Seminars in Cell & Developmental Biology 91 (2019) 2–12

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Evolution and development of the cartilaginous skull: From a lancelet towards a human face

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ARTICLE INFO

Article history:
Received 22 April 2017
Received in revised form
27 November 2017
Accepted 9 December 2017
Available online 14 December 2017

Keywords:
Chondrocranium
Evolution
Embryonic development
Cartilage function in the head
Invertebrate cartilage
Cartilage in chordates
Facial shape
Protection of central nervous system
Support of feeding apparatus
Face
Cartilage
Cranial evolution

ABSTRACT

Chrondrocranium, the cartilaginous skull, is one of the major innovations that underlie evolution of the vertebrate head. Control of the induction and shaping of the cartilage is a key for the formation of the facial bones and largely defines facial shape. The appearance of cartilage in the head enabled many new functions such as protection of central nervous system and sensory structures, support of the feeding apparatus and formation of muscle attachment points ensuring faster and coordinated jaw movements. Here we review the evolution of cartilage in the cranial region and discuss shaping of the chondrocranium in different groups of vertebrates.

Contents

1. General role of cartilage during the evolution of the head

The head represents the most complex part of the vertebrate body. Despite enduring efforts to cast light on the evolutionary origins of the head, unambiguous answers remain elusive. Since the head is a highly composite compartment, and includes many tissue types assembled together during morphogenesis, the precise sequence of evolutionary transitions, innovations, and tissue coordination events are at the core of cranial evolution and its understanding. In animals that possess a cartilaginous skeleton only, cartilage plays a major supporting role for the pharynx, muscles, and other organs in the body. During evolution, cranial cartilage began to protect the central nervous system (CNS) and

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https://doi.org/10.1016/j.semcdb.2017.12.007

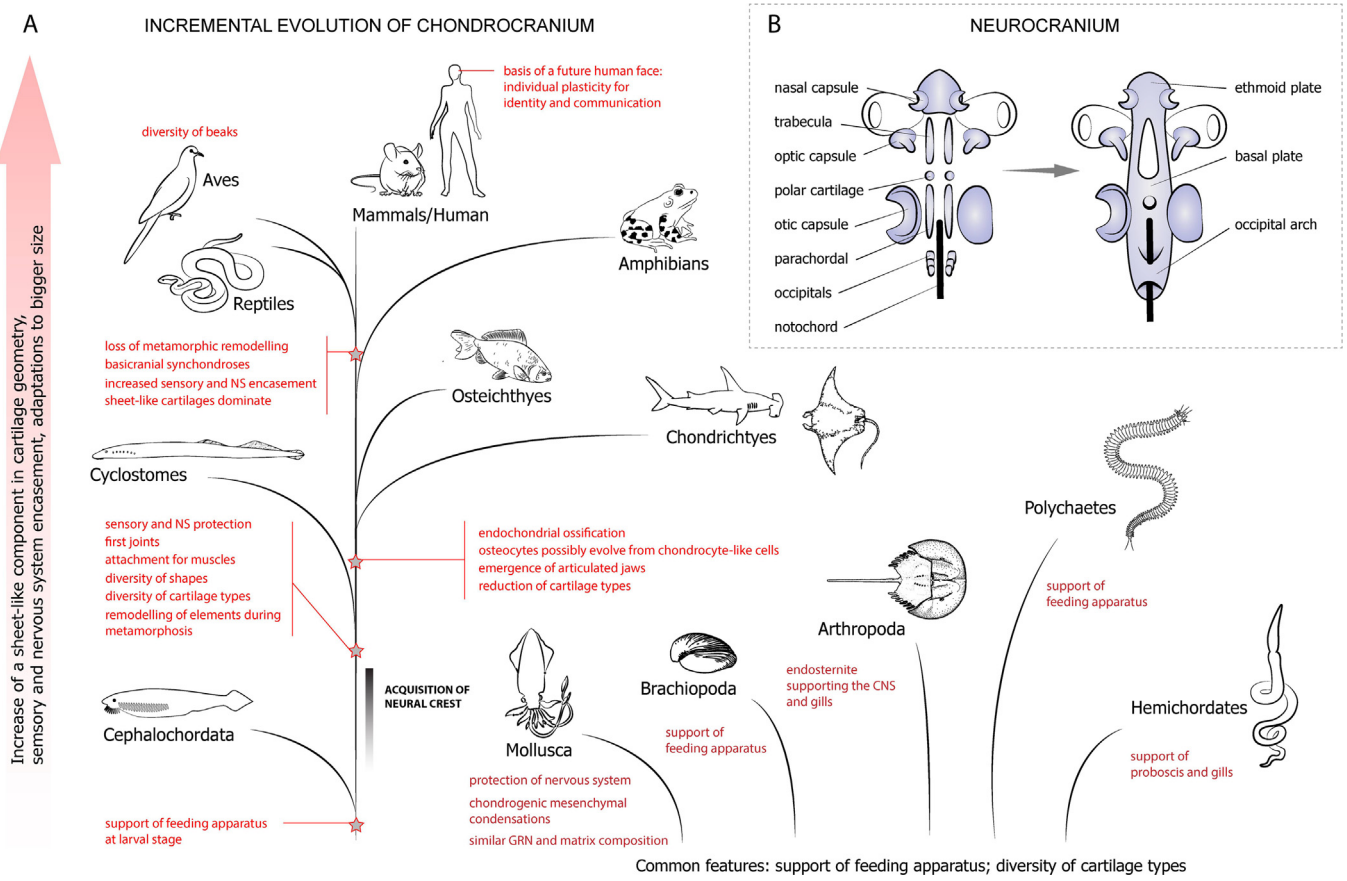

Fig. 1. Major advancements during the incremental evolution of the chondrocranium. (A) Gain of multiple functions during the evolution of the cranial/head cartilage. (B) Evolutionary and developmental trends shaping the gnathostome neurocranium.

sensory organs from displacement or damage. During the development of vertebrates, cartilage played a leading role in facial outgrowth and shaping [1,2]. Other developmental functions of cartilage account for the programmable placement, expansion, and shaping of bones in the process of endochondral ossification [3–5].

