed.) Genoways, H., pp. 335–374. New York: Plenum Press.

Cordero, D. R., Schneider, R. A., and Helms, J. A. 2002. Morphogenesis of the face. In *Craniofacial Surgery: Science & Surgical Technique* (Eds.) Lin, K. Y., Ogle, R. C., and Jane, J. A., pp. 75–83. Philadelphia, PA: W. B. Saunders Company.

Couly, G., Grapin-Botton, A., Coltey, P., and Le Douarin, N. M. 1996. The regeneration of the cephalic neural crest, a problem revisited: the regenerating cells originate from the contralateral or from the anterior and posterior neural fold. *Development* 122: 3393–3407.

Couly, G., Creuzet, S., Bennaceur, S., Vincent, C., and Le Douarin, N. M. 2002. Interactions between Hox-negative cephalic neural crest cells and the foregut endoderm in patterning the facial skeleton in the vertebrate head. *Development* 129: 1061–1073.

Couly, G. F., Coltey, P. M., and Le Douarin, N. M. 1993. The triple origin of skull in higher vertebrates: A study in quail–chick chimeras. *Development* 117: 409–429.

Creuzet, S., Couly, G., Vincent, C., and Le Douarin, N. M. 2002. Negative effect of Hox gene expression on the development of the neural crest-derived facial skeleton. *Development* 129(18): 4301–4313.

Crumly, C. R. and Sanchez-Villagra, M. R. 2004. Patterns of variation in the phalangeal formulae of land tortoises (Testudinidae): Developmental constraint, size, and phylogenetic history. *J Exp Zool Part B (Mol Dev Evol)* 302B: 134–146.

Crump, J. G., Maves, L., Lawson, N. D., Weinstein, B. M., and Kimmel, C. B. 2004. An essential role for Fgfs in endodermal pouch formation influences later craniofacial skeletal patterning. *Development* 131: 5703–5716.

Darwin, C. 1859. *The Origin of Species*. 1962 ed. New York: The Crowell-Collier Publishing.

David, N. B., Saint-Etienne, L., Tsang, M., Schilling, T. F., and Rosa, F. M. 2002. Requirement for endoderm and FGF3 in ventral head skeleton formation. *Development* 129: 4457–4468.

de Beer, G. R. 1930. *Embryology and Evolution*. Oxford, UK: Clarendon Press.

de Beer, G. R. 1937. *The Development of the Vertebrate Skull*. Chicago, IL: University of Chicago Press.

de Beer, G. R. 1940. *Embryos and ancestors*. Oxford, UK: Clarendon Press.

de Beer, G. R. 1954. *Embryos and Ancestors*. Revised ed. *Monographs on Animal Biology*. Oxford, UK: Clarendon Press.

de Beer, G. R. 1958. *Embryos and Ancestors*. 3rd ed. Oxford, UK: Oxford University Press.

de Crombrugghe, B., Lefebvre, V., Behringer, R. R., Bi, W., Murakami, S., and Huang, W. 2000. Transcriptional mechanisms of chondrocyte differentiation. *Matrix Biol* 19: 389–394.

De Renzi, M. 2009. Developmental and historical patterns at the crossroads in the work of Pere Alberch. In *Pere Alberch: The Creative Trajectory of an Evo-Devo Biologist* (Eds.) Rasskin-Gutman, D. and De Renzi, M., pp. 45–66. Valencia, Spain: Universidad de València.

De Renzi, M., Moya, A., and Peretó, J. 1999. Evolution, development and complexity in Pere Alberch (1954–1998). *J Evol Biol* 12: 624–626.

Deacon, T. W. 1990. Problems of ontogeny and phylogeny in brain-size evolution. *Int J Primatol* 11: 237–282.

Dechambre, E. 1949. La théorie de foetalization et la formation des races de chiens et de porc. *Mammalia* 13: 129–137.

Depew, M. J., Lufkin, T., and Rubenstein, J. L. 2002. Specification of jaw subdivisions by Dlx genes. *Science* 298: 381–385.

Depew, M. J. and Olsson, L. 2008. Symposium on the evolution and development of the vertebrate head. *J Exp Zool Part B (Mol Dev Evol)* 310: 287–293.

Dietrich, M. R. 2000. From hopeful monsters to homeotic effects: Richard Goldschmidt's integration of development, evolution, and genetics. *Amer Zool* 40: 738–747.

Dobzhansky, T. 1937. *Genetics and the Origin of Species*, *Columbia Biological Series*. New York: Columbia University Press.

Dobzhansky, T. 1951. *Genetics and the Origin of Species*, 3d ed., *Columbia Biological Series*. New York: Columbia University Press.

Doufexi, A. E. and Mina, M. 2008. Signaling pathways regulating the expression of Prx1 and Prx2 in the chick mandibular mesenchyme. *Dev Dyn* 237: 3115–3127.

Drake, A. G. 2011. Dispelling dog dogma: An investigation of heterochrony in dogs using 3D geometric morphometric analysis of skull shape. *Evol Dev* 13: 204–213.

Drissi, H., Hushka, D., Aslam, F., Nguyen, Q., Buffone, E., Koff, A., van Wijnen, A., Lian, J. B., Stein, J. L., and Steinm, G. S. 1999. The cell cycle regulator p27kip1 contributes to growth and differentiation of osteoblasts. *Cancer Res* 59: 3705–3711.

Duboule, D. 1994. Temporal colinearity and the phylotypic progression: A basis for the stability of a vertebrate Bauplan and the evolution of morphologies through heterochrony. *Development* 135–142.

Ducy, P., Starbuck, M., Priemel, M., Shen, J., Pinero, G., Geoffroy, V., Amling, M., and Karsenty, G. 1999. A Cbfa1-dependent genetic pathway controls bone formation beyond embryonic development. *Genes Dev* 13: 1025–1036.

Ducy, P., Zhang, R., Geoffroy, V., Ridall, A. L., and Karsenty, G. 1997. Osf2/Cbfa1: A transcriptional activator of osteoblast differentiation. *Cell* 89: 747–754.

Dunlop, L. L. and Hall, B. K. 1995. Relationships between cellular condensation, preosteoblast formation and epithelial-mesenchymal interactions in initiation of osteogenesis. *Int J Devel Biol* 39: 357–371.

Ealba, E. L., Jheon, A. H., Hall, J., Curantz, C., Butcher, K. D., and Schneider, R. A. 2015. Neural crest-mediated bone resorption is a determinant of species-specific jaw length. *Dev Biol* 408: 151–163.

Ealba, E. L. and Schneider, R. A. 2013. A simple PCR-based strategy for estimating species-specific contributions in chimeras and xenografts. *Development* 140: 3062–3068.

Eames, B. F., de la Fuente, L., and Helms, J. A. 2003. Molecular ontogeny of the skeleton. *Birth Defects Res Part C Embryo Today* 69: 93–101.

Eames, B. F. and Schneider, R. A. 2005. Quail-duck chimeras reveal spatiotemporal plasticity in molecular and histogenic programs of cranial feather development. *Development* 132: 1499–1509.

Eames, B. F. and Schneider, R. A. 2008. The genesis of cartilage size and shape during development and evolution. *Development* 135: 3947–3958.

Eames, B. F., Sharpe, P. T., and Helms, J. A. 2004. Hierarchy revealed in the specification of three skeletal fates by Sox9 and Runx2. *Dev Biol* 274: 188–200.

Egeblad, M., Shen, H. C., Behonick, D. J., Wilmes, L., Eichten, A., Korets, L. V., Kheradmand, F., Werb, Z., and Coussens, L. M. 2007. Type I collagen is a genetic modifier of matrix metalloproteinase 2 in murine skeletal development. *Dev Dyn* 236: 1683–1693.

Ekanayake, S. and Hall, B. K. 1994. Hypertrophy is not a prerequisite for type X collagen expression or mineralization of chondrocytes derived from cultured chick mandibular ectomesenchyme. *Int J Dev Biol* 38: 683–694.

Ekanayake, S. and Hall, B. K. 1997. The in vivo and in vitro effects of bone morphogenetic protein-2 on the development of the chick mandible. *Int J Dev Biol* 41: 67–81.

Eldredge, N. and Gould, S. J. 1972. Punctuated equilibria: An alternative to phyletic gradualism. In *Models in Paleobiology* (Ed.) Schopf, T. J. M., pp. 82–115. San Francisco, CA: Freeman Cooper.

