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Review

The sea urchin's siren

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Abstract

This issue of *Developmental Biology* features articles that constitute a new wave of insights into how a genome interacts with itself (as DNA) and with effectors—proteins and probably RNAs, collectively operating as a kind of "cis-trans" dualism. We learned a test for allelism in genetics class that bore that Latin name but now it comes as a new day for biological science—a welcome era in which a phenomenon as complex as development can be envisioned from principles of chemical binding energy and specificity. The buzzword (the term is just—as there is deserved buzz) is that the genome is hard-wired, in the sense that it has been shaped to both encode and react to a regulatory network, of which it is itself a part. I here review some of the milestones of embryology in which the sea urchin was the key player, segueing into the modern era in which this organism launched an entirely new intellectual construct of genome organization and gene expression during development. This essay also contains a number of personal perspectives as well as some views on the overall epistemological fabric of developmental biology. Like all of us, I am excited to see the *S. purpuratus* genome appear and heartily congratulate, by writing this essay, the trailblazers whose intellectual courage and persistence has brought us to this happy position.

Keywords: Sea urchin embryo; Genes; Regulatory genomics

"*In all things of nature there is something of the marvelous*."
Aristotle, *Parts of Animals, Book I, Chapter 5*

Introduction

The editors of *Developmental Biology* have invited me to write an essay about how sea urchins have historically figured in embryology on the one hand, and how – as we all now foresee – the revealed genome sequence of this animal will empower a new era. The question of how the sea urchin figured in embryology is like asking whether or not bacteriophage had something to do with the origins of molecular biology. There is also a surprising aspect to this invitation because with the exception of one publication (Ruzdijic and Pederson, 1987), I do not even work on sea urchin embryos. (My research employs cultured mammalian cell lines that are, in their virtually nullipotent state, developmentally about as far from an oocyte, egg or early embryo as can be imagined.) But this invitation is indeed a privilege and I have tried to do my best. That said, the reader is warned that what follows is a highly personal reflection which may be found idiosyncratic by some. It is also emphasized that the space allotment precluded a comprehensive historical treatment of each and every facet of experimental and modern embryology in which the sea urchin figured. Readers seeking a more in-depth exposition of the historical background are referred to highly authoritative accounts (e.g., Davidson, 1985; Ernst, 1997) and a superb timeline of landmarks in sea urchin embryology that is just appearing (Cameron and Davidson, Submitted for publication).

The echinoderms radiated out of the explosive Cambrian ~400 Ma ago. It is thought that there have been ~7000 species of sea urchins, of which ~900 are believed to be extant. The Greek philosopher, naturalist and grand-scale intellectual Aristotle investigated all the animals he encountered, including sea urchins. His charming yet quite insightful description is reproduced in the on-line Supplementary Material. I cannot resist commenting in passing that we have lost something today

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when we no longer take our students back prior to the past 25 years or so. We should desperately want them to know that there was such an extraordinary mind as Aristotle, working and thinking about all of biology, nature and philosophy 2300 years ago (he lived from 384 to 322 B.C.).

Sea urchins came into prominence in embryology in the mid- to late 19th century. No arguments about their phyletic position or potential biochemical tractability, as in "buckets of gametes" attended the initial decisions to employ this creature in embryological science. The actual reasons were simply pragmatic—the abundance and accessibility of gravid animals. Although primarily benthic (like almost all echinoderms), the range of sea urchins often includes the coastal zone and at such sites they can be collected from tide pools, or from under a protective cover of algae or in algal forests that often are not too far off shore.