Chordates first acquired and developed the head compartment during the Cambrian explosion, a major evolutionary event related to the origin and diversification of body plans in animal phyla [6]. Starting from a simple filter-feeding lifestyle, chordates beneficiated to becoming rather active predators and changed their body size [7]. In line with the shift from passive to active predatory lifestyle, a stiffened feeding apparatus became an indisputable advantage for food acquisition and survival. Thus, one of the driving forces behind the evolution of the chondrocranium is likely to be optimization and strengthening of the oral apparatus, which subsequently led to the acquisition of articulated jaws before/around the early Devonian [8]. It is worth mentioning that diverse cellular and acellular cranial cartilage elements are well represented in cyclostomes lacking articulated jaws. It seems that one of the most important evolutionary directions is represented by the variations in mechanisms driving the shaping and scaling of cartilage. The acquisition of jaws, as well as other morpho-functional innovations, could stimulate the development of further complex geometrical features, rather than generating additional types of cartilage with different histological properties.

Species with an active feeding mode also underwent an extensive centralisation and further enlargement of the nervous tissue. Furthermore, they established an optimal niche for the evolution and engagement of sensory organs and motor relays. Such development of sensory organs, oral apparatuses, and CNS integration led to an increase in the complexity of the chondrocranium, which serves as a load-bearing physical integrator of multiple tissues, and as a protective building block of the evolving head. Despite the large diversity of "stiff" matrix tissue types in different animal groups [9], its evolutionary purpose looks similar - the protection of sensitive nervous tissues, stabilization of the feeding apparatus, and a scaffold for muscle attachment, enabling faster and more coordinated locomotion.

Gans and Northcutt proposed a hypothesis for the developmental origin of the vertebrate head as a new body unit [10]. This hypothesis established the cranial neural crest, placodes, and other integrating tissues as the evolutionary substrates and powerful propellants for further cranial evolution, resulting in increased complexity. Cartilage, being derived from both the neural crest and mesoderm [11], played a key role in these processes, and is inevitably linked to the origin of the vertebrate head and the formation of articulated jaws.

2. Cartilages in invertebrates: support for the feeding apparatus and protection of the nervous system

Cartilaginous tissue is not an exclusive prerogative of chordates. Many distant groups of invertebrates developed a specialized connective tissue that is morphologically, histologically, and molecularly similar to the classical vertebrate cartilage (see Fig. 1A) [12]. However, it is unknown whether these cartilage-like connective tissues evolved independently, or have been inherited from the common ancestor.

For instance, annelid worms (Sabellid polychaetes) develop long feeding tentacles that are reinforced by internal cartilaginous tissue [12,13]. Similarly, brachiopod feeding tentacles possess a tissue similar to cartilage in terms of its extracellular matrix, which

includes collagen, acidic mucopolysaccharides, elastin, chondroitin sulphate, and keratan sulphate [12]. The proboscis and gills of enteropneust hemichordates are supported by a tissue that strongly resembles acellular cartilage, and contains collagen [14].

Molluscs also demonstrate the presence of cartilage in multiple locations. For instance, gastropod snails possess a cartilaginous odontophore supporting the radula, their main feeding organ [12,15]. Cephalopod molluscs have an internal skeleton that is partially represented by the remnants of the shell, but also composed of numerous separated cellular cartilaginous elements, including cranial cartilage protecting the brain, pallial and funnel cartilage, nuchal and dorsal cartilage, diaphragm and branchial cartilage, as well as cartilage supporting the fin [16].

When it comes to molecular deep homology, the recent evidence gathered from distant invertebrate species, the horseshoe crab (*Limulus polyphemus, Arthropoda*) and cuttlefish (*Sepia bandensis, Mollusca*), suggests that the evolution of the chondrogenic gene regulatory network might have already started in the common ancestor of *Bilateria* [17].

The horseshoe crab, known as a living fossil, is an armoured marine arthropod. Despite its solid external skeletal armour, the horseshoe crab has internal cartilaginous structures: the endosternite, supporting the CNS and cartilaginous plates, as well as "branchial cartilage", in the book gills [9,18–22]. The cuttlefish, a marine cephalopod mollusc, displays a well-developed centralized nervous system that is surrounded by a simple cartilaginous skull providing necessary protection and support [9].

Tarazona et al. [17] observed remarkable similarities in the process of cartilage formation amongst cuttlefish (*Sepia bandensis*), horseshoe crab (*Limulus polyphemus*), and vertebrate species, with common underlying molecular mechanisms and cartilage histology. According to the authors, the development of cartilage is initiated by the formation of chondrogenic mesenchymal condensations in all analysed species. These condensations later differentiate into early and subsequently mature chondrocytes (or chondrocyte-like cells) that secrete the matrix. An investigation of matrix composition and gene expression in developing cuttlefish and horseshoe crab shed new light on the evolution of the chondrogenic gene regulatory network. Indeed, the comparison of the structural and chemical composition of cartilage obtained from cuttlefish and horseshoe crab revealed the presence of a collagen-rich matrix, comprised of acidic glycosaminoglycans, similar to the composition of vertebrate cartilage. Both organisms were also found to express pro-orthologues of vertebrate collagen (Col2α1). Moreover, the cartilage from both organisms was positive for hyaluronan, an abundant element in vertebrate cartilage [17,23].

These findings highlighted the shared key cartilage structural components amongst invertebrate and vertebrate species, suggesting the existence of a shared common genetic program. In vertebrates, Hedgehog signalling induces cartilage formation and differentiation, whereas canonical WNT signalling inhibits it [2,24,25]. Sonic Hedgehog, a transcriptional activator of Sox5/6/9, is expressed during early chondrogenesis, where it directs the placement of mesenchymal condensations, while Indian Hedgehog regulates chondrocyte proliferation and differentiation [2,26,27]. Tarazona et al. revealed that SoxE and SoxD (pro-orthologues of vertebrate Sox9 and Sox5/6) are co-expressed with ColA, while β-catenin is downregulated in the developing cartilage of *Sepia* embryos. They also demonstrated that the cartilage-forming locations were adjacent to the Hedgehog-expressing epithelium in the area of the future funnel cartilage. Consistently, the authors reported that the co-expression of SoxE and ColA coincided with the downregulation of β-catenin found in the region of developing endosternite in *Limulus* embryos. Notably, that cartilage-forming region is also adjacent to the Hedgehog-expressing ventral nerve cords [17]. Despite recent progress in the field, it remains unknown whether cartilage evolved once or several times independently, and which cell or tissue types developed this innovative program or co-opted the gene regulatory network responsible for matrix secretion.

In summary, there are interesting general trends that direct the placement and function of cartilage, even in very distant invertebrate groups: protection of the CNS (cephalopods and horseshoe crab), and support of the feeding apparatus (marine polychaetae worms, brachiopods, hemichordates, and molluscs). Both of these initial functions support the idea that the first cartilaginous tissue evolved in the head or anterior compartment of a common bilateralian ancestor. However, later, these purposes converged during the evolution of the chondrocranium in chordates.