Engsig, M. T., Chen, Q. J., Vu, T. H., Pedersen, A. C., Therkidsen, B., Lund, L. R., Henriksen, K. et al. 2000. Matrix metalloproteinase 9 and vascular endothelial growth factor are essential for osteoclast recruitment into developing long bones. *J Cell Biol* 151: 879–889.

Enlow, D. H., Moyers, R. E., and Merow, W. W. 1975. *Handbook of Facial Growth*. Philadelphia, PA: Saunders.

Ettinger, L. and Doljanski, F. 1992. On the generation of form by the continuous interactions between cells and their extracellular matrix. *Biol Rev Camb Philos Soc* 67: 459–489.

Etxeberria, A. and De la Rosa, L. N. 2009. A world of opportunity within constraint: Pere Alberch's early evo-devo. In *Pere Alberch: The Creative Trajectory of an Evo-Devo Biologist* (Eds.) Rasskin-Gutman, D. and De Renzi, M., pp. 21–44. Valencia, Spain: Universidad de València.

Fassler, P. E. 1996. Hans Spemann (1869–1941) and the Freiburg School of Embryology. *Int J Dev Biol* 40: 49–57.

Ferguson, C. A., Tucker, A. S., and Sharpe, P. T. 2000. Temporospatial cell interactions regulating mandibular and maxillary arch patterning. *Development* 127: 403–412.

Filvaroff, E. and Derynck, R. 1998. Bone remodelling: A signalling system for osteoclast regulation. *Curr Biol* 8:R679–R682.

Fish, J. L. and Schneider, R. A. 2014a. On the origins of species-specific size. *The Node*. http://thenode.biologists.com/on-the-origins-of-species-specific-size/research/.

Fish, J. L. and Schneider, R. A. 2014b. Assessing species-specific contributions to craniofacial development using quail-duck chimeras. *J Vis Exp* 87(e51534): 1–6.

Fish, J. L. and Schneider, R. A. 2014c. Neural crest-mediated tissue interactions during craniofacial development: The origins of species-specific pattern. In *Neural Crest Cells* (Ed.) Trainor, P. A., pp. 101–124. Boston, MA: Academic Press.

Fish, J. L., Sklar, R. S., Woronowicz, K. C., and Schneider, R. A. 2014. Multiple developmental mechanisms regulate species-specific jaw size. *Development* 141: 674–684.

Fisher, R. A. 1930. *The Genetical Theory of Natural Selection*. Oxford, UK: The Clarendon Press.

Fondon, J. W., and Garner, H. R. 2004. Molecular origins of rapid and continuous morphological evolution. *Proc Natl Acad Sci USA* 101: 18058–18063.

Foppiano, S., Hu, D., and Marcucio, R. S. 2007. Signaling by bone morphogenetic proteins directs formation of an ectodermal signaling center that regulates craniofacial development. *Dev Biol* 312: 103–114.

Foster, D. W. and Kaesler, R. L. 1988. Shape analysis: Ideas from the Ostracoda. In *Heterochrony in Evolution: A Multidisciplinary Approach* (Ed.) McKinney, M. L., pp. 53–69. New York: Plenum Press.

Fowler, T. W., Acevedo, C., Mazur, C. M., Hall-Glenn, F., Fields, A. J., Bale, H. A., Ritchie, R. O., Lotz, J. C., Vail, T. P., and Alliston, T. 2017. Glucocorticoid suppression of osteocyte perilacunar remodeling is associated with subchondral bone degeneration in osteonecrosis. *Sci Rep* 7: 44618.

Francis-West, P. H., Robson, L., and Evans, D. J. 2003. Craniofacial development: The tissue and molecular interactions that control development of the head. *Adv Anat Embryol Cell Biol* 169: 1–138.

Francis-West, P. H., Tatla, T., and Brickell, P. M. 1994. Expression patterns of the bone morphogenetic protein genes Bmp-4 and Bmp-2 in the developing chick face suggest a role in outgrowth of the primordia. *Dev Dyn* 201: 168–178.

Francis-West, P., Ladher, R., Barlow, A., and Graveson, A. 1998. Signalling interactions during facial development. *Mech Dev* 75: 3–28.

Galilei, G. 1914. *Dialogues Concerning Two New Sciences*. Translated from the Italian and Latin into English by Crew, H. and De Salvio, A. New York: Macmillan.

Galindo, M., Pratap, J., Young, D. W., Hovhannisyan, H., Im, H. J., Choi, J. Y., Lian, J. B., Stein, J. L., Stein, G. S., and van Wijnen, A. J. 2005. The bone-specific expression of Runx2 oscillates during the cell cycle to support a G1-related antiproliferative function in osteoblasts. *J Biol Chem* 280: 20274–20285.

Gans, C. and Northcutt, R. G. 1983. Neural crest and the origin of vertebrates: A new head. *Science* 220: 268–274.

Garrod, D. R. 1986. Specific inductive flypaper. *Bioessays* 5: 172–173.

Garstang, W. 1928. The morphology of the Tunicata, and its bearings on the phylogeny of the Chordata. *Quart J Microsc Sci* 75: 51–187.

Garstang, W. 1922. The theory of recapitulation: A critical restatement of the biogenic law. *Je Linn Soc Lond, Zool* 35: 81–101.

Gayon, J. 2000. History of the concept of allometry. *Amer Zool* 40: 748–758.

Geist, V. 1987. On speciation in ice age mammals, with special reference to cervids and caprids. *Can J Zool* 65: 1067–1084.

Gendron-Maguire, M., Mallo, M., Zhang, M., and Gridley, T. 1993. Hoxa-2 mutant mice exhibit homeotic transformation of skeletal elements derived from cranial neural crest. *Cell* 75: 1317–1331.

Gilbert, S. F., Opitz, J. M., and Raff, R. A. 1996. Resynthesizing evolutionary and developmental biology. *Dev Biol* 173: 357–372.

Godfrey, L. R. and Sutherland, M. R. 1995a. What's growth got to do with it? Process and product in the evolution of ontogeny. *J Human Evol* 29: 405–431.

Godfrey, L. R. and Sutherland, M. R. 1995b. Flawed Inference: Why size-based tests of heterochronic processes do not work. *J Theor Biol* 172: 43–61.

Goldschmidt, R. 1938. *Physiological Genetics*. New York: McGraw-Hill.

Goldschmidt, R. 1940. *The Material Basis of Evolution*. 1982 ed. New Haven, CT: Yale University Press.

Goldschmidt, R. 1953. Homeotic mutants and evolution. *Acta Biotheoretica* 10: 87–104.

Gorlin, R.J., Cohen, M. M., and Levin, L. S. 1990. *Syndromes of the Head and Neck*. 3rd edition, 1 vols. Vol. 1, *Oxford Monographs on Medical Genetics*. New York: Oxford University Press.

Gould, S. J. 1966. Allometry and size in ontogeny and phylogeny. *Biol Rev Camb Philos Soc* 41: 587–640.

Gould, S. J. 1971. Geometric similarity in allometric growth: A contribution to the problems of scaling in the evolution of size. *Amer Nat* 105: 113–136.

Gould, S. J. 1977. *Ontogeny and Phylogeny*. Cambridge, MA: Harvard University Press.

Gould, S. J. 1981. *The Mismeasure of Man*. New York: W. W. Norton & Company.

Gould, S. J. 1982a. Change in developmental timing as a mechanism of macroevolution. In *Evolution and Development* (Ed.) Bonner, J., pp. 333–346. Berlin, Germany: Springer-Verlag.

Gould, S. J. 1982b. The uses of heresy: An introduction to Richard Goldschmidt's *The Material Basis of Evolution*. In *The Material Basis of Evolution*, pp. 13–42. New Haven, CT: Yale University.

Gould, S. J. 2002. *The Structure of Evolutionary Theory*. Cambridge, MA: Belknap Press of Harvard University Press.

Gould, S. J. and Lewontin, R. C. 1979. The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptionist programme. *Proc R Soc Lond* B205: 581–598.

Gould, S. J. and Vrba, E. S. 1982. Exaptation-a missing term in the science of form. *Paleobiology*: 4–15.

Govindarajan, V. and Overbeek, P. A. 2006. FGF9 can induce endochondral ossification in cranial mesenchyme. *BMC Dev Biol* 6: 7.

Graham, A. 2003. The neural crest. *Curr Biol* 13: R381–R384.

Graham, A., Begbie, J., and McGonnell, I. 2004. Significance of the cranial neural crest. *Dev Dyn* 229: 5–13.

Grammatopoulos, G. A., Bell, E., Toole, L., Lumsden, A., and Tucker, A. S. 2000. Homeotic transformation of branchial arch identity after Hoxa2 overexpression. *Development* 127: 5355–5365.