Determinants determined, and the road to maternal messenger RNA

As we all know, some of the most intellectually powerful concepts in 19th and 20th century embryology, such as the inducer and homeotic genes, came from studies on frog and fruit fly embryos, respectively. But the sea urchin can hold its head (if it had one) high in several arenas. The most well known of the early experiments were those of Hans Driesch, which revealed the "equipotent" developmental potential of the first two blastomeres (Driesch, 1892). Driesch's results dramatically expanded embryology's horizons beyond Weismann's germ plasm theory and Roux's concept of unequal segregation of determinants. Later, Sven Horstadius' studies with separated sea urchin blastomeres and merogones refined Driesch's conclusion, revealing localized determinants even in this "regulative" egg and early embryo (Horstadius, 1935, 1939). Of course, all these results were correct in their own way, and for the particular embryos investigated, and yet they have naturally undergone a degree of deconstruction and revision. For example, Horstadius' experiments were reinterpreted by Davidson (1986) and Wilt (1987) to reflect intercellular communication networks, laying the foundation for subsequent advances in embryonic cell signaling pathways, notably by McClay.

Science proceeds by results on a laboratory bench coupled with what an investigator was thinking in the first place. One of the richest exemplifications of this doctrine in all of biology was the work of Theodor Boveri. His work on centrosomes in *Ascaris* is enjoying renewed popularity today in cell biology quarters because of his prescient idea that these enigmatically duplicating structures (Pederson, 2006a) direct equal chromosome segregation during mitosis and, when operating in error, might cause mis-segregation. Boveri speculated that centrosome dysfunction might cause cancer and although genomic instability is now regarded as a downstream event following the clonal emergence of a growth-altered cell, this was a perspicacious insight indeed. But Boveri did not confine his work to a nematode. He also studied sea urchins and these contributions are perhaps less well known today. His studies led him to conclude that the properties of both the egg and the embryo descend from the action of genes during oogenesis (Boveri, 1918), a tremendous insight and one that anticipated its modern rendering by more than half a century. His studies of dispermic eggs in which various blastomeres inherit normal or aneuploid chromosome sets led him to conclude that normal development was thwarted by aneuploidy and assured by a normal chromosome set (Boveri, 1902). This principle is now so familiar to us that we may forget what scientific talent was necessary to see it for the first time, and what intellectual courage was required to promote the concept to initially skeptical peers, a key epistemological milestone in the history of embryology that has been duly emphasized by numerous scholars (particularly Davidson, 1968, 1976, 1985). Boveri's work on sea urchins not only proved that embryos amalgamate maternal factors with the activity of embryonic genes, he provided an enabling cornerstone into the entire edifice of the chromosomal basis of heredity.

Another epochal experiment in embryology in which the sea urchin figured was of course Jacques Loeb's demonstration of parthenogenesis, a finding that not only constituted a milestone in developmental biology but also made its way into the layperson mainstream, setting some factions on edge at then time as regards perceived ethical issues as applied to the human (Weissmann, 2006). Beyond its extraordinary impact on embryological thinking, Loeb's demonstration of parthenogenesis had an even broader epistemological impact on biology in general, for it was among the factors that led him to the position that processes such as cell division and development could be conceptualized, and even studied, as chemistry and physics—a paradigm shift for which Loeb was both the architect and a leading practitioner (Pauly, 1987). This was a "school" of thinking taken further in later years by Daniel Mazia, to mention only one of the most catalytic figures.

There is arguably no aspect of 19th and early 20th century embryology in which the sea urchin embryo figured more prominently than in studies of fertilization. The earliest history of this field is covered beautifully in the comprehensive essay by Briggs and Wessel in this issue, so I will comment only on the subsequent era. Paul Ehrlich is credited with introducing the concept of reciprocally shaped biological molecules. His 1908 Nobel Prize for discovering what today we would call a small molecule drug for syphilis evolved from his recognition, while a medical student doing a histochemistry project, that the reason various dyes (later known as biological stains) bind differentially to certain cell and tissue types is because these dyes fit into chemical constituents that are present to various extents, a truly prescient idea. We also know that Louis Pasteur manually separated the distinctively shaped crystals of D- and L-tartaric acid under his microscope and there is reason to believe that this was a watershed event in the evolution of his thinking about biology as chemistry (Dubos, 1976). But it is Linus Pauling who probably deserves the major credit for transposing the concept of "reciprocal fit" into the arena of fertilization (much later of course), by emphasizing this principle to his Caltech colleague Albert Tyler, who was working on sea urchins at Corona del Mar (Kay, 1993). Despite the attractiveness of the "lock and key" notion of molecular shape complementarity to