3. Evolution of the chondrocranium in chordates: amphioxus – cartilage of the feeding apparatus

An adult lancelet is characterised by the presence of a stiff but acellular cartilage-like matrix, with incorporated fibrillar collagen forming the pharyngeal endoskeleton [28]. During metamorphosis, the oral skeleton supporting the tentacles (oral cirri) is comprised of a cellularised matrix without fibrillar collagen [29,30]. The transient presence of a true cellular cartilage during the development of the oral cirri endoskeleton suggests that the lancelet may be the potential forefather of vertebrate cartilage. This vertebrate-like cartilage is formed during the late larval stage, and is comprised of tightly packed polygonal or disc-shaped cells secreting a matrix that contains fibrillar collagen and chondroitin sulphate proteoglycans, both common components of vertebrate cartilage [31].

The overall histology of this transiently-existing cartilage in amphioxus is highly similar to that of the gill bar cartilage in larval lampreys and zebrafish. A recent study showed that, like in vertebrates, the differentiation of cellular cartilage in the nascent oral cirri of late larval stage amphioxus involves the production of ColA and is FGF-dependent [31]. Moreover, the conserved molecular traits of developing vertebrate embryonic cellular cartilage, such as the expression of SoxD, SoxE, and FGFR, were also present in the oral chondrocytes and surrounding mesothelium of amphioxus larvae [31,32]. This evidence, along with similarity to the chondrogenic program in *Sepia*, supports the idea that cartilage, as a tissue, has always been present in the ancestors of chordates and other phyla, and therefore, was not developed *de novo* by the chordates as previously suggested.

Importantly, cartilage in amphioxus larvae only serves as a support for the feeding apparatus [33]. The individual cartilaginous bars are not connected in the larvae, and might represent a blueprint of the most ancestral chondrocranium, despite the fact that the anatomical pattern of the amphioxus head is very different from that found in vertebrate embryos.

Amphioxus, belonging to the cephalochordates, does not have cranial neural crest cells responsible for the pro-chondrogenic program in the vertebrate face [34,35]. There is ongoing debate on the acquisition of a novel regulatory element specifically activated in cephalic crest cell lineages, which would enable co-option of the coordinated expression of the chondrogenic gene regulatory network. Hypothetically, such a chondrogenic regulatory network could initially be elaborated elsewhere, for instance, in the mesoderm. The pharyngeal gill bars, located between the endoderm and ectoderm in amphioxus, express a typical neural crest cell marker, Id [36]. This observation led to the hypothesis that collagen-secreting mesoderm, endoderm, or both, from the amphioxus pharynx could have retained the ancestral chondrogenic gene regulatory network in earliest chordates [14,28,36]. Later, such a program might have been co-opted by the cranial crest.

An investigation into the non-coding cis-regulatory sequences of SoxE from amphioxus indicated that two important incremental achievements propelled further evolution of the chordate head: first, the spread of collagenous tissue from the oral cirri towards the pharynx, and further in the head. Second, the evolution of new cis-regulatory elements to direct the expression of SoxE in the newly developed cranial neural crest cells [31].

4. Chondrocranium in extant and extinct agnathans

The term agnatha (agnathans) was first introduced in the 19th century by Cope to describe jawless vertebrates. It embraced extinct and quite diverse "armoured fishes", or so called "ostracoderms" (informal polyphyletic group including stem gnathostomes and stem cyclostomes), and currently living cyclostomes. The evolution and systematics of agnathans, as well as the origin of gnathostomes/cyclostomes crown groups, was recently reviewed by Philippe Janvier [37].

Cyclostomes are monophyletic relict jawless (agnathan) fishes that split from the common ancestor they share with vertebrates around 450 million years ago. Extant cyclostomes are only represented by two quite distant lineages: lampreys and hagfishes. They lack the hinged biting jaws and possess only one nostril, which, among many other anatomical features, clearly differentiates them from all other living vertebrates [38–40]. Despite the fact that lampreys and hagfishes are more closely related to each other than to any other extant chordates, they have substantial difference in their craniofacial build up, making any direct comparisons very difficult [41]. The currently living cyclostomes appear to have lost many features during the evolutionary process, and therefore, do not necessarily represent the basal state.

After initial development, the larval stages (ammocoete) of cyclostomes survive buried in the mud and then live as filter-feeders until undergoing metamorphosis [42]. Both lampreys and hagfishes possess a cartilaginous non-calcified internal skeleton. Unlike amphioxus, cyclostomes developed multipotent neural crest cells that gave rise to a significant portion of the cartilaginous skeleton present in their head, in addition to the cartilaginous part produced by the axial sclerotome ([43,44], reviewed elsewhere by [40]). During fate specification, the cranial neural crest expresses a chondrogenic gene regulatory network, including SoxE, SoxD, Twist, Tfap2, Ets, and Id (reviewed elsewhere by [45]).

Cyclostomes, unlike amphioxus, developed a diversity of cellular and acellular cartilages. Interestingly, cyclostome cartilage is divided into regions that possess distinct properties. For instance, the acellular mucocartilage, with a matrix that is dissimilar to the gnathostome cartilage, represents a major supportive tissue in both the ventral pharynx and oral region. This matrix is formed by mucopolysaccharides, and contains some embedded scattered mesenchymal cells [46,47]. The cellular branchial basket cartilage shares many histological and biochemical properties with the gnathostome modern cellular cartilage, including cell morphology, gene expression profile, and alcian-blue reactivity.

The expression of the two type-II-collagen genes, together with a co-expressed orthologue of Sox9, clearly occurs during the development of the cyclostome cartilaginous skeleton. Moreover, it has been shown that the adult lamprey skeleton is rich in Col2α1 protein [48,49]. Despite the overall histological similarity between the cyclostome and the gnathostome cellular cartilage, they use slightly distinct gene regulatory networks. Lamprey modern type of cellular cartilage only uses Alx genes (and not Runx, Barx, and Alx together, as in gnathostomes), whereas, mucocartilage, despite being morphologically different, was surprisingly shown to utilize every component of the gnathostome cartilage gene regulatory network [45]. A hypothesis has been proposed that suggests that a significant reduction in the diversity of skeletal tissues occurred during the subsequent evolution of the gnathostome head. This process was likely a result of merging gene expression programs by various cyclostome skeletal tissues, leading to the consolidation of a single chondrogenic gene regulatory network [45].