Grant, P. R., Grant, B. R., and Abzhanov, A. 2006. A developing paradigm for the development of bird beaks. *Biol J Linn Soc Lond* 88: 17–22.

Gregory, W. K. 1934. Polyisomerism and anisomerism in cranial and dental evolution among vertebrates. *Proc Natl Acad Sci USA* 20: 1–9.

Gunter, H. M., Koppermann, C., and Meyer, A. 2014. Revisiting de Beer's textbook example of heterochrony and jaw elongation in fish: Calmodulin expression reflects heterochronic growth, and underlies morphological innovation in the jaws of belonoid fishes. *Evodevo* 5: 8.

Hafner, J. C. and Hafner, M. S. 1988. Heterochrony in rodents. In *Heterochrony in Evolution: A Multidisciplinary Approach* (Ed.) McKinney, M. L., pp. 217–235. New York: Plenum Press.

Haldane, J. B. S. 1926. On being the right size. *Harper's Magazine* 152: 424–427.

Haldane, J. B. S. 1932. *The Causes of Evolution*, 1990 Reprint ed. Princeton, NJ: Princeton University Press.

Hall, B. K. 1978. Initiation of osteogenesis by mandibular mesenchyme of the embryonic chick in response to mandibular and non-mandibular epithelia. *Arch Oral Biol* 23: 1157–1161.

Hall, B. K. 1980. Tissue interactions and the initiation of osteogenesis and chondrogenesis in the neural crest-derived mandibular skeleton of the embryonic mouse as seen in isolated murine tissues and in recombinations of murine and avian tissues. *J Embryol Exp Morphol* 58: 251–264.

Hall, B. K. 1981. The induction of neural crest-derived cartilage and bone by embryonic epithelia: An analysis of the mode of action of an epithelial-mesenchymal interaction. *J Embryol Exp Morphol* 64: 305–320.

Hall, B. K. 1982a. Distribution of osteo- and chondrogenic neural crest-derived cells and of osteogenically inductive epithelia in mandibular arches of embryonic chicks. *J Embryol Exp Morphol* 68: 127–136.

Hall, B. K. 1982b. The role of tissue interactions in the growth of bone. In *Factors and Mechanisms Influencing Bone Growth* (Eds.) Dixon, A. D. and Sarnat, B. G., pp. 205–215. New York: Alan R. Liss.

Hall, B. K. 1984. Developmental processes underlying heterochrony as an evolutionary mechanism. *Can J Zool* 62: 1–7.

Hall, B. K. 1987. Tissue interactions in the development and evolution of the vertebrate head. In *Developmental and Evolutionary Aspects of the Neural Crest* (Ed.) Maderson, P. F. A., pp. 215–260. New York: John Wiley & Sons.

Hall, B. K. 1999. *The Neural Crest in Development and Evolution*. New York: Springer.

Hall, B. K. 2000a. Balfour, Garstang and de Beer: The first century of evolutionary embryology. *Amer Zool* 40: 718–728.

Hall, B. K. 2000b. The neural crest as a fourth germ layer and vertebrates as quadroblastic not triploblastic. *Evol Dev* 2: 3–5.

Hall, B. K. 2005. *Bones and Cartilage: Developmental and Evolutionary Skeletal Biology.* San Diego, CA: Elsevier Academic Press.

Hall, B. K. and Hörstadius, S. 1988. *The Neural Crest*. London, UK: Oxford University Press.

Hall, B. K. and T. Miyake. 1992. The membranous skeleton: the role of cell condensations in vertebrate skeletogenesis. *Anat Embryol (Berl)* 186: 107–124.

Hall, B. K. and Miyake, T. 1995. Divide, accumulate, differentiate: Cell condensation in skeletal development revisited. *Int J Dev Biol* 39: 881–893.

Hall, B. K. and Miyake, T. 2000. All for one and one for all: Condensations and the initiation of skeletal development. *Bioessays* 22: 138–147.

Hall, B. K. and Van Exan, R. J. 1982. Induction of bone by epithelial cell products. *J Embryol Exp Morphol* 69: 37–46.

Hall, B. K., Van Exan, R. J., and Brunt, S. L. 1983. Retention of epithelial basal lamina allows isolated mandibular mesenchyme to form bone. *J Craniofac Genet Dev Biol* 3: 253–267.

Hall, J., Jheon, A. H., Ealba, E. L., Eames, B. F., Butcher, K. D., Mak, S. S., Ladher, R., Alliston, T., and Schneider, R. A. 2014. Evolution of a developmental mechanism: Species-specific regulation of the cell cycle and the timing of events during craniofacial osteogenesis. *Dev Biol* 385: 380–395.

Hallgrimsson, B., Percival, C. J., Green, R., Young, N. M., Mio, W., and Marcucio, R. 2015. Morphometrics, 3D imaging, and craniofacial development. *Curr Top Dev Biol* 115: 561–597.

Haluska, F. and Alberch, P. 1983. The cranial development of Elaphe obsoleta (Ophidia, Colubridae). *J Morphol* 178: 37–55.
Hancox, N. M. 1949. The osteoclast. *Biol Rev Camb Philos Soc* 24: 448–471.
Hanken, J. 1989. Development and evolution of the neural crest. *Evolution* 43: 1337–1338.
Hanken, J. and Hall, B. K. 1984. Variation and timing of the cranial ossification sequence of the Oriental fire-bellied toad, *Bombina orientalis* (Amphibia, Discoglossidae). *J Morphol* 182: 245–255.
Hanken, J. and Hall, B. K. (Eds.) 1993. *The Skull*. Chicago, IL: University of Chicago Press.
Harrison, R. G. 1933. Some difficulties of the determination problem. *Amer Nat* 67: 306–321.
Havens, B. A., Rodgers, B., and Mina, M. 2006. Tissue-specific expression of Fgfr2b and Fgfr2c isoforms, Fgf10 and Fgf9 in the developing chick mandible. *Arch Oral Biol* 51: 134–145.
Havens, B. A., Velonis, D., Kronenberg, M. S., Lichtler, A. C., Oliver, B., and Mina, M. 2008. Roles of FGFR3 during morphogenesis of Meckel's cartilage and mandibular bones. *Dev Biol* 316: 336–349.
Haworth, K. E., Wilson, J. M., Grevellec, A., Cobourne, M. T., Healy, C., Helms, J. A., Sharpe, P. T., and Tucker, A. S. 2007. Sonic hedgehog in the pharyngeal endoderm controls arch pattern via regulation of Fgf8 in head ectoderm. *Dev Biol* 303: 244–258.
Healy, C., Uwanogho, D., and Sharpe, P. T. 1996. Expression of the chicken Sox9 gene marks the onset of cartilage differentiation. *Ann N Y Acad Sci* 785: 261–262.
Healy, C., Uwanogho, D., and Sharpe, P. T. 1999. Regulation and role of Sox9 in cartilage formation. *Devel Dyn* 215: 69–78.
Helms, J. A. and Schneider, R. A. 2003. Cranial skeletal biology. *Nature* 423: 326–331.
Hersh, A. H. 1934. Evolutionary allometric growth in the titanotheres. *Amer Nat* 68: 537–561.
Hirano, K., Hirano, M., Zeng, Y., Nishimura, J., Hara, K., Muta, K., Nawata, H., and Kanaide, H. 2001. Cloning and functional expression of a degradation-resistant novel isoform of p27Kip1. *Biochem J* 353: 51–57.
Hoberg, E. P. 1987. Recognition of larvae of the Tetrabothriidae Eucestoda: Implications for the origin of tapeworms in marine homeotherms. *Can J Zool* 65: 997–1000.
Hu, D. and Marcucio, R. S. 2009. Unique organization of the frontonasal ectodermal zone in birds and mammals. *Dev Biol* 325: 200–210.
Hu, D. and Marcucio, R. S. 2012. Neural crest cells pattern the surface cephalic ectoderm during FEZ formation. *Dev Dyn* 241: 732–740.
Hu, D., Marcucio, R. S., and Helms, J. A. 2003. A zone of frontonasal ectoderm regulates patterning and growth in the face. *Development* 130: 1749–1758.
Hu, D., Young, N. M., Li, X., Xu, Y., Hallgrimsson, B., and Marcucio, R. S. 2015a. A dynamic Shh expression pattern, regulated by SHH and BMP signaling, coordinates fusion of primordia in the amniote face. *Development* 142: 567–574.
Hu, D., Young, N. M., Xu, Q., Jamniczky, H., Green, R. M., Mio, W., Marcucio, R. S., and Hallgrimsson, B. 2015b. Signals from the brain induce variation in avian facial shape. *Dev Dyn* 244: 1133–1143.
Hunt, P., Clarke, J. D., Buxton, P., Ferretti, P., and Thorogood, P. 1998. Stability and plasticity of neural crest patterning and branchial arch Hox code after extensive cephalic crest rotation. *Devel Biol* 198: 82–104.
Hunt, P., Ferretti, P., Krumlauf, R., and Thorogood, P. 1995. Restoration of normal Hox code and branchial arch morphogenesis after extensive deletion of hindbrain neural crest. *Dev Biol* 168: 584–597.
Huxley, J. S. 1924. Constant differential growth-ratios and their significance. *Nature* 114: 895–896.
Huxley, J. S. 1932. *Problems of Relative Growth*. London, UK: Methuen.
Huxley, J. S. 1942. *Evolution, the Modern Synthesis*. London, UK: G. Allen & Unwin.
Huxley, J. S. 1950. Relative growth and form transformation. *Proc R Soc Lond (B)* 137: 465–469.