the problem of fertilization, Tyler did not succeed in this endeavor. Meanwhile, in Woods Hole, Frank Lillie was pursuing the same concept in collaboration with Ernest Just—his gifted African–American student (Manning, 1983). While the idea of complementary shapes later came to dominate thinking in the fields of immunology and nucleic acid structure and function, there can be no doubt that the principles were all explicitly laid down earlier in the fertilization field, almost entirely based on work with sea urchins. It took the subsequent discovery of sperm ligands for egg surface receptors to finally place the mystery of fertilization specificity on a sure molecular footing (Vacquier and Moy, 1977).

Although the focus of this essay is on the role of sea urchins in embryology, this organism also played an epochal role in studies of cell division, obviously a perfectly legitimate branch of developmental biology as regards the early embryo and a major domain of cell physiology in general. Thus, the sea urchin embryo was the basis of a major theater of investigations in the 1950s and 1960s relating to the metabolic energy requirements of mitosis (Pederson, 2003). The mitotic apparatus was first isolated from sea urchin embryos (Mazia and Dan, 1952) and the first steps toward defining the molecular composition of microtubules were taken with sea urchin embryos (Borisy and Taylor, 1967). This period also saw a renewed focus on a longstanding topic from the earlier eras, *viz*., the role of calcium ions in the post-fertilization activation of the sea urchin egg (Steinhardt and Epel, 1974). Later, in 1983, sea urchin embryos provided one of the most far-reaching cell division discoveries ever, that of cyclins (Evans et al., 1983; Evans, 2004; Hunt, 2004).

The sea urchin embryo has also been the theater of powerful insights into how the intercellular biology of blastomeres and cells of the later embryo constitute the phenotypic readout of the genome, integrating cell–cell signaling with migration and morphogenesis on the one hand, and feeding back on the genome on the other. These studies in the sea urchin system lie at the "cellularity core" of embryogenesis and morphogenesis and have been beautifully exemplified by the work of David McClay (e.g., Peterson and McClay, 2005; Croce and McClay, 2006).

When the central dogma (DNA makes RNA makes protein) reached embryology in general, its favorite target was the sea urchin embryo. Cyrus Levinthal and colleagues had done a lovely experiment in *Bacillus subtilis* that indicated the bulk of messenger RNA in this microbe is very short-lived. Like most important experiments, it was simple: new RNA synthesis was blocked with a drug and the timecourse with which protein synthesis declined was measured (Levinthal et al., 1962). Paul Gross and colleagues applied this experimental strategy to the sea urchin and confirmed the existence of long-lived messenger RNA in the egg (Gross and Cousineau, 1964; Gross et al., 1964). I say "confirmed" not to minimize the finding but to recognize that this idea had been very strongly suggested by earlier experiments by Tyler (1963), Brachet et al. (1963), Monroy and Tyler (1963) and Denny and Tyler (1964). A detailed analysis of this discovery chain, somewhat controversial as to priority, is beyond the scope of this essay but, in brief, I would argue that Tyler and Brachet both deserve credit for the initial insight, both by the timeline and by the cogency of the evidence.

The end of the pre-modern era

I look at embryology in the 1960s as the end of the "pre-modern era"—a period in which cogent polyspermy and blastomere micromanipulation experiments had given us the broad outlines of development. That pre-modern era of embryology also had a loss—Thomas Hunt Morgan. He abandoned his years of study on marine embryos as a window on genes and development (in which he presaged "evo-devo") and turned to *Drosophila* (Allen, 1978). Not only did he triumph using the fly, the Caltech Biology Division he launched in 1927 became one of the key places where today's embryology unfolded, defined by the impact of the central dogma on embryology as first manifest in the work of Albert Tyler, and the parallel application of genetics to the problem, as led by Ed Lewis. The modern era of embryology involved the impact of molecular biology as well as advances in fluorescence microscopy and related methods of cell biology, as well as of course a dramatic expansion of the utility of genetic approaches, notably transgenics.