Oisi et al. performed an in-depth analysis of the cyclostome chondrocranium in terms of anatomy, 3D structure, and possible homology, and also provide a review of the literature [50]. During pre-metamorphic development and ontogenetic transitions between different larval stages, the chondrocranium significantly changes and undergoes serious remodelling at the level of individual elements [51]. Cranial cartilage elements start to diversify in terms of shape, including sheet (or plate)-like flattened cartilages (for example, the posterior dorsal plate in the chondrocranium of the adult lamprey). This diversity points towards the development of innovative and sophisticated shaping and scaling mechanisms, taking place within the cartilage of cyclostomes [50].

There are many cyclostome-specific traits, including cartilage elements of the lingual apparatus, velum, proximity of parachordalis, and otic capsule, amongst others [50]. However, despite the differences in patterns of cranial skeletons between hagfish and lampreys, it seems reasonable to assume the existence of a common pattern during their early developmental stages. In the adult animals, establishing any homology between individual elements comprising the chondrocranium is difficult. When it comes to comparing them with gnathostome chondrocrania, only modular cartilaginous units can be, to some extent, reliably compared in terms of homology analysis [50], even with assistance from comparative gene expression studies [52].

It seems that the major functions of cyclostome cartilage are to support the feeding apparatus and provide stiffness to the sensory appendages. Additionally, the formation of the otic capsule and the cartilages underlying the brain [50] suggests that a structure protecting neural and sensory components started to appear, which was not the case for amphioxus. Such support might be required because of a dramatic size increase, creating the necessity for the tissue to withstand gravity and accommodate its own pressure. Oisi et al. suggested that the posterior part of the hagfish trabeculae (that is generally located in a more rostral position compared to lamprey), as well as that of the lamprey, correspond to the parachordalis in gnatostomes [50]. Indeed, the "parachordals" of hagfish and lamprey trabeculae are associated with the posterior part of the anterior notochord and, despite being dissimilar, both provide functional support of the internal structures, including the nervous system [53]. Thus, these structures may represent a prototypical neurocranium. Oisi *et al.* wisely noted that the in-depth analysis of various developmental stages of the extinct stem gnathostomes, including cephalaspids (Osteostraci) and galeaspids (Galeaspida), is required to understand the major transitions that occurred during the evolution of the chondrocranium [50].

When it comes to the analogy or homology to the gnatostome viscerocranium, no clear homologues of the jaw cartilages have been found or suggested, even in the case of the upper jaw. Patterning of the upper and lower jaws in gnatostomes is provided by the differential Dlx code, which is dissimilar in terms of the expression pattern in cyclostomes [52], which has been previously discussed in [50]. The molecules patterning the jaw joint in gnathostomes (Nkx3.2 (Bapx1), Gdf5, Gdf6, and Gdf7) are missing in the first lamprey arch [54,55]. Shimeld and Donoghue suggested that during the evolutionary transition from agnathans to gnathostomes, the chordates acquired a very focused patterning system of jaw joint specification, which was a prerequisite for elaborating hinged jaws [40].

However, the joints *per se* are present in the various parts of the cyclostome chondrocranium. Indeed, unlike in the amphioxus, the cranial cartilage elements in cyclostomes are assembled into

a sophisticated framework that forms dynamic joints between the various parts [54]. Thus, joints as a concept were also developed in agnathans (at least in a common ancestor of lamprey and hagfish). In line with this, McCoy et al. pointed out that the proboscis in an extinct vertebrate, *Tullimonstrum,* possessed an internal skeleton with joints, which, similarly to the lingual apparatus of cyclostomes, was not a simple elastic tube [56,57].

Finally, in agnathans (as evidenced in cyclostomes), for the very first time, muscles of the head started to attach to the internal cranial cartilage, pioneering an innovative support for the muscle apparatus. The cartilage elements of the nasal basket of the hagfish provide attachment points for three different muscles. The *nasalis* muscle reaches the top of the head and inserts into a dorsal nasal tube membrane, the second arch, and a pre-nasal cartilaginous rod. Another example includes the *tentacularis* posterior muscle, which attaches to the upper nasohypophyseal process, the tentacular cartilage, and the oral tentacular cartilage [58].

Bone already appears in agnathans, and many extinct groups of "ostracoderms" possessed bony armour, which could also serve a skeletal role. However, currently living cyclostomes do not possess any bone, which may be a derived condition. A variety of extinct agnathan groups possessed membranous bones only, while several ostracoderms, for example osteostracans, clearly possessed perichondrial bones and calcified cartilage elements inside their endoskeleton (synapomorphy common for galeaspids, pituriaspids, osteostracans, and placoderms), as reviewed by Janvier [37]. At this point in evolutionary history, no obvious signs of innovative endochondral ossification can be observed. Recently, Gomez-Picos and Eames suggested a new evolutionary relationship between chondrocytes and osteocytes. On the basis of gene expression analysis and histology, the authors hypothesized that a significant part of the genetic program underlying bone formation, based on the Runx2 gene regulatory network, was co-opted from the mature cartilage and enabled further development of a new cell type [59,60]. If this assumption is correct, agnathan cartilage could provide derived chordates with a powerful mineralized bone. In line with this, a recent study demonstrated a direct lineage transition from chondrocytes into osteocytes, supporting the idea that genetic programs of cartilage and bone might be closely related and compatible [61]. Consistently, in the cranial skeleton of zebrafish, the *Osterix*-expressing chondrocyte-like cells simultaneously possess chondrocyte and osteocyte differentiation programs, and produce extensive mineralization [62], while the repair chondrocytes can originate from the $Runx2^{+}/Sp7^{-}$cells residing in the periosteum [63]. Therefore, many observations support the hypothesis that bone as a tissue could evolve *via* the recruitment of cartilage-specific genetic programs into mesenchymal cells, or even more directly, be generated by the immediate progenitors of cartilage.

5. Evolution of chondrocranium in gnathostomes

The transition from agnathans into gnathostomes is vital for understanding the evolution of a cranial skeleton in a chordate lineage. Notably, from the systematics point of view, many groups of fossil agnathans (ostracoderms) are considered to be gnathostomes by some researchers, since they appeared after the split of the cyclostomes (agnathans is a paraphyletic group). The mammalian chondrocranium should not be considered as an exact result of a series of graded updates when, for instance, cyclostome and shark chondrocrania are compared in this review. In fact, animal lineages diversified through successive splitting, branching out as clades. The discussion below explains the different designs and evolutionary transitions at the cellular level, without directly deducing the amphibian or amniote chondrocranium, for instance, from the skull of a shark.