Huxley, J. S. and de Beer, G. R. 1934. *The Elements of Experimental Embryology*. Cambridge, UK: The University Press.

Huxley, J. S., and Teissier, G. 1936. Terminology of relative growth. *Nature* 137: 780–781.

Hwang, S. Y. and Putney, J. W. Jr. 2011. Calcium signaling in osteoclasts. *Biochim Biophys Acta* 1813: 979–983.

Jauregui, E. J., Akil, O., Acevedo, C., Hall-Glenn, F., Tsai, B. S., Bale, H. A., Liebenberg, E. et al. 2016. Parallel mechanisms suppress cochlear bone remodeling to protect hearing. *Bone* 89: 7–15.

Jheon, A. H. and Schneider, R. A. 2009. The cells that fill the bill: Neural crest and the evolution of craniofacial development. *J Dent Res* 88: 12–21.

Johansson, N., Saarialho-Kere, U., Airola, K., Herva, R., Nissinen, L., Westermarck, J., Vuorio, E., Heino, J., and Kähäri, V. M. 1997. Collagenase-3 (MMP-13) is expressed by hypertrophic chondrocytes, periosteal cells, and osteoblasts during human fetal bone development. *Dev Dyn* 208: 387–397.

Jotereau, F. V. and Le Douarin, N. M. 1978. The development relationship between osteocytes and osteoclasts: A study using the quail-chick nuclear marker in endochondral ossification. *Devel Biol* 63: 253–265.

Kahn, J., Shwartz, Y., Blitz, E., Krief, S., Sharir, A., Breitel, D. A., Rattenbach, R. et al. 2009. Muscle contraction is necessary to maintain joint progenitor cell fate. *Dev Cell* 16: 734–743.

Kajiya, H. 2012. Calcium signaling in osteoclast differentiation and bone resorption. *Adv Exp Med Biol* 740: 917–932.

Kavumpurath, S. and Hall, B. K. 1990. Lack of either chondrocyte hypertrophy or osteogenesis in Meckel's cartilage of the embryonic chick exposed to epithelia and to thyroxine in vitro. *J Craniofac Genet Devel Biol* 10: 263–275.

Kermack, K. A. and Haldane, J. B. S. 1950. Organic correlation and allometry. *Biometrika* 37: 30–41.

Keyte, A. L. and Smith, K. K. 2014. Heterochrony and developmental timing mechanisms: Changing ontogenies in evolution. *Semin Cell Dev Biol* 34: 99–107.

Kikuchi, Y., Agathon, A., Alexander, J., Thisse, C., Waldron, S., Yelon, D., Thisse, B., and Stainier, D. Y. 2001. Casanova encodes a novel Sox-related protein necessary and sufficient for early endoderm formation in zebrafish. *Genes Dev* 15: 1493–1505.

Kimmel, C. B., Miller, C. T., Kruze, G., Ullmann, B., BreMiller, R. A., Larison, K. D., and Snyder, H. C. 1998. The shaping of pharyngeal cartilages during early development of the zebrafish. *Dev Biol* 203: 245–263.

Kimmel, C. B., Ullmann, B., Walker, C., Wilson, C., Currey, M., Phillips, P. C., Bell, M. A., Postlethwait, J. H., and Cresko, W. A. 2005. Evolution and development of facial bone morphology in threespine sticklebacks. *Proc Natl Acad Sci USA* 102: 5791–5796.

Kirschner, M. and Gerhart, J. 1998. Evolvability. *Proc Natl Acad Sci USA* 95: 8420–8427.

Klingenberg, C. P. and Spence, J. R. 1993. Heterochrony and allometry: Lessons from the water strider genus *Limnoporus*. *Evolution* 47: 1834–1853.

Klingenberg, C. P. 1998. Heterochrony and allometry: The analysis of evolutionary change in ontogeny. *Biol Rev Camb Philos Soc* 73: 79–123.

Kollmann, J. 1885. Das Ueberwintern von europäischen Frosch- und Triton-larven und die Umwandlung des mexikanischen Axolotl. *Verhandlungen der Naturforschenden Gesellschaft in Basel* 7: 387–398.

Komori, T., Yagi, H., Nomura, S., Yamaguchi, A., Sasaki, K., Deguchi, K., Shimizu, Y. et al. 1997. Targeted disruption of Cbfa1 results in a complete lack of bone formation owing to maturational arrest of osteoblasts. *Cell* 89: 755–764.

Köntges, G. and Lumsden, A. 1996. Rhombencephalic neural crest segmentation is preserved throughout craniofacial ontogeny. *Development* 122: 3229–3242.

Lande, R. 1979. Quantitative genetic analysis of multivariate evolution, applied to brain: Body size allometry. *Evolution* 33: 402–416.

Langille, R. M. and Hall, B. K. 1993. Pattern formation and the neural crest. In *The Skull* (Eds.) Hanken, J. and Hall, B. K., pp. 77–111. Chicago, IL: University of Chicago Press.

Le Douarin, N. M., Creuzet, S., Couly, G., and Dupin, E. 2004. Neural crest cell plasticity and its limits. *Development* 131: 4637–4650.

Le Lièvre, C. S. 1978. Participation of neural crest-derived cells in the genesis of the skull in birds. *J Embryol Exp Morphol* 47: 17–37.

Le Lièvre, C. S. and Le Douarin, N. M. 1975. Mesenchymal derivatives of the neural crest: Analysis of chimaeric quail and chick embryos. *J Embryol Exp Morphol* 34: 125–154.

Leevers, S. J. and McNeill, H. 2005. Controlling the size of organs and organisms. *Curr Opin Cell Biol* 17: 604–609.

Lezot, F., Chesneau, J., Battaglia, S., Brion, R., Castaneda, B., Farges, J. C., Heymann, D., and Redini, F. 2014. Preclinical evidence of potential craniofacial adverse effect of zoledronic acid in pediatric patients with bone malignancies. *Bone* 68: 146–152.

Liu, W., Selever, J., Murali, D., Sun, X., Brugger, S. M., Ma, L., Schwartz, R. J., Maxson, R., Furuta, Y., and Martin, J. F. 2005. Threshold-specific requirements for Bmp4 in mandibular development. *Dev Biol* 283: 282–293.

Lord, K., Schneider, R. A., and Coppinger, R. P. 2016. Evolution of working dogs. In *The Domestic Dog* (Ed.) Serpell, J., pp. 42–68. Cambridge, UK: Cambridge University Press.

Lufkin, T., Mark, M., Hart, C., Dollé, P., Lemeur, M., and Chambon, P. 1992. Homeotic transformation of the occipital bones of the skull by ectopic expression of a homeobox gene. *Nature* 359: 835–841.

Lumer, H. 1940. Evolutionary allometry in the skeleton of the domesticated dog. *Amer Nat* 76: 439–467.

Lumer, H., Anderson, B. G., and Hersh, A. H. 1942. On the Significance of the Constant b in the Law of Allometry $y = bx^a$. *Amer Nat* 76: 364–375.

Lumer, H. and Schultz, A. H. 1941. Relative growth of the limb segments and tail in macaques. *Human Biol* 13: 283–305.

Lumsden, A. G. 1988. Spatial organization of the epithelium and the role of neural crest cells in the initiation of the mammalian tooth germ. *Development* 103: 155–169.

Lwigale, P. Y. and Schneider, R. A. 2008. Other chimeras: Quail-duck and mouse-chick. *Methods Cell Biol* 87: 59–74.

