Box 5 | **European Parliament directive on patenting**

Directive 98/44/EC of the European Parliament and of the Council of the 6 July 1998 on the legal protection of biotechnological inventions, Official Journal L 213, 30/07/1998 p. 0013–0021 Article 5:

- **The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.**
- **An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.**
- **The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.**

concern may motivate some institutions to defer publication in precisely the circumstances that it motivates other institutions to make prompt disclosure. The difference depends on whether they believe that preempting future patents is good or bad. Apart from concern about preserving their own patent rights, public research sponsors and publicly funded research performers may worry that premature public disclosure could prevent them from complying with their mandate under the Bayh–Dole Act to promote technology transfer and product development by patenting research results. Indeed, this concern was cited by former NIH director Bernadine Healy in support of the decision to file patent applications on the first ESTs identified by Craig Venter when he was at NIH[25].

In fact, it does not seem that publication of raw genomic DNA sequence will prevent the issuance of patents on genes that are subsequently found to lie within that sequence under United States law. The situation in Europe is less certain and awaits clarification of national laws in response to a 1998 directive of the European Parliament on the legal protection of biotechnological inventions (BOX 5). Although the patent system has not yet resolved many of the legal issues that will determine what portions of the human genome may be patented, for the time being there seems to be little threat that disclosure of the human genome in the public domain will leave future researchers who identify and characterize genes with nothing left to patent.

Conclusion

Complex and interrelated strategies for endowing the public domain are at work in the field of genomics. These strategies arise out of the varied plans of different institutions for extracting value out of genomic information, complicated by the interplay of the public domain with the patent system. Public disclosure of genomic information advances some interests while harming others, with no simple distinction between the interests of public and private institutions. Understanding these interests might do more to enlighten public policy debates about the importance of the public domain in genomics research than appeals to ethical imperatives.

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Links

COMPANIES Celera | Monsanto | Merck | Incyte |Human Genome Sciences

FURTHER INFORMATION Human Genome Project | Joint statement by Bill Clinton and Tony Blair | The SNP Consortium | The Bermuda rules | National Human Genome Research Institute policy on patenting of human genomic sequence | Interim utility guidelines and written description guidelines for Patent Examiners | European Parliament directive on patenting

OPINION

Evo-devo: the evolution of a new discipline

Rudolf A. Raff

The history of life documented in the fossil record shows that the evolution of complex organisms such as animals and plants has involved marked changes in morphology, and the appearance of new features. However, evolutionary change occurs not by the direct transformation of adult ancestors into adult descendants but rather when developmental processes produce the features of each generation in an evolving lineage. Therefore, evolution cannot be understood without understanding the evolution of development, and how the process of development itself biases or constrains evolution. A revolutionary synthesis of developmental biology and evolution is in progress.

Developmental and evolutionary biology are two disciplines that explore morphological change in organisms over time. However, the processes involved are different. Development is genetically programmed and cyclical. Evolution is non-programmed and contingent. Although a

link between the two processes was recognized in the late nineteenth century, an effective connection of evolutionary and developmental biology awaited the appearance of developmental data that contained a strong and marked evolutionary signal. This happened in the 1980s, when the growth of developmental genetics established a link between genes and development. As developmental regulatory genes were cloned and sequenced — notably those of the *Hox* gene family, which are important in specification of the identity of insect segments — it was realized that the same regulatory genes were shared by animals with different body plans (for example, insects and vertebrates). More importantly, shared regulatory genes have conserved roles in development, which some have taken to indicate homologies in the development of body architecture among different animal body plans[1]. Developmental biology has once again become relevant to understanding both evolutionary mechanisms and the patterns of evolutionary history that are revealed by palaeontology and PHYLOGENETIC studies.