The bauplan of the vertebrate chondrocranium includes subdivisions into viscerocranium, supporting the pharyngeal apparatus, and neurocranium, surrounding neural and sensory structures [64,65]. The development of the articulated jaws propelled the evolutionary success of the vertebrates, along with other anatomical and physiological innovations. However, it is still unclear whether the existence of biting jaws represents the main factor clearly defining the rise of gnathostomes, and the extinction of the majority of the agnathan groups [40]. Paleontological evidence points out that during the transition from agnathans into gnathostomes, the articulated jaws originated in an extinct group suggestively similar to the diplorhinic ostracoderms, more than 400 million years ago [66,67]. Then, after the acquisition of the jaw, acanthodians, placoderms, chondrichthyans, and osteichthyans followed their own evolutionary paths [68], as discussed in [69].

The evolution of jaw plasticity could proceed according to the 'Hinge and Caps' model (recently proposed by [70]). This model combines a special logic of interaction between signalling centres in developing jaw regions, with the establishment of a particular patterning polarity. The 'Hinge and Caps' model is supposed to explain the heterotopic and heterochronic differences in jaw development across various gnathostome groups, which would place the evolution of jaw morphology into the context of clear developmental logic. Some experimental studies performed on shark and mouse embryos have already provided substantial support for this theoretical framework [69,71].

One of the most classical views suggests that jaws are the evolutionary derivatives of segmented gill arches. In such a scenario, neural crest cells should have contributed cellular material to the forming jaws, while the location of the jaws was consistent with gill elements. However, as proposed by L. Olsson et al., this fine logical arrangement does not mean that this assumption is true, especially since the agnathan velar skeletal elements could alternatively have given rise to the jaws [72,73]. Additionally, some doubts exist amongst the scientific community regarding the presence of a velum in the last common ancestor. Another alternative idea is called the "composite theory", and was proposed by Erik Jarvik. It suggests that the elements composing the jaws are derived from the pre-mandibular arch [74]. However, the question of jaw element homology remains unanswered [68,72]. In-depth patterning studies, as well as mapping of the nasal, postoptic, and mandibular neural crest streams in relevant animals, might help to answer this question in the future (reviewed in [72]). The gnathostome-related homology of the jaw elements in agnathans is complicated, since the patterning mechanisms could be co-opted, while the neural crest streams might be flexible in terms of navigation programs and final destinations. If the problem is approached strictly, the term "homology" may be insufficient and therefore, simply avoided, replacing it by very exact descriptions related to gene expression shifts, co-options, heterotopy, heterochrony, heterotopy, and other precise molecular and cellular mechanisms explaining the transformation of the jaw elements (widely discussed in Ref. [72]). There is at least consensus that patterning shifts in the branchial arch apparatus were at the core of jaw acquisition.

Both the neural crest and mesoderm (paraxial and somitic) contribute to the development of the chondrocranium, making it a composite structure [75], as discussed in [76,77]. Neural crest cells contribute to the anterior part of the neurocranium and, partly, to the otic vesicles and jaws of the crown gnathostomes, while the paraxial mesoderm gives rise to the posterior chondrocranium, the large part of the otic vesicle, and several other elements. There is no visible border between the cartilage produced by either the crest or the mesoderm, which suggests the neat convergent production of the exactly same fate in both lineages [78]. The somitic mesoderm, characteristic of a segmented trunk, also contributes to the most posterior elements of the skull [77]. Indeed, the poste-

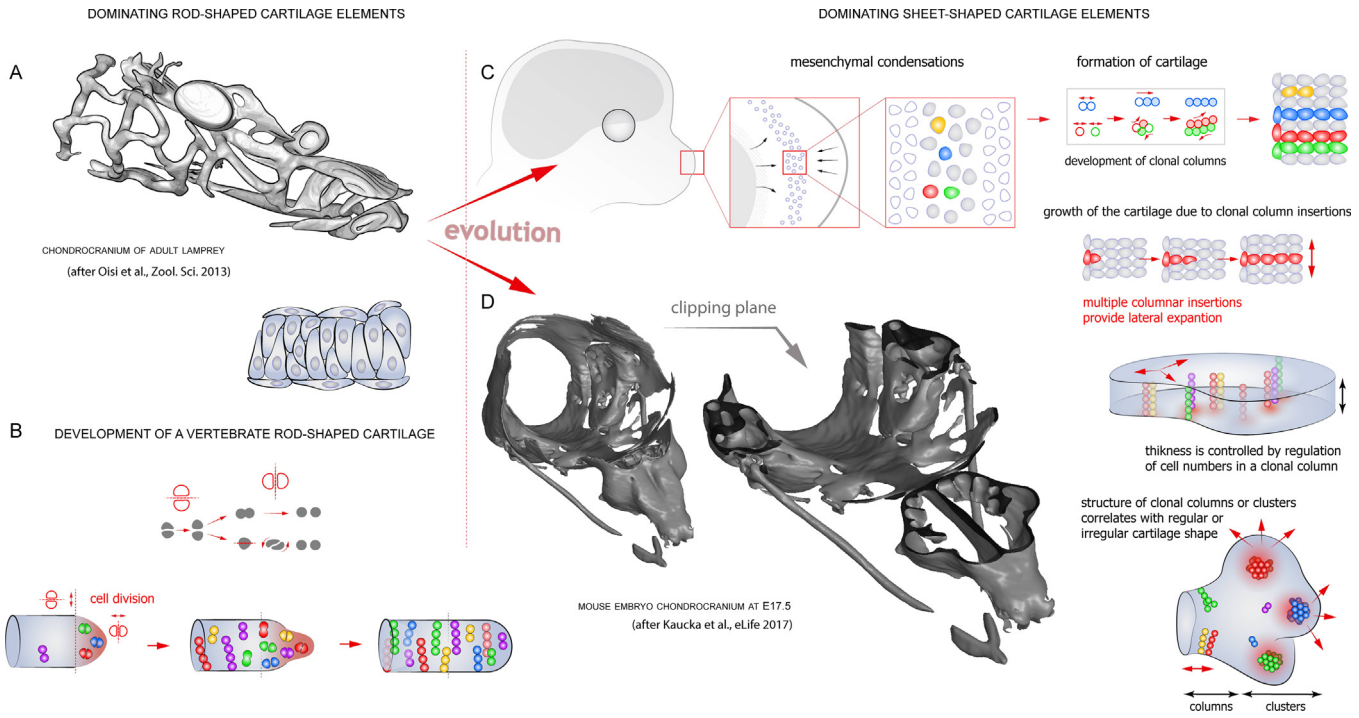

Fig. 2. Evolution of cranial cartilage shapes and cell dynamics of early cranial cartilage growth. (A) Drawing of an adult lamprey chondrocranium (after Oisi et al. Zoological Sciences, 2013). Note the dominating bar- and rod-shaped geometry of the cranial cartilage elements. (B) Cell dynamics governing the development of rod-shaped cartilage. Colours show chondrogenic clones. Note oriented daughter cell positioning after mitosis during cartilage formation. (C) Cell dynamics governing the development of sheet-shaped cartilage. Colours show chondrogenic clones. Note oriented cell positioning during proliferation. (D) 3D-rendered mouse embryonic chondrocranium, with dominating sheet-like cartilage elements (whole structure and chondrocranium with the clipping plane) (after Kaucka et al., eLife 2017).