MacDonald, M. E., Abbott, U. K., and Richman, J. M. 2004. Upper beak truncation in chicken embryos with the cleft primary palate mutation is due to an epithelial defect in the frontonasal mass. *Dev Dyn* 230: 335–349.

MacDonald, M. E., and Hall, B. K. 2001. Altered timing of the extracellular-matrix-mediated epithelial-mesenchymal interaction that initiates mandibular skeletogenesis in three inbred strains of mice: Development, heterochrony, and evolutionary change in morphology. *J Exp Zool* 291: 258–273.

Maderson, P. F. A. 1987. *Developmental and Evolutionary Aspects of the Neural Crest*. New York: John Wiley & Sons.

Maderson, P. F. A., Alberch, P., Goodwin, B. C., Gould, S. J., Hoffman, A., Murray, J. D., Raup, D. M. et al. 1982. The role of development in macroevolutionary change. Evolution and development. In *Evolution and Development* (Ed.) Bonner, J. T., pp. 279–312. Berlin, Germany: Springer-Verlag.

Maeno, T., Moriishi, T., Yoshida, C. A., Komori, H., Kanatani, N., Izumi, S., Takaoka, K., and Komori, T. 2011. Early onset of Runx2 expression caused craniosynostosis, ectopic bone formation, and limb defects. *Bone* 49: 673–682.

Marcucio, R. S., Cordero, D. R., Hu, D., and Helms, J. A. 2005. Molecular interactions coordinating the development of the forebrain and face. *Dev Biol* 284: 48–61.

Marcucio, R. S., Young, N. M., Hu, D., and Hallgrimsson, B. 2011. Mechanisms that underlie co-variation of the brain and face. *Genesis* 49: 177–189.

Marcus, L. F. 1996. *Advances in Morphometrics*, *NATO ASI Series. Series A, Life Sciences; v. 284*. New York: Plenum Press.

Martin, T. J. and Ng, K. W. 1994. Mechanisms by which cells of the osteoblast lineage control osteoclast formation and activity. *J Cell Biochem* 56: 357–366.

Maunz, M. and German, R. Z. 1996. Craniofacial heterochrony and sexual dimorphism in the short-tailed opossum (*Monodelphis domestica*). *J Mammal* 77: 992–1005.

Mayr, E. 1963. *Animal Species and Evolution*. Cambridge, MA: Harvard University Press.

Mayr, E. 1983. How to carry out the adaptionist program? *Amer Nat* 121: 24–34.

McKinney, M. L. 1988a. Classifying heterochrony: Allometry, size, and time. In *Heterochrony in Evolution: A Multidisciplinary Approach* (Ed.) McKinney, M. L., pp. 17–34. New York: Plenum Press.

McKinney, M. L. 1988b. *Heterochrony in Evolution: A Multidisciplinary Approach*. New York: Plenum Press.

Merrill, A. E., Eames, B. F., Weston, S. J., Heath, T., and Schneider, R. A. 2008. Mesenchyme-dependent BMP signaling directs the timing of mandibular osteogenesis. *Development* 135: 1223–1234.

Miller, C. T., Schilling, T. F., Lee, K., Parker, J., and Kimmel, C. B. 2000. sucker encodes a zebrafish Endothelin-1 required for ventral pharyngeal arch development. *Development* 127: 3815–3828.

Mina, M., Gluhak, J., Upholt, W. B., Kollar, E. J., and Rogers, B. 1995. Experimental analysis of Msx-1 and Msx-2 gene expression during chick mandibular morphogenesis. *Dev Dyn* 202: 195–214.

Mina, M., Upholt, W. B., and Kollar, E. J. 1994. Enhancement of avian mandibular chondrogenesis in vitro in the absence of epithelium. *Arch Oral Biol* 39: 551–562.

Mina, M., Wang, Y. H., Ivanisevic, A. M., Upholt, W. B., and Rodgers, B. 2002. Region- and stage-specific effects of FGFs and BMPs in chick mandibular morphogenesis. *Dev Dyn* 223: 333–352.

Minkin, C. 1982. Bone acid phosphatase: Tartrate-resistant acid phosphatase as a marker of osteoclast function. *Calcif Tissue Int* 34: 285–290.

Minot, C. S. 1908. *The Problem of Age, Growth, and Death: A Study of Cytomorphosis, Based on Lectures at the Lowell Institute, March, 1907*, *The progressive science series*. London, UK: John Murray.

Mitgutsch, C., Wimmer, C., Sanchez-Villagra, M. R., Hahnloser, R., and Schneider, R. A. 2011. Timing of ossification in duck, quail, and zebra finch: Intraspecific variation, heterochronies, and life history evolution. *Zool Sci* 28: 491–500.

Mitsiadis, T. A., Caton, J., and Cobourne, M. 2006. Waking-up the sleeping beauty: Recovery of the ancestral bird odontogenic program. *J Exp Zoolog B Mol Dev Evol* 306: 227–233.

Mitsiadis, T. A., Cheraud, Y., Sharpe, P., and Fontaine-Perus, J. 2003. Development of teeth in chick embryos after mouse neural crest transplantations. *Proc Natl Acad Sci USA* 100: 65416545.

Moore, W. J. 1981. *The Mammalian Skull* (Eds.) Harrison, R. J. and McMinn, R. M., Vol. 8, *Biological Structure and Function*. Cambridge, UK: Cambridge University Press.

Morgan, T. H. 1919. *The Physical Basis of Heredity*, *Monographs on Experimental Biology*. Philadelphia, PA: Lippincott.

Morgan, T. H., Bridges, C. V., Muller, H. J., and Sturtevant, A. H. 1915. *The Mechanism of Mendelian Heredity*. London, UK: Constable & Robinson.

Murakami, S., Kan, M., McKeehan, W. L., and de Crombrugghe, B. 2000. Up-regulation of the chondrogenic Sox9 gene by fibroblast growth factors is mediated by the mitogen-activated protein kinase pathway. *Proc Natl Acad Sci USA* 97: 1113–1118.

Nagai, H., Mak, S. S., Weng, W., Nakaya, Y., Ladher, R., and Sheng, G. 2011. Embryonic development of the emu, Dromaius novaehollandiae. *Dev Dyn* 240: 162–175.

Needham, J. and Lerner, M. I. 1940. Terminology of relative growth-rates. *Nature* 146: 618.

Nguyen, J., Tang, S. Y., Nguyen, D., and Alliston, T. 2013. Load regulates bone formation and Sclerostin expression through a TGFbeta-dependent mechanism. *PLoS One* 8: e53813.

Nikitina, N., Sauka-Spengler, T., and Bronner-Fraser, M. 2008. Dissecting early regulatory relationships in the lamprey neural crest gene network. *Proc Natl Acad Sci USA* 105: 20083–20088.

Noden, D. M. 1978. The control of avian cephalic neural crest cytodifferentiation. I. Skeletal and connective tissues. *Dev Biol* 67: 296–312.

Noden, D. M. 1982. Patterns and organization of craniofacial skeletogenic mesenchyme: A perspective. In *Factors and Mechanisms Influencing Bone Growth* (Eds.) Dixon A. D., and Sarnat, B. G., pp. 168–203. New York: Alan R. Liss.

Noden, D. M. 1983. The role of the neural crest in patterning of avian cranial skeletal, connective, and muscle tissues. *Devel Biol* 96: 144–165.

Noden, D. M. and Schneider, R. A. 2006. Neural crest cells and the community of plan for craniofacial development: Historical debates and current perspectives. *Adv Exp Med Biol* 589: 1–23.

Noden, D. M. and Trainor, P. A. 2005. Relations and interactions between cranial mesoderm and neural crest populations. *J Anat* 207: 575–601.

Northcutt, R. G. 2005. The new head hypothesis revisited. *J Exp Zool Part B (Mol Devel Evol)* 304B: 274–297.

Nunn, C. L. and Smith, K. K. 1998. Statistical analyses of developmental sequences: The craniofacial region in marsupial and placental mammals. *Amer Nat* 152: 82–101.

O'Brien, C. A., Plotkin, L. I., Galli, C., Goellner, J. J., Gortazar, A. R., Allen, M. R., Robling, A. G. et al. 2008. Control of bone mass and remodeling by PTH receptor signaling in osteocytes. *PLoS One* 3: e2942.

Oster, G. and Alberch, P. 1982. Evolution and bifurcation of developmental programs. *Evolution* 36: 444–459.