Now we have standing before us the post-modern era, as we witness the sea urchin genome unfolding and the regulatory genomics that we are learning, both from the DNA sequence and from actual experiments—each enabling the other (Davidson, 2006; reviewed in Dawid, 2006). This post-modern era has had many tributaries. For historical perspective, let us take a look back.

The persistence of the sea urchin into the post-modern era of embryology

In 1931 Joseph Needham published "Chemical Embryology", a book that has almost always been mentioned with the adjective "monumental" (Needham, 1931). It probably was, viewed as Cambridge erudition, but I am less convinced that it "created" a new breed of embryologists to the extent some have claimed (i.e., it may have not been as influential as Schrödinger's "What is Life?" was to many nascent molecular biologists.) My own view is that Loeb was more influential than Needham in getting embryologists to think along the lines of chemistry and cell physiology, and that others such as Jean Brachet were more responsible for ushering in what was then called (entirely accurately) "biochemical embryology". But notwithstanding the antecedents, when chemical–biochemical embryology was ready to become transformed into the science of embryonic gene expression in the mid-1960s, there were two obvious candidates as regards the ideal experimental systems, frog and sea urchin. (Sydney Brenner was still working on the coding problem and had not yet launched his brilliantly prescient *C. elegans* program.) Neither the amphibian nor echinoderm systems were short on deep roots in embryology, each having been the source of core principles that virtually defined the science. Nor was one system much less accessible than the other as material (the frog in fact being more tractable at inland labs). And, as regards gene expression, some of the most important discoveries were being made in the amphibian system by the mid-1960s, such as the role of the nucleolus in ribosome

production (Brown and Gurdon, 1964). In his postdoctoral years at Rockefeller, Eric Davidson studied gene expression in *Xenopus* oocytes (a new venture in the Mirsky laboratory) so he was certainly familiar with the positive features of this embryo and its deep lore in embryology. Why then did the sea urchin embryo become the leading system in the 1970 to 1980 period for dissecting embryonic gene expression and, in the 1990s and early 2000s, a key factor in establishing the field of metazoan regulatory genomics?

In my opinion this intellectual momentum started with a seminal paper I can still remember reading when my issue of Science arrived one day that summer, *viz*. the paper by Britten and Kohne (1968). I will never forget my first look at Fig. 2 in that paper (see Fig. 1), not having ever anticipated seeing such a profoundly quantitative representation of the genetic complexity of various creatures in my lifetime. This figure is burned deeply into my memory bank like no other.

The Carnegie Institution of Washington's Department of Terrestrial Magnetism seemed an unlikely place for progress in gene expression in the 1960s, partly because the department's name suggested a program on sliding plates within the earth's mantle more than transfer RNAs and ribosomes sliding along messenger RNA, and also because most attention was on other laboratories, notably the MRC Laboratory of Molecular Biology, Cambridge, where Sydney Brenner and Francis Crick were brilliantly racing ahead. As a graduate student (1963–68), I had come across several engaging papers on protein synthesis from the Carnegie Department of Terrestrial Magnetism in my late night library rumblings and was greatly impressed by how Richard Roberts, Elias Bolton and their colleagues were studying gene expression. (For readers under the age of 60: this Richard Roberts was a different person than the restriction enzyme pioneer and adenovirus molecular biologist who discovered mRNA splicing; this earlier Roberts is also the one to whom we owe the term "ribosome".) I applied to the Carnegie group for a postdoctoral position, but was told by Dr. Bolton that one was not available that year. He encouraged me to apply again the following year but I needed to move ahead, and so I went elsewhere. But I closely followed the Carnegie work each year thereafter. Shortly after Eric Davidson left Rockefeller, I heard that Roy Britten was leaving Carnegie—also for Caltech. Like most people who heard the news, I suddenly saw the tremendous appeal and strategic power of this new partnership. While *Drosophila* and *C. elegans* later came to the fore for appropriate reasons, no other embryo in the 1970s and early 1980s was subjected to an analysis of gene expression carried out at such a quantitative scale as the Caltech sea urchin program. In addition, and this cannot never be emphasized enough, this group's contributions to the physical chemistry of nucleic acid hybridization and their development of ever-more refined methods of nucleic acid sequence complexity analysis incalculably benefited the field of gene expression as a whole. Nobel Prizes have been given for such advances (Pederson, 2006b).