Cardinal issues

What constitutes the fundamental problems for a science of evolutionary developmental biology (evo-devo) depends on whether the scientist is a developmental biologist, a palaeontologist or an evolutionary biologist. Some of the main issues (and controversies) are summarized in BOX 1. Developmental genetics now dominates a wide swathe of biology, and powerful genetic and molecular tools have made it possible to define the machinery of development in terms of gene action and the operation of regulatory genes. These studies revealed that regulatory genes are conserved across phyla, which provides an impetus to think about the evolutionary dimension of development. The experimental tools have led to an understanding of the development of a few heavily studied species, and allowed us to compare developmental features among a range of species. For developmental biologists, the principal and inter-related problems are how development has evolved, and how developmental evolution has resulted in changes in particular structures or features of body organization.

Palaeontologists would seem to be unlikely partners in any enterprise with developmental biologists. Palaeontologists focus on the appearance of novel features and new body plans during evolutionary history — a view that constitutes an overlap of interests, if not of methods, with developmental biologists. But palaeontology provides insights available in no other way. For example, the discovery that the earliest (fossil) TETRAPODS had feet with eight toes rather than five[2] was a complete surprise, and was important in providing us with a new view of what ancestral limbs were actually like, and for giving us clues as to how limb development evolved.

Finally, evolutionary biologists are faced with understanding how small genotypic modifications are translated into phenotypic changes during evolution, and how micro-evolutionary changes contribute to the MACRO-EVOLUTIONARY events on the timescale observed in the fossil record. Their interests also converge on those of evolutionary developmental biologists in asking whether developmental processes themselves bias the possible directions of evolution by constraining the relationship between allelic and phenotypic variation. Any limitation imposed by developmental programmes on the phenotype would affect the kinds of morphological variation that are possible, and its response to selection[3]. Leroi[4] has argued strongly that micro-evolution and macro-evolution result from the same processes. Orr[5] showed that mutations of both large and small effect can be fixed (see glossary) in evolution. Haag and True[6] note that genes identified by mutations which cause developmental phenotypes can, in some cases, have similar effects during evolution. However, this correlation drops with phylogenetic distance, making genes identified by developmental mutations most useful in comparisons of related taxa.

> "Development is genetically programmed and cyclical. Evolution is non-programmed and contingent."

The contribution of phylogenetics

Evolutionary biology is comparative, and requires tracking events over long time frames, and across phylogeny. Although phylogenetic relationships have not been regarded as important for the study of developmental mechanisms, they become crucial once we begin to consider the evolution of developmental processes[3]. New analytical methods provided by CLADISTICS and the avalanche of gene sequence data have revolutionized phylogeny.

Phylogeny imparts three important kinds of information. First, we can determine the direction in which developmental features are evolving. Second, knowing the divergence times of branches in a tree allows evolution rates to be inferred. (There is, at present, controversy about using extrapolations of rates of gene evolution to determine important divergences that pre-date visible fossil evidence; the divergence among animal phyla is such a case[7].) Third, phylogenetic trees allow homologies to be inferred or, conversely, show that apparently homologous features are not so. The consequences can be profound, as seen, for example, in studies of the evolution of fish fins and tetrapod limbs. Modern fish and tetrapods build their fins or limbs using different parts of the shared ancestral fin. So to avoid mistaken comparisons of gene expression pattern in non-homologous features[8], it is important to understand the evolutionary relationship between structures that are being compared in different organisms. Furthermore, phylogenetics shows us that, to understand better the variation in developmental mechanisms, and to map the origins of novel features, we must widen the sample of organisms on which our developmental models are based. This has been especially noticeable in the

Box 1 | **Current issues and controversies in evo-devo**

- **How do developmental constraints bias the direction of evolution?**
- **How do micro-evolutionary processes relate to macro-evolutionary differences?**
- **Do genes identified by mutations that affect development within a species correspond to genes that produce differences between species?**
- **What are the roles of modules in development and evolution?**
- **How should we make an appropriate phylogenetic sampling of organisms for evo-devo studies?**
- **Can gene expression patterns be used to establish homologies between developmental features of distantly related organisms?**
- **Why is there a conflict between molecular clocks and the fossil record in timing the metazoan radiation?**
- **Were Pre-Cambrian metazoan ancestors similar to larvae or to miniature adults?**

study of the insect head[9]. The head of *Drosophila melanogaster*, the most-studied insect, is highly specialized but its development is not typical of head development in insects. So the evolution of insect head development can only be understood by investigating other groups, using molecular–genetic tools originally devised for the study of *Drosophila*.