Oster, G. F., Shubin, N., Murray, J. D., and Alberch, P. 1988. Evolution and morphogenetic rules–The shape of the vertebrate limb in ontogeny and phylogeny. *Evolution* 42: 862–884.

Otto, F., Thornell, A. P., Crompton, T., Denzel, A., Gilmour, K. C., Rosewell, I. R., Stamp, G. W. et al. 1997. Cbfa1, a candidate gene for cleidocranial dysplasia syndrome, is essential for osteoblast differentiation and bone development. *Cell* 89: 765–771.

Parsons, K. J. and Albertson, R. C. 2009. Roles for Bmp4 and CaM1 in shaping the jaw: Evo-devo and beyond. *Annu Rev Genet* 43: 369–388.

Pasqualetti, M., Ori, M., Nardi, I., and Rijli, F. M. 2000. Ectopic Hoxa2 induction after neural crest migration results in homeosis of jaw elements in *Xenopus*. *Development* 127: 5367–5378.

Petiot, A., Ferretti, P., Copp, A. J., and Chan, C. T. 2002. Induction of chondrogenesis in neural crest cells by mutant fibroblast growth factor receptors. *Dev Dyn* 224: 210–221.

Piotrowski, T. and Nusslein-Volhard, C. 2000. The endoderm plays an important role in patterning the segmented pharyngeal region in zebrafish (*Danio rerio*). *Dev Biol* 225: 339–356.

Pointer, M. A., Kamilar, J. M., Warmuth, V., Chester, S. G., Delsuc, F., Mundy, N. I., Asher, R. J., and Bradley, B. J. 2012. RUNX2 tandem repeats and the evolution of facial length in placental mammals. *BMC Evol Biol* 12: 103.

Powder, K. E., Ku, Y. C., Brugmann, S. A., Veile, R. A., Renaud, N. A., Helms, J. A., and Lovett, M. 2012. A cross-species analysis of microRNAs in the developing avian face. *PLoS One* 7:e35111.

Pratap, J., Galindo, M., Zaidi, S. K., Vradii, D., Bhat, B. M., Robinson, J. A., Choi, J. Y. et al. 2003. Cell growth regulatory role of Runx2 during proliferative expansion of preosteoblasts. *Cancer Res* 63: 5357–5362.

Qing, H., Ardeshirpour, L., Pajevic, P. D., Dusevich, V., Jahn, K., Kato, S., Wysolmerski, J., and Bonewald, L. F. 2012. Demonstration of osteocytic perilacunar/canalicular remodeling in mice during lactation. *J Bone Miner Res* 27: 1018–1029.

Qiu, M., Bulfone, A., Ghattas, I., Meneses, J. J., Christensen, L., Sharpe, P. T., Presley, R., Pedersen, R. A., and Rubenstein, J. L. 1997. Role of the Dlx homeobox genes in proximodistal patterning of the branchial arches: mutations of Dlx-1, Dlx-2, and Dlx-1 and -2 alter morphogenesis of proximal skeletal and soft tissue structures derived from the first and second arches. *Dev Biol* 185: 165–184.

Radlanski, R. J. and Klarkowski, M. C. 2001. Bone remodeling of the human mandible during prenatal development. *J Orofac Orthop* 62: 191–201.

Radlanski, R. J., Renz, H., Lajvardi, S., and Schneider, R. A. 2004. Bone remodeling during prenatal morphogenesis of the human mental foramen. *Eur J Oral Sci* 112: 301–310.

Raff, R. A. 1996. *The Shape of Life: Genes, Development, and the Evolution of Animal Form*. Chicago, IL: University of Chicago Press.

Raff, R. A. and Kaufman, T. C. 1983. *Embryos, Genes, and Evolution*. New York: Macmillan Publishing.

Reeve, E. C. R. 1950. Genetical aspects of size allometry. *Proc Roy Soc Lond Series B Biol Sci* 137: 515–518.

Reiss, J. O., Burke, A. C., Archer, C. W., De Renzi, M., Dopazo, H., Etxeberría, A., Gale, E. A. et al. 2008. Pere alberch: Originator of evodevo. *Biol Theory* 3: 351–356.

Rensch, B. 1948. Histological changes correlated with evolutionary changes of body size. *Evolution* 2: 218–230.

Reponen, P., Sahlberg, C., Munaut, C., Thesleff, I., and Tryggvason, K. 1994. High expression of 92-kD type IV collagenase (gelatinase B) in the osteoclast lineage during mouse development. *J Cell Biol* 124: 1091–1102.

Richardson, M. K. 1995. Heterochrony and the phylotypic period. *Dev Biol* 172: 412–421.

Richardson, M. K., Hanken, J., Gooneratne, M. L., Pieau, C., Raynaud, A., Selwood, L., and Wright, G. M. 1997. There is no highly conserved embryonic stage in the vertebrates: Implications for current theories of evolution and development. *Anat Embryol* 196: 91–106.

Richman, J. M., Herbert, M., Matovinovic, E., and Walin, J. 1997. Effect of fibroblast growth factors on outgrowth of facial mesenchyme. *Dev Biol* 189: 135–147.

Richman, J. M. and Tickle, C. 1992. Epithelial-mesenchymal interactions in the outgrowth of limb buds and facial primordia in chick embryos. *Dev Biol* 154: 299–308.

Richman, J. M. and Tickle, C. 1989. Epithelia are interchangeable between facial primordia of chick embryos and morphogenesis is controlled by the mesenchyme. *Dev Biol* 136: 201–210.

Ricklefs, R. E. and Starck, J. M. 1998. Embryonic growth and development. In *Avian Growth and Development: Evolution within the Altricial-Precocial Spectrum* (Eds.) Matthias Starck, J. and Ricklefs, R. E., pp. 31–58. New York: Oxford University Press.

Ridley, M. 1985. Embryology and classical zoology in Great Britain. In *A History of Embryology: The Eighth Symposium of the British Society for Developmental Biology* (Eds.) Horder, T. J., Witkowski, J., and Wylie, C. C., pp. 35–67. Cambridge, UK: Cambridge University Press.

Rijli, F. M., Mark, M., Lakkaraju, S., Dierich, A., Dolle, P., and Chambon, P. 1993. A homeotic transformation is generated in the rostral branchial region of the head by disruption of *Hoxa-2*, which acts as a selector gene. *Cell* 75: 1333–1349.

Riska, B. 1986. Some models for development, growth. and morphometric correlation. *Evolution* 40: 1303–1311.

Riska, B. and Atchley, W. R. 1985. Genetics of growth predict patterns of brain-size evolution. *Science* 229: 668–671.

Robb, R. C. 1935. A study of mutations in evolution. *J Genet* 31: 39–46.

Rohlf, F. J. and Bookstein, F. L. Eds. 1990. *Proceedings of the Michigan Morphometrics Workshop*. Vol. Special Publication Number 2. Ann Arbor, MI: University of Michgan Museum of Zoology.

Roth, G. and Wake, D. B. 1989. Conservatism and Innovation in the evolution of feeding in vertebrates. In *Complex Organismal Functions: Integration and Evolution in Vertebrates* (Eds.) Wake, D. B. and Roth, G., pp. 7–21. New York: John Wiley & Sons.

Roth, V. L. 1984. How elephants grow: Heterochrony and the calibration of developmental stages in some living and fossil species. *J Vert Paleont* 4: 126–145.

Roth, V. L. and Mercer, J. M. 2000. Morphometrics in development and evolution. *Amer Zool* 40: 801–810.

Rowe, A., Richman, J. M., and Brickell, P. M. 1992. Development of the spatial pattern of retinoic acid receptor-beta transcripts in embryonic chick facial primordia. *Development* 114: 805–813.

Russell, E. S. 1916. *Form and Function: A Contribution to the History of Animal Morphology*. London, UK: John Murray Publishers.

Sanchez-Villagra, M. R., Geiger, M., and Schneider, R. A. 2016. The taming of the neural crest: A developmental perspective on the origins of morphological covariation in domesticated mammals. *R Soc Open Sci* 3: 160107.

Sanford, G. M., Lutterschmidt, W. I., and Hutchison, V. H. 2002. The comparative method revisited. *Bioscience* 52: 830–836.

Santagati, F. and Rijli, F. M. 2003. Cranial neural crest and the building of the vertebrate head. *Nat Rev Neurosci* 4: 806–818.

Sasano, Y., Zhu, J. X., Tsubota, M., Takahashi, I., Onodera, K., Mizoguchi, I., and Kagayama, M. 2002. Gene expression of MMP8 and MMP13 during embryonic development of bone and cartilage in the rat mandible and hind limb. *J Histochem Cytochem* 50: 325–332.