rior part of the early neurocranium, the parachordalis, adjoins with even more posterior somitic elements to form the rest of the rear neurocranium [64,65,79]. In this region, materials generated from five somites fuse together during chick development to build the posterior chondrocranium as a segmented structure [65,76,80–82].

Although one might expect that the contribution from the neural crest and mesoderm should be very stable and region-specific, comparative investigations showed that this is not entirely the case. Indeed, differences can be observed relative to the neural crest/mesodermal border in chondrocranial elements across the major vertebrate taxa [83,84]. While the skeletal elements may retain their general purpose, shape, and position, their composition in terms of origin might be flexible (discussed in [76,84]). Generally, the analysis of neural crest streams and their contribution to skeletal elements serves as a tool towards establishing the homology of cartilaginous elements in different taxa. The patterning imposed by the cells of origin has fueled a discussion about the segmentation of the cranial compartment and the corresponding skeletal elements (discussed in [72]).

Heterotopic shifts in expression of patterning genes could have modified the branchial arch apparatus at the core of jaw acquisition, and could also have been responsible for defining new areas, with neural crest molecular programs being freed from previous adaptive evolutionary pressure [85]. In turn, this could have given rise to the trabecula - a major element in the developing neurocranium [86,87].

Despite the focus dedicated to the development of the jaw joint and its related patterning codes, the transformation of the neurocranium is also widely discussed. The neurocranium underwent very serious transitions during the early steps of gnathostome evolution, and turned into a much more solid and unified structure, compared to that of agnathans. During these evolutionary transitions, parachordal cartilages and trabeculae fused to form basilar and ethmoid plates – a prototype of the cranial base that was retained further, without dramatic modifications in the entire vertebrate lineage [65] (Fig. 1B). The hypophyseal foramen was formed by the fusing trabeculae [88]. Couly et al. [89] demonstrated that the ontogeny of the neurocranium depends on the presence of the rostral endoderm (including pre-oral gut) in chick embryos. Meanwhile, the selective deletion of more distal endodermal regions leads to abnormalities in the mandibular arch skeleton, including the jaw joints. Therefore, the endoderm provides necessary patterning information to the developing endoskeleton [90], as discussed in [88], which could have enormous evolutionary implications. It is worth mentioning that a large body of reasoning regarding neurocranium evolution during the transition from agnathans into gnathostomes is derived from comparative embryology rather than paleontological evidence.

As opposed to the dominant bar or rod-like cartilage found in cyclostomes (although they develop some plate-like cartilages, for instance, in lamprey pericardium and hagfish chondrocranium), the sheet-like cartilages of the gnathostome cranium become more apparent, and start to bend around the neural and sensory tissues to protect them and provide them with physical support (Fig. 2). For example, in elasmobranchs, the roof of the chondrocranium is complete and encases the brain, while in other groups this is not the case, and the dermal bones should form to complete the cranium [76]. Plate-like cartilage elements bend to form sockets, for instance, for the eyes. Olfactory capsules form, in addition to the otic capsules. Specialised openings in the cranial cartilages allow for passage of the bundles of cranial nerves. Increases in animal size obviously required larger cartilage elements, and the scaling mechanisms adapted to this need. The gnathostome skull expanded from the bent cartilaginous plates built from a much larger number of chondrocytes, contrasting with the thin elegant cartilages of the cyclostomes, consisting of several lines of stacked chondrocytes only. Special cartilage subtypes present in cyclostomes are never found in stem gnathostomes, probably due to their absence

in the last common ancestor or, if they were present, because of their subsequent loss [45]. The co-evolution of a muscle apparatus and skeletal parts of the chondrocranium also becomes more apparent in multiple groups of jaw-possessing fishes (see the summary in Fig. 1A).

6. Chondrocrania in amphibians and beyond

During further evolution of the vertebrates, the chondrocrania gained diversity in terms of shape and components, while the postnatal/post-hatching remodelling capacity was eventually lost, which we will discuss below.

Tailless amphibians have an interesting and complicated life cycle. In these animals, the cartilaginous skull develops in two steps, which include both the embryonic period and metamorphosis, when the composition, size, and shape of the cartilage elements change [91]. This is conceptually similar to bony fish larvae metamorphosis, which has been well described in zebrafish [92]. Highly sophisticated hyobranchial apparatuses, and several other features of the metamorphosing amphibian chondrocranium, disappear during metamorphosis, and this capacity resembles the remodelling of the cyclostome cranial cartilage during larval development [93].

What is the developmental origin and cellular sources of the post-metamorphic chondrocranium in amphibians? Several studies attempted to determine whether the origin of the adult cranial cartilage resides in the expansion of the pre-metamorphic cartilage, whether chondrocytes de- and then re-differentiate, or whether there is a quiescent pool of chondrogenic progenitors that are activated during the metamorphosis to create the adult post-metamorphic cartilage (compartmentalized differentiation) [91].

One of the pioneering works performed in salamanders demonstrated that, despite the fact that larval epibranchial cartilage is similar to the adult one, the latter has a separate (not related to pre-existing cartilage) cellular source [94]. Studies performed in another amphibian model, *Xenopus laevis*, showed the extent of new cartilage induction *via* freshly induced chondrogenic condensations (in this case, termed compartmentalized differentiation) in the tadpole skull during cranial metamorphosis [95]. Using transgenic systems, a linear differentiation (origin of adult cartilage from larval chondrocytes) has been revealed for Meckel's cartilage, the otic capsule, tecti anterius, posterius, and ceratohyal cartilage. Contrastingly, the authors suggested compartmentalized differentiation of the nasal capsule and the ends of Meckel's cartilage. In line with this, during metamorphosis, the processes connecting the palatoquadrate to the neurocranium are disconnected, and a new process was established to accommodate for the elongation of the lower jaw. Some typical larval cartilage (ceratobranchial and planum antorbital) resorbs without contributing to any adult cartilage structure. Additionally, several adult-specific cartilage is clearly derived from cellular sources other than larval chondrocytes, further supporting the necessity for the induction of mesenchymal chondrogenic condensations *de novo* during metamorphosis [91].