Developmental regulatory genes

The richest source of data, at present, comes from empirical evolutionary studies of the developmental regulation of body plan, of individual adult body features and of early development.

Studies on the evolution of development have revolved around the astonishing finding that principal regulatory genes are conserved across phyla. Genes of the *HOX* CLUSTER are integrated into animal axial differentiation, and are even present in CNIDARIANS, such as corals[10]. Detailed examination of expression patterns of individual *Hox* genes has been used to unravel the individualization of arthropod body segments and appendages from a primitive pattern of equivalent segments. Homologies are being drawn among insect groups that have highly divergent mouthparts to infer how these ecologically driven modifications evolved[9]. Comparisons also reveal homologies among insect, crustacean and chelicerate (notably spider) segments[11,12], as well as insights into the origins of segmental differentiation in these arthropods and in more primitive arthropod relatives such as the velvet worm, Peripatus (an onychophoran[13]).

Hox genes also regulate the development of the vertebrate body axis. However, evolution of *Hox* gene regulation in vertebrates has been different from insects. The expression of individual *Hox* genes in insects is linked to segment number, although downstream responses in individual segments, leading to distinct segment identities, differ among taxa[14]. Therefore, although the third thoracic segment in both taxa expresses the same *Hox* gene code, a second pair of wings is produced in butterflies, compared with HALTERES in flies. In vertebrates, the *Hox* gene expression pattern is linked to segment identity rather than segment number[15,16]. So all cervical vertebrae have the same *Hox* gene code, whether there be seven as in mammals or 14 as in the chick. A radical change in *Hox* gene expression, involving changes in *Hox* gene expression domains, correlates with the great expansion of thoracic identity in the axial skeleton in snake body plan evolution (FIG. 1)[17]. This broad comparison between insects and vertebrates shows that there is considerable flexibility in the mode of regulatory evolution, and that analogous effects can result from quite different evolutionary modifications of complex regulatory systems.

> "Chordates… have a dorsal central nervous system, a notochord and paired muscle groups, which are present from trout to tyrannosaur."

There is an unexpected theme to the developmental regulatory systems underlying such organs as the heart[18], eyes[19] and appendages[20] of insects and vertebrates, indicating that many phyla may share homologous precursors to these organs. However, it is important to be sceptical about apparent homologies, however seductive. Although many developmental regulatory genes are conserved across phyla, conserved genes and gene pathways can be and are co-opted to new functions. For example, only about 16 basic eukaryotic signal transduction pathways[21] must control the development of about 35 phyla, each with a unique body plan. Among closely related taxa, such as insects, the same developmental regulatory genes probably control homologous features. However, as phylogenetic distances increase, the probability of co-option to non-homologous roles grows, and interpretations become more controversial. This is potentially most frustrating precisely where we seek homologies between phyla. Nonetheless, some deeply conserved gene expression patterns probably remain for us to tease out.

Although we expect to find a larger number of common mechanisms in similar organisms, we are discovering that changes in genetic regulatory systems have also been marked among quite closely related taxa. For instance, all vertebrates show internal left–right asymmetry, but there are important differences in how this is genetically controlled in various vertebrates[22]. Although all tetrapods have similar limb structures, the expression of regulatory genes in the developing frog limb bud is different from that observed in birds and mammals[23]. Finally, although the gene regulatory machinery used to develop the vertebrate fore- and hindlimbs is the same, specific genes control fore- and hindlimb identity[24].