Scherson, T., Serbedzija, G., Fraser, S., and Bronner-Fraser, M. 1993. Regulative capacity of the cranial neural tube to form neural crest. *Development* 118: 1049–1062.

Schilling, T. F. 1997. Genetic analysis of craniofacial development in the vertebrate embryo. *Bioessays* 19: 459–468.

Schlosser, G. and Wagner, G. P. 2004. *Modularity in Development and Evolution*. Chicago, IL: University of Chicago Press.

Schmalhausen, I. I. 1949. *Factors of Evolution: The Theory of Stabilizing Selection*. Translated by I. Dordick. (Ed.) Dobzhansky, T. Chicago, IL: University of Chicago Press.

Schneider, R. A. 1999. Neural crest can form cartilages normally derived from mesoderm during development of the avian head skeleton. *Devel Biol* 208: 441–455.

Schneider, R. A. 2005. Developmental mechanisms facilitating the evolution of bills and quills. *J Anat* 207: 563–573.

Schneider, R. A. 2007. How to tweak a beak: Molecular techniques for studying the evolution of size and shape in Darwin's finches and other birds. *Bioessays* 29: 1–6.

Schneider, R. A. 2015. Regulation of jaw length during development, disease, and evolution. *Curr Top Dev Biol* 115: 271–298.

Schneider, R. A. and Helms, J. A. 2003. The cellular and molecular origins of beak morphology. *Science* 299: 565–568.

Schneider, R. A., Hu, D., and Helms, J. A. 1999. From head to toe: Conservation of molecular signals regulating limb and craniofacial morphogenesis. *Cell Tissue Res* 296: 103–109.

Schneider, R. A., Hu, D., Rubenstein, J. L., Maden, M., and Helms, J. A. 2001. Local retinoid signaling coordinates forebrain and facial morphogenesis by maintaining FGF8 and SHH. *Development* 128: 2755–2767.

Schowing, J. 1968. Influence inductrice de l'encéphale embryonnaire sur le développement du crâne chez le Poulet. *J Embryol Exp Morphol* 19: 9–32.

Seales, E. C., Micoli, K. M., and McDonald, J. M. 2006. Calmodulin is a critical regulator of osteoclastic differentiation, function, and survival. *J Cell Biochem* 97: 45–55.

Sears, K. E., Goswami, A., Flynn, J. J., and Niswander, L. A. 2007. The correlated evolution of Runx2 tandem repeats, transcriptional activity, and facial length in carnivora. *Evol Dev* 9: 555–565.

Sechrist, J., Nieto, M. A., Zamanian, R. T., and Bronner-Fraser, M. 1995. Regulative response of the cranial neural tube after neural fold ablation: spatiotemporal nature of neural crest regeneration and up-regulation of Slug. *Development* 121: 4103–4115.

Shea, B. T. 1983. Paedomorphosis and neoteny in the pygmy chimpanzee. *Science* 222: 521–522.

Shea, B. T. 1985. Ontogenetic allometry and scaling: A discussion based on the growth and form of the skull in African Apes In *Size and Scaling in Primate Biology* (Ed.) Jungers, W. L., pp. 175–205. New York: Springer.

Shea, B. T. 1989. Heterochrony in human evolution: The case for neoteny reconsidered. *Yearbook Physical Anthropol* 32: 69–101.

Shigetani, Y., Nobusada, Y., and Kuratani, S. 2000. Ectodermally derived FGF8 defines the maxillomandibular region in the early chick embryo: Epithelial-mesenchymal interactions in the specification of the craniofacial ectomesenchyme. *Dev Biol* 228: 73–85.

Shubin, N. H. and Alberch, P. 1986. A morphogenetic approach to the origin and basic organization of the tetrapod limb. In *Evolutionary Biology* (Eds.) Hecht, M. K. and Wallace, B., pp. 319–387. New York: Plenum Press.

Siegel, A. F. and Benson, R. H. 1982. A robust comparison of biological shapes. *Biometrics* 38: 341–350.

Sinnott, E. W. and Dunn, L. C. 1932. *Principles of Genetics: A Textbook with Problems.* London, UK: McGraw-Hill.

Slatkin, M. 1987. Quantitative genetics of heterochrony. *Evolution* 41: 799–811.

Smith, F. J., Percival, C. J., Young, N. M., Hu, D., Schneider, R. A., Marcucio, R. S., and Hallgrimsson, B. 2015. Divergence of craniofacial developmental trajectories among avian embryos. *Dev Dyn* 415: 188–197.

Smith, K. K. 1997. Comparative patterns of craniofacial development in Eutherian and Metatherian Mammals. *Evolution* 51: 1663–1678.

Smith, K. K. 2001. Heterochrony revisited: The evolution of developmental sequences. *Biol J Linn Soc Lond* 73: 169–186.

Smith, K. K. 2002. Sequence heterochrony and the evolution of development. *J Morphol* 252: 82–97.

Smith, K. K. 2003. Time's arrow: Heterochrony and the evolution of development. *Int J Dev Biol* 47: 613–621.

Smith, K. K. and Schneider, R. A. 1998. Have gene knockouts caused evolutionary reversals in the Mammalian first arch? *BioEssays* 20: 245–255.

Smith, M. M. and Hall, B. K. 1990. Development and evolutionary origins of vertebrate skeletogenic and odontogenic tissues. *Biol Rev Camb Philos Soc* 65: 277–373.

Sohal, G. S. 1976. Effects of reciprocal forebrain transplantation on motility and hatching in chick and duck embryos. *Brain Res* 113: 35–43.

Solem, R. C., Eames, B. F., Tokita, M., and Schneider, R. A. 2011. Mesenchymal and mechanical mechanisms of secondary cartilage induction. *Dev Biol* 356: 28–39.

Spemann, H. 1938. *Embryonic Development and Induction*. New Haven, CT: Yale University Press.

Spemann, H. and Mangold, H. 1924. *Induction of Embryonic Primordia by Implantation of Organizers from a Different Species* (Eds.) Willier, B. H. and Oppenheimer, J. M., *Foundations of Experimental Embyology.* New York: Hafner Press.

Spemann, H. and Schotté, O. 1932. Über xenoplastische Transplantation als Mittel zur Analyse der embryonvalen Induktion. *Naturwissenschaften* 20: 463–467.

Starck, J. M. 1989. Zeitmuster der Ontogenesen bei nestflüchtenden und nesthockenden Vögeln. *Cour Forsch-Inst Senckenberg* 114: 1–319.

Starck, J. M. and Ricklefs, R. E. 1998. *Avian Growth and Development: Evolution within the Altricial-Precocial Spectrum*, *Oxford Ornithology Series; 8*. New York: Oxford University Press.

Stern, D. L. and Emlen, D. J. 1999. The developmental basis for allometry in insects. *Development* 126: 1091–1101.

Szabo-Rogers, H. L., Geetha-Loganathan, P., Nimmagadda, S., Fu, K. K., and Richman, J. M. 2008. FGF signals from the nasal pit are necessary for normal facial morphogenesis. *Dev Biol* 318: 289–302.

Tang, S. Y., Herber, R. P., Ho, S. P., and Alliston, T. 2012. Matrix metalloproteinase-13 is required for osteocytic perilacunar remodeling and maintains bone fracture resistance. *J Bone Min Res* 27: 1936–1950.

Teitelbaum, S. L. 2000. Bone resorption by osteoclasts. *Science* 289: 1504–1508.

Teitelbaum, S. L., Tondravi, M. M., and Ross, F. P. 1997. Osteoclasts, macrophages, and the molecular mechanisms of bone resorption. *J Leukocyte Biol* 61: 381–388.

Thomas, D. M., Johnson, S. A., Sims, N. A., Trivett, M. K., Slavin, J. L., Rubin, B. P., Waring, P. et al. 2004. Terminal osteoblast differentiation, mediated by runx2 and p27KIP1, is disrupted in osteosarcoma. *J Cell Biol* 167: 925–934.

Thompson, D. W. 1917. *On Growth and Form*. Cambridge, UK: Cambridge University Press.

Thompson, D. W. 1952. *On Growth and Form*. 2nd edition. Cambridge, UK: Cambridge University Press.

Thorogood, P. 1987. Mechanisms of morphogenetic specification in skull development. In *Mesenchymal-Epithelial Interactions in Neural Development* (Eds.) Sievers, J. and Berry, M., Wolff, J. R., pp. 141–152. Berlin, Germany: Springer-Verlag.