The origins of a genomic regulatory systems approach to embryology

When then did sea urchin embryo regulatory genomics "begin"? In my mind it was when recombinant DNA technology was first applied. The first eukaryotic genes to be cloned were from the sea urchin, ones that encode histone proteins (Kedes et al., 1975). But as important as this was as a proof of principle, it was not followed up in terms of investigating embryonic development. In contrast, the initial cloning of a sea urchin actin gene (Durica et al., 1980) was centered on developmental biology. I had recruited Bill Crain to the Worcester Foundation from Roy Britten's laboratory, having sensed his talent and

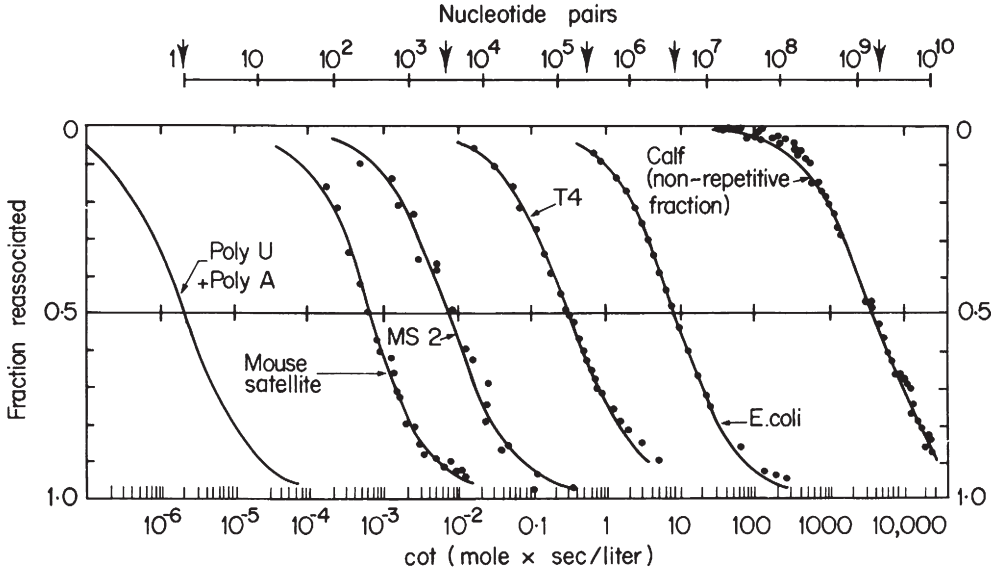

Fig. 1. An epistemological milestone in genetics. This figure shows the kinetics of reassociation of sheared, denatured DNA from several organisms. Like many people, this author can still recall the very moment when he first saw this figure. Reproduced from Britten and Kohne (1968) with permission of the American Association for the Advancement of Science.

determination. Soon after his 1980 paper, an expanded article on the *S. purpuratus* actin gene family appeared (Scheller et al., 1981) that in my opinion can be regarded as the launch of the Caltech group into subsequent studies, catalyzed in particular by their prudent focus on *cyIIIa and endo16*. After years of dissection fueled by many industrious students and post-docs, and with important and acknowledged input from Lee Hood, a bold program of systems biology was developed around the sea urchin system (Davidson, 2001).