On the basis of results from developmental genetic studies done in model systems, such as *Drosophila*, mutations in genes controlling early development would be expected to be deleterious, as they are bound to affect all of later development. Early development should therefore evolve slowly or not at all. However, studies of many organisms give the counter-intuitive result — early development evolves freely, allowing highly divergent ontogenies to evolve among closely related species[3]. By this method distinct developmental modes and larval features have evolved among sea urchins, starfish, ascidians, salamanders, frogs, nematodes and even polyembryonic

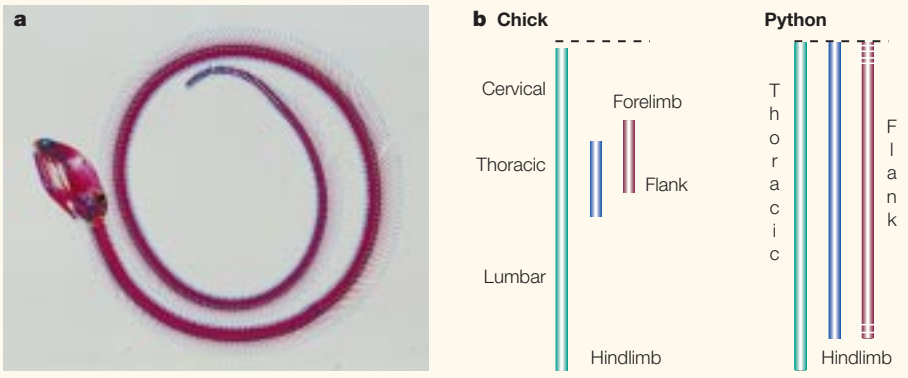

Figure 1 | **Hox gene expression in the evolution of snakes — a dramatic modification of the vertebrate body axis. a** | The skeleton of a python embryo stained with Alcian blue (cartilage) and Alizarin red (bone). **b** | Schematic diagram comparing domains of *Hox* gene expression in chick and snake embryos: *HoxB5*, green; *HoxC8*, blue; *HoxC6*, red. *Hox* genes are involved in the regionalization of the lateral plate mesoderm into forelimb, flank and hindlimb, to specify limb position. The expansion of HoxC8 and HoxC6 domains in python correlates with the expansion of thoracic identity and can account for the absence of forelimbs. (Adapted with permission from *Nature* (REF. 17) © (1999) Macmillan Magazines Ltd.)

insects, where a single egg gives rise to 2,000 separate embryos through a completely new developmental pathway[25]. These studies show that early development can evolve as radically as later development, and that it also can contribute marked evolutionary novelties.

Origins of body plans

Animal phyla each have visibly distinct body plans — the arrangement of their body parts. Chordates, for instance, have a dorsal central nervous system, a notochord and paired muscle groups, which are present from trout to tyrannosaur. However, gene sequence data show that all phyla (animal and non-animal) are evolutionarily related[3]. The origin of body plans is an important issue, combining studies of developmental biology, palaeontology and molecular evolution[26,27]. Although the origins of most phyla have not yet emerged from the fossil record, fossil remains of BASAL MEMBERS of phyla show that body plans evolved their features sequentially, and even that some apparent intermediate forms between phyla may occur[26,27]. One of the main surprises from molecular biology concerns the long-known inversion of the dorsal–ventral axis of arthropods and other PROTOSTOMES compared with vertebrates. This anatomical switch is accompanied by an inversion in the expression of genes that determine the dorsal and ventral axes, indicating that the lineages that stem from a common PROTOSTOME–DEUTEROSTOME ancestormay share the same developmental mechanism[28]. Progress in gene expression studies may allow us to understand even more extreme morphological transformations, such as how echinoderms with pentameral symmetry have evolved from a bilateral ancestor.