Thorogood, P. 1988. The developmental specification of the vertebrate skull. *Development* 103: 141–153.

Thorogood, P. 1993. Differentiation and morphogenesis of cranial skeletal tissues. In *The Skull* (Eds.) Hanken, J. and Hall, B. K., pp. 112–152. Chicago, IL: University of Chicago Press.

Thorogood, P., Bee, J., and von der Mark, K. 1986. Transient expression of collagen type II at epitheliomesenchymal interfaces during morphogenesis of the cartilaginous neurocranium. *Dev Biol* 116: 497–509.

Tokita, M., Kiyoshi, T., and Armstrong, K. N. 2007. Evolution of craniofacial novelty in parrots through developmental modularity and heterochrony. *Evol Dev* 9: 590–601.

Tokita, M. and Schneider, R. A. 2009. Developmental origins of species-specific muscle pattern. *Dev Biol* 331: 311–325.

Trainor, P. A., Melton, K. R., and Manzanares, M. 2003. Origins and plasticity of neural crest cells and their roles in jaw and craniofacial evolution. *Int J Dev Biol* 47: 541–553.

Tucker, A. S. and Lumsden, A. 2004. Neural crest cells provide species-specific patterning information in the developing branchial skeleton. *Evol Dev* 6: 32–40.

Tucker, A. S., Yamada, G., Grigoriou, M., Pachnis, V., and Sharpe, P. T. 1999. Fgf-8 determines rostral-caudal polarity in the first branchial arch. *Development* 126: 51–61.

Tyler, M. S. 1978. Epithelial influences on membrane bone formation in the maxilla of the embryonic chick. *Anat Rec* 192: 225–233.

Tyler, M. S. 1983. Development of the frontal bone and cranial meninges in the embryonic chick: An experimental study of tissue interactions. *Anat Rec* 206: 61–70.

Tyler, M. S. and Hall, B. K. 1977. Epithelial influences on skeletogenesis in the mandible of the embryonic chick. *Anat Rec* 188: 229–240.

Vaglia, J. L. and Smith, K. K. 2003. Early differentiation and migration of cranial neural crest in the opossum, *Monodelphis domestica*. *Evol Dev* 5: 121–135.

Van Exan, R. J. and Hall, B. K. 1984. Epithelial induction of osteogenesis in embryonic chick mandibular mesenchyme studied by transfilter tissue recombinations. *J Embryol Exp Morphol* 79: 225–242.

Veitch, E., Begbie, J., Schilling, T. F., Smith, M. M., and Graham, A. 1999. Pharyngeal arch patterning in the absence of neural crest. *Curr Biol* 9: 1481–1484.

von Bonin, G. 1937. Brain-weight and body-weight of mammals. *J General Psychol* 16: 379–389.

Waddington, C. H. 1939. *An Introduction to Modern Genetics*. London: G. Allen & Unwin.

Waddington, C. H. 1940. *Organisers & Genes*. Cambridge, UK: Cambridge University Press.

Waddington, C. H. 1950. The biological foundations of measurements of growth and form. *Proc RoySoc Lond. Ser B, Biol Sci* 137: 509–515.

Waddington, C. H. 1957a. *The Strategy of the Genes*. London, UK: George Allan Unwin.

Waddington, C. H. 1957b. *The Strategy of the Genes; A Discussion of some Aspects of Theoretical Biology*. London, UK: Allen & Unwin.

Waddington, C. H. 1962. *New Patterns in Genetics and Development*, *Columbia Biological Series*. New York: Columbia University Press.

Waddington, C. H. 1975. *The Evolution of an Evolutionist*. Ithaca, NY: Cornell University Press.

Wagner, G. 1959. Untersuchungen an *Bombinator-Triton*-Chimaeren. *Roux' Archiv Entwicklungsmech der Organismen* 151: 136–158.

Wake, D. B. 1998. Pere Alberch (1954–98). *Nature* 393: 632.

Wake, D. B. and Roth, G. (Eds.) 1989. *Complex Organismal Functions: Integration and Evolution in Vertebrates*, *Complex Organismal Functions: Integration and Evolution in Vertebrates*. New York: John Wiley & Sons.

Wall, N. A. and Hogan, B. L. 1995. Expression of bone morphogenetic protein-4 (BMP-4), bone morphogenetic protein-7 (BMP-7), fibroblast growth factor-8 (FGF-8) and sonic hedgehog (SHH) during branchial arch development in the chick. *Mech Dev* 53: 383–392.

Wang, Y. H., Rutherford, B., Upholt, W. B., and Mina, M. 1999. Effects of BMP-7 on mouse tooth mesenchyme and chick mandibular mesenchyme. *Dev Dyn* 216: 320–335.

West-Eberhard, M. J. 2003. *Developmental Plasticity and Evolution*. New York: Oxford University Press.

Wilson, J. and Tucker, A. S. 2004. Fgf and Bmp signals repress the expression of Bapx1 in the mandibular mesenchyme and control the position of the developing jaw joint. *Dev Biol* 266: 138–150.

Wright, S. 1931. Evolution in Mendelian populations. *Genetics* 16: 97–159.

Wu, P., Jiang, T. X., Shen, J. Y., Widelitz, R. B., and Chuong, C. M. 2006. Morphoregulation of avian beaks: Comparative mapping of growth zone activities and morphological evolution. *Dev Dyn* 235: 1400–1412.

Wu, P., Jiang, T. X., Suksaweang, S., Widelitz, R. B., and Chuong, C. M. 2004. Molecular shaping of the beak. *Science* 305: 1465–1466.

Xia, S. L. and Ferrier, J. 1996. Localized calcium signaling in multinucleated osteoclasts. *J Cell Physiol* 167: 148–155.

Xiong, J. and O'Brien, C. A. 2012. Osteocyte RANKL: new insights into the control of bone remodeling. *J Bone Miner Res* 27: 499–505.

Xiong, J., Piemontese, M., Thostenson, J. D., Weinstein, R. S., Manolagas, S. C., and O'Brien, C. A. 2014. Osteocyte-derived RANKL is a critical mediator of the increased bone resorption caused by dietary calcium deficiency. *Bone* 66: 146–154.

Yamashita, T. and Sohal, G. S. 1986. Development of smooth and skeletal muscle cells in the iris of the domestic duck, chick and quail. *Cell Tissue Res* 244: 121–131.

Young, D. W., Hassan, M. Q., Pratap, J., Galindo, M., Zaidi, S. K., Lee, S. H., Yang, X. et al. 2007. Mitotic occupancy and lineage-specific transcriptional control of rRNA genes by Runx2. *Nature* 445: 442–446.

Young, D. L., Schneider, R. A., Hu, D., and Helms, J. A. 2000. Genetic and teratogenic approaches to craniofacial development. *Crit Rev Oral Biol Med* 11: 304–317.

Young, N. M., Chong, H. J., Hu, D., Hallgrimsson, B., and Marcucio, R. S. 2010. Quantitative analyses link modulation of sonic hedgehog signaling to continuous variation in facial growth and shape. *Development* 137: 3405–3409.

Young, N. M., Hu, D., Lainoff, A. J., Smith, F. J., Diaz, R., Tucker, A. S., Trainor, P. A., Schneider, R. A., Hallgrimsson, B., and Marcucio, R. S. 2014. Embryonic bauplans and the developmental origins of facial diversity and constraint. *Development* 141: 1059–1063.

Zavitz, K. H. and Zipursky, S. L. 1997. Controlling cell proliferation in differentiating tissues: Genetic analysis of negative regulators of G_1-->S-phase progression. *Curr Opin Cell Biol* 9: 773–781.

Zayzafoon, M. 2006. Calcium/calmodulin signaling controls osteoblast growth and differentiation. *J Cell Biochem* 97: 56–70.

Zelditch, M. 2004. *Geometric Morphometrics for Biologists: A Primer.* Boston, MA: Elsevier Academic Press.

Zelditch, M. L., Bookstein, F. L., and Lundrigan, B. A. 1992. Ontogeny of integrated skull growth in the cotton rat *Sigmodon fulviventer*. *Evolution* 46: 1164–1180.

Zhang, W., Bergamaschi, D., Jin, B., and Lu, X. 2005. Posttranslational modifications of p27kip1 determine its binding specificity to different cyclins and cyclin-dependent kinases in vivo. *Blood* 105: 3691–3698.

Zhao, Q., Eberspaecher, H., Lefebvre, V., and De Crombrugghe, B. 1997. Parallel expression of Sox9 and Col2a1 in cells undergoing chondrogenesis. *Deel Dyn* 209: 377–386.