It seems that amphibian chondrocrania are plastic and can be easily remodelled, although the precise regulatory signals controlling such process remain unclear. What are the possible mechanisms driving such plasticity? Likely, they are rooted in developmental properties of the chondrocranium shaping logic. Developmentally, chondrocrania are induced as several independent elements that later fuse together to generate one solid structure. Indeed, even a mouse chondrocranium is initially induced as 14 independent pairs of cartilage that grow directionally under the control of numerous feedback mechanisms, and later adjoin together forming one solid structure [47,82]. Contrastingly, elements induced as single pieces can break apart by forming joints. The waves of newly formed chondrogenic condensations can be induced during metamorphic phases. At the same time, old cartilage can resorb without leaving a trace. In amphibians, sheet-like cartilage becomes even more apparent in addition to diminishing rod-shaped cartilage [93].

During the transition into amniotes, metamorphosis was lost, and, thus, the metamorphic remodelling of the chondrocranium does not proceed. Other alternative mechanisms enabling fast expansion of the skeleton are installed to accommodate for cranial expansion. Such mechanisms include, for example, basicranial synchondroses [96,97].

Many parts of the chondrocranium can undergo endochondral ossification. However, there are differences in mechanisms for turning cartilage into bone. For example, chondro-bone metaplasia represents a direct ossification of the cartilage without massive expansive growth of the region. In fishes, metaplastic conversion occurs when the heterotopic cartilage is directly remodelled into bone inside the developing vertebrae [98–100].

Alternatively, the innovative basicranial synchondroses not only accommodate for the conversion of cranial cartilage into bone, but also allow for the simultaneous predominantly uni-directional expansion of the neurocranium. For instance, a "brachyrrhine" mouse mutant with abnormal synchondroses displays frontonasal dysplasia, with a shortened snout ("pugnose") and sphenoidal malformations [87,88]. To our knowledge, basicranial synchondroses, which are technically growth plate-like endochondral ossification centres [101], are only found in amniotes [102,103], which might be linked to animal growth in the absence of intermediate metamorphic stages and may also relate to the much bigger sizes which amniotes managed to attain. During amphibian and fish larval metamorphosis, the expansive re-building and enlargement of the chondrocranium partially allows for bigger cranial size, which, in its post-metamorphic condition, is much closer to adult proportions. Therefore, in the case of amniotes, the loss of metamorphosis must have led to specific adaptations (including basicranial synchondroses) that allow for dramatic cranial expansion during growth.

When it comes to the evolutionary origin of basicranial synchondroses, it seems reasonable to suggest that these might have been co-opted reasonably early from the vertebrae or limb growth plate-like ossification zones [104].

If synchondroses-based ossification is an adaptation for fast cranial expansion and scaling, how does the chondrocranium grow in large cartilaginous fishes such as tiger or whale sharks? What are the cellular mechanisms driving the massive, and at the same time orchestrated, scaling of the cranial cartilage with such a degree of shape complexity?

In mice, early sheet-like cartilage elements in the chondrocranium expand massively without involving the formation of synchondroses or growth zone-like regions, since these occur more postnatally (with the exception of basisphenoid). Furthermore, despite the fact that some parts of the chondrocranium will eventually (postnatally) undergo endochondral ossification (presphenoid and basisphenoid, cribriform plate, Meckelś cartilage, olfactory septum, nasal concha, labyrinth of ethmoid, vomer, and tympanic bulla), the majority of the bones found in the facial compartment form through dermal membranous ossifications [105]. Therefore, synchondroses in the chondrocranium only represent an additional growth mechanism that accounts mostly for uni-directional expansion of the existing cartilaginous structures, involving simultaneous substitution of the cartilage template with a mineralized bone matrix.

The logic of the synchondroses-independent growth of individual cartilaginous pieces and further fine-tuning of their shapes has been revealed in a recent study [106], where authors performed clonal genetic tracing and novel 3D analysis of cartilage