Systems biology is a term I dislike, as it embraces chemical engineering—a science which I believe cannot be intelligently applied to biological systems at this time. In a chemical plant, the concentrations of reactants are known, hydrostatic and rheological parameters are controllable, and valves can be adjusted. In cells, we do not know—even today, the true concentrations of most molecules, much less their activities, the more relevant physical chemical parameter (Pederson, 2000). One huge problem is that we do not know the state of water—is the nuclear interior 54.5 M water? One of our well-known east coast medical schools (typically known for its conservatism) has launched an academic department based on the notion that systems biology has arrived. I am not convinced. On the other hand, what the sea urchin embryology school has brought us is a wonderful *empirical* platform, not so much for systems biology but for regulatory biology. To paraphrase Yogi Berra's famous remark about the concept of *déjà vu*, the regulatory biology the sea urchin embryology school at Caltech has brought us is "Jacob and Monod all over again". The difference is that now we are talking not about bacterial reactions to a food supply—enabling though that was. We are now talking about how a few feet of DNA make an animal. This legacy comes to us from years of heavy-going through various transcription factors as biochemistry, but always with the context in clear view—the embryo (Davidson, 2006; reviewed in Dawid, 2006).

The regulatory genomic era of the sea urchin arrives—what will it bring?

Launching the sea urchin genome sequencing project involved a cogent "white paper" by leaders in the developmental biology of this creature (www.genome.gov/Pages/Research/Sequencing/SeqProposals/SeaUrchin_Genome.pdf). As might be anticipated, the case presented for sequencing the sea urchin genome took off from the venerable status of this embryo and the rich archive of developmental biology information it holds. But the most enabling argument was that, in this particular creature, knowing the genome will allow the most fundamental principles of development to be investigated anew—in the context of a regulatory genome. There can be no doubt that in the near future the key principles of embryonic development—maternal inheritance, regulative vs. mosaic landscapes, morphogenetic fields and gradients and cell–cell signaling, *inter alia*, will be dramatically powered forward by having the sea urchin genome. Indeed, if I were to teach a developmental biology course this year, I would include nematode and fruitfly core beliefs but would center a good half of the course on presenting the classical sea urchin embryo experiments of Horstadius, Boveri, Lillie et al. and then asking the students to write proposals on how those revealed phenomena could be now approached in molecular, cell and structural biology detail with the genome in hand. Most students today dislike the past, but that is because most topics they study have no obvious link between the past and the present, much less the future. Sea urchin development trumps all three time zones, and I suspect that any of us who decides to teach embryology this fall from this codex will be pleasantly surprised by the students' activation.

It is already clear that the sea urchin genome will advance the gene regulatory network analysis of development in this creature. Having the genome will not only allow classical studies to be now undertaken in this new framework, but will likely lead to surprises. Do mRNAs move between cells in the embryo? This is an old idea that can now be examined with the new probes to track RNAs (Politz, 1999; Pederson, 2001). The completed sea urchin genome will also now reveal the microRNAs of this organism and launch studies of their various functions in regulating gene expression, probably at multiple levels. It is fascinating to consider how microRNAs are themselves regulated in the sea urchin (or any) embryo, and this line of investigations gives added meaning to the concept of the regulatory genome. Every other genome that has been completed so far has brought home one deep lesson: we were not operating with a sufficiently open mind. The sea urchin genome will not be different in this regard. Perhaps the most exciting impact of having the sea urchin genome will be to examine how the various protein non-coding regions may operate.

Conclusion

In *The Odyssey*, Ulysses ordered wax to be put in his shipmates' ears, so they would not be tempted by the Sirens, whose voices beckoned from ashore and had been the cause of many previous shipwrecks. (Ulysses commanded that he be lashed to the mast, but kept his ears open.) The sea urchin's siren has for centuries sounded in the opposite direction—shoreward, from tidal pools to inquiring biologists like Aristotle. In the modern era, this creature has brought us almost everything we know about the chromosomal basis of development, maternal determinants, fertilization and maternal messenger RNA. In the past decade, the sea urchin embryo has enabled one of the most detailed gene expression analyses of any embryonic event (mesoendoderm specification) and has been the basis for the most comprehensive dissection of gene regulatory networks in any metazoan creature. Praise be to those who led the way in the preceding eras, and to those now advancing this frontier.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ydbio.2006.10.006.

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