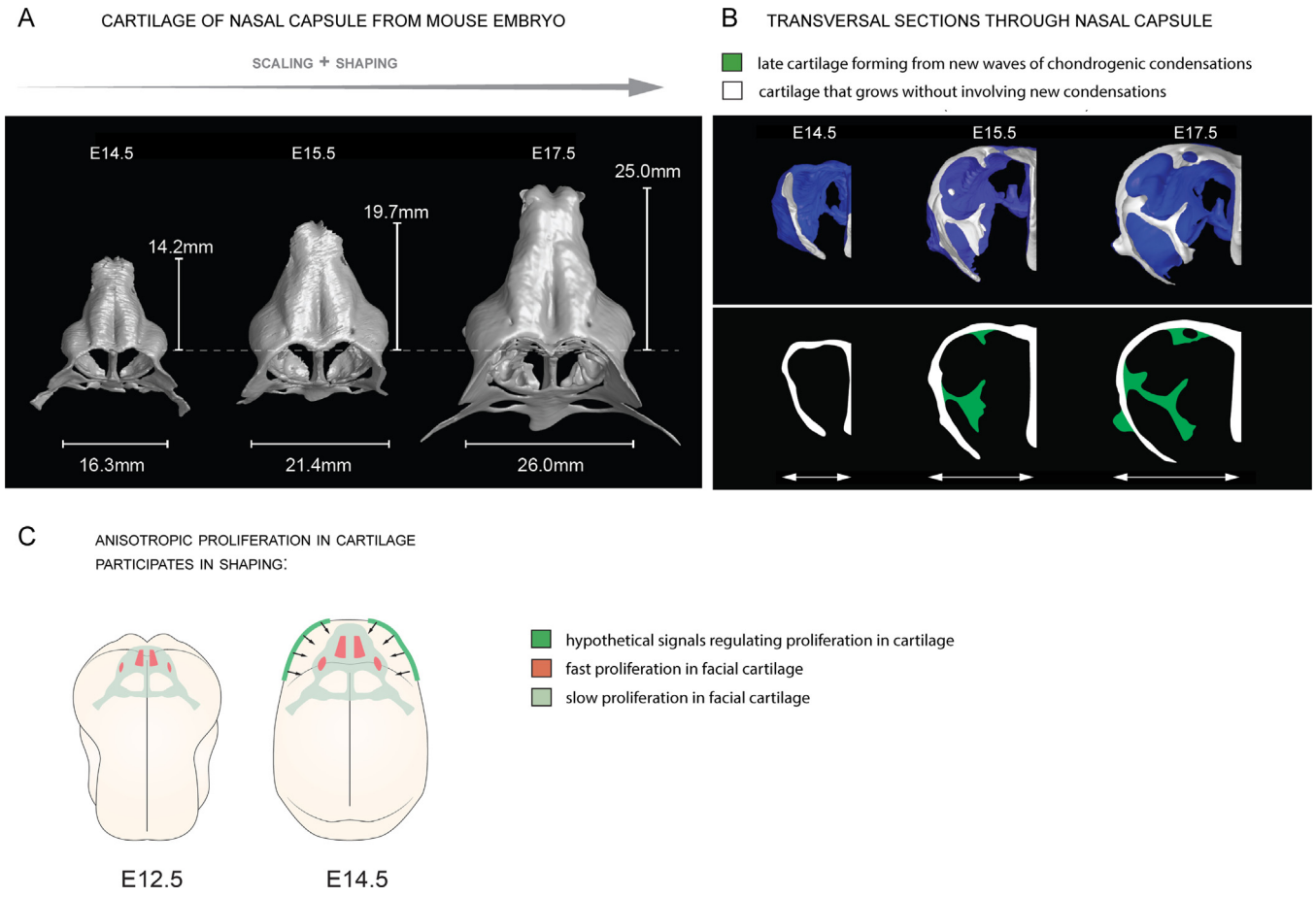

Fig. 3. Anisotropic proliferation in mammalian cartilage and sequential induction of adjoining chondrogenic condensations participate in chondrocranial scaling and shaping. (A) Scaling of mouse embryo nasal capsule cartilage during embryonic development. (B) Scheme showing the formation of important geometrical features (nasal conchae) from sequential waves of adjoining chondrogenic mesenchymal condensations. (C) Anisotropic proliferation in cranial cartilage influences macro-shaping processes and may cause bending of the entire structure.

geometry [107]. Already within the mesenchymal condensations, the chondrogenic cells have highly regulated oriented clonal cell dynamics. Progenitor cells divide in an oriented manner that results in an oriented integration of clonal cell columns or clusters into the pre-existing cartilaginous elements. Perturbations of clonal orientations and shapes lead to dramatic changes in local macro-geometry and geometric regularity of cartilage. The authors showed the importance of the bone morphogenetic protein (BMP) signalling pathway in the control of clonal orientations and micro-shapes. This elegant mechanism of oriented cell behaviour accounts for the lateral expansion of the sheet-like cartilaginous elements, without affecting their thickness. In contrast, the thickness of the expanding sheet- or rod-like cartilaginous structures is regulated by a different mechanism, which controls the number of chondrocyte cell divisions within a clone. Thus, the lateral (or longitudinal) expansion is independent from thickness or diameter control mechanisms, which might enable wider evolutionary variation in cartilage shapes and structural stiffnesses, independently from each other (Fig. 2).

In addition to oriented cell dynamics and its control, there are other tools that nature uses to shape highly diverse chondrocrania. For instance, anisotropic proliferation in the cartilage, in addition to sequential timely coordinated waves of induced mesenchymal chondrogenic condensations, might also represent important evolutionary substrates that account for the existing diversity of shapes [106] (Fig. 3). However, little is still known about the evolution of various molecular and cellular mechanisms responsible for cartilage shaping. The variety of geometrical features and size of cranial cartilage elements increases throughout evolution, which suggests the incremental development of scaling and shaping logics, and requires further investigation.

The aforementioned variation in chondrocranial geometry enabled new adaptive powers and more efficient colonization of new niches. Thus, the mechanisms controlling the plasticity of vertebrate chondrocrania could not only account for developmental transitions, but also contribute to the fast radiation of species. Birds colonize an immense variety of ecological niches, and the variation of beaks reflects their enormous adaptability [108]. The two main skeletal components forming the avian beak include the pre-nasal cartilage (originating from the frontonasal mass) and the premaxillary bone (forming from maxillary prominence). The specification of these structures and subsequent induction of chondrogenic elements represents at least a two-step process, driven by distinct sets of molecules [2,109,110]. Birds seem to represent the first evidence of the remarkable influence of the epithelium that provides signals shaping the chondrocranium [89]. Thus, the existence of facial ectodermal signalling zones, and the presence of instructing gradients, might be the key evolutionary innovations that, for the first time, enabled the emergence of a stunning variety of snouts, beaks, and faces.

Finally, in humans, plasticity of the facial geometry provides for our unique capacity to communicate a person's identity [111]. The interplay between the individuality of each human face and the nerve circuits responsible for facial recognition represents a

unique, and probably the most sophisticated, trait in the evolution of vertebrate heads [112]. The embryonic timing determining when individual facial features are introduced is currently unknown. However, if we keep in mind that achondroplasia phenotypes strongly affect facial appearance [113], we can hypothesise that the geometry of the human facial chondrocranium is extraordinarily plastic, and at the same time, individually genetically encoded.

7. Conclusion

The evolutionary history of the cartilaginous endoskeleton in the head begins with the development of cartilage as a tissue, likely for the support of the feeding apparatus, and providing primary protection to the nervous and sensory systems. Starting with simple rod-like structures, cranial cartilages evolved into a multitude of complex shapes, including bent sheets as key elements. Individual cartilages started to be interconnected by joints, while other trends included the attachment of muscle to the cartilage, and the co-evolution of the muscle-endoskeletal apparatus. These transitions played a role in the development of articulated jaws during the transition from agnathans to gnathostomes. Meanwhile, the neurocranium expanded and encased the brain, as well as the sensory apparatuses. The plasticity of the facial cartilage has reached its maximum in humans, likely providing an evolutionary substrate for the individuality of human facial features. In line with this, mammalian cranial cartilage elements operate a very sophisticated logic of shaping and scaling, allowing the variety in body sizes and facial designs. The evolutionary history of mechanisms shaping cartilage is intriguing and enigmatic. Developmental studies in emerging non-canonical model chordates, as well as in-depth paleontological analyses, should provide new exciting insights in this field.

Acknowledgements

We would like to thank to Per Ahlberg for his valuable comments and help with our manuscript. We also thank to Olga Kharchenko for illustrations. IA was supported by Bertil Hållsten Foundation, Åke Wiberg Foundation, Swedish Research Council, EMBO YIP and ERC Consolidator grants. MK was supported by SSMF Fellowship.

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