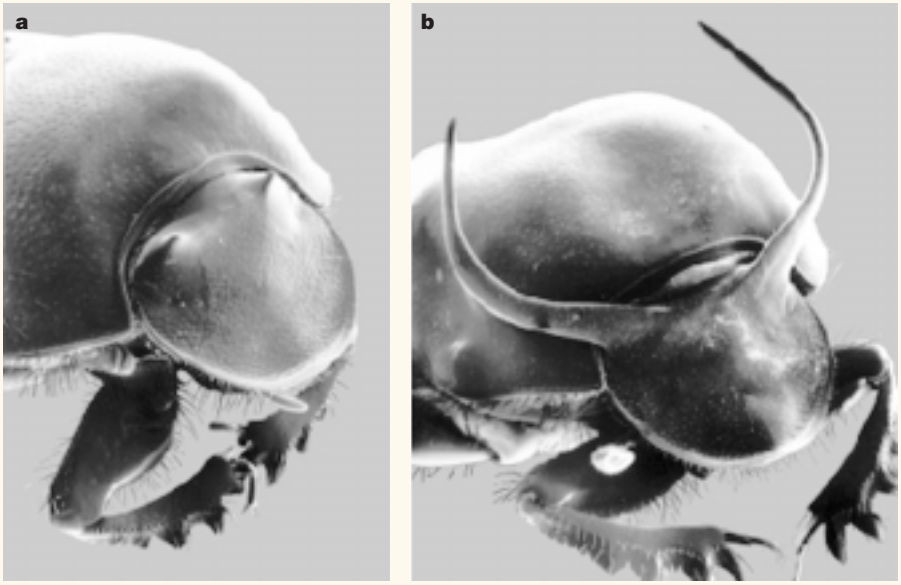

Figure 2 | **Polymorphism in the development of horns in the male dung beetle, *Onthophagus taurus*. a** | Small horns, produced by males below threshold size. **b** | Fully developed horns in a male over threshold size. (Adapted with permission from *Development* (REF. 34) © (1999) The Company of Biologists Ltd.)

As the fossil record has not revealed the ancestral animal, or any of the important ancestors to principal animal clades (such as the protostome–deuterostome ancestor), attempts to infer the properties of these ancestors are based largely on the shared genes and developmental features among living clades. Current models of METAZOAN ancestors are closely linked to ideas on the evolution of development. The larvae of most animals are built quite differently from the adults. It has been argued[29] that early animals were similar to larvae of living marine invertebrates, and used gene regulatory systems similar to those used to produce modern larvae. Adult body plans and their different gene regulatory systems would have evolved at a later stage with the origin of 'set aside' cells that produce the adult body plan within the quite dissimilar larval body. This model requires that animal development acquired a new step, and demands a great deal of convergent evolution of genetic systems regulating adult development. The hypothesis is challenged by evidence of how developmental features are phylogenetically distributed. These indicate that feeding larvae arose after adult body plans[26,30,31], and that set aside cells are not homologous among all taxa[32]. A second hypothesis therefore states that the ancestral

Glossary

CLADISTICS
An approach to inferring evolutionary relationships among organisms, on the basis of identifying shared features among diverging clades.

HOX CLUSTER
A group of linked regulatory genes involved in patterning the animal body axis during development.

MACRO-EVOLUTION
Evolutionary change above the species level. Evolutionary changes in populations within a species are termed micro-evolution.

METAZOANS
Multicellular animals.

ONTOGENY
The course of development in an organism from embryo to adult.

PHYLOGENETICS
The study of evolutionary relationships among organisms.

TETRAPOD
Four-legged vertebrate animals.

FIXATION (OF AN ALLELE)
When an allele replaces all other alleles in a population, so that its frequency is equal to one (that is, 100%).

EPIGENETICS
Events in development that depend on interactions with other parts of an embryo or the environment.

HALTERES
In Diptera (true flies), the second or hind wings have become modified into a pair of club-like balancing organs called halteres.

SOMITES
Axial blocks of mesoderm along the vertebrate body axis that further differentiate into dermal skin, bone and muscle.

PROTOSTOME/DEUTEROSTOME
The two principal divisions of animal phyla, based on how the mouth forms in the embryo.

BASAL MEMBERS
Lineages or branches that diverge at the base of a phylogenetic tree; more primitive lineages.

BILATERIAN
Animals with bilateral body symmetry.

CNIDARIANS
Radially symmetric animals such as jelly fish, corals, hydra and anemonies.

CAMBRIAN EXPLOSION
The rapid diversification of animal life observed in the fossil record in rocks of early-mid Cambrian age (540–530 million years ago). Many of the major phyla that characterize modern animal life evolved at this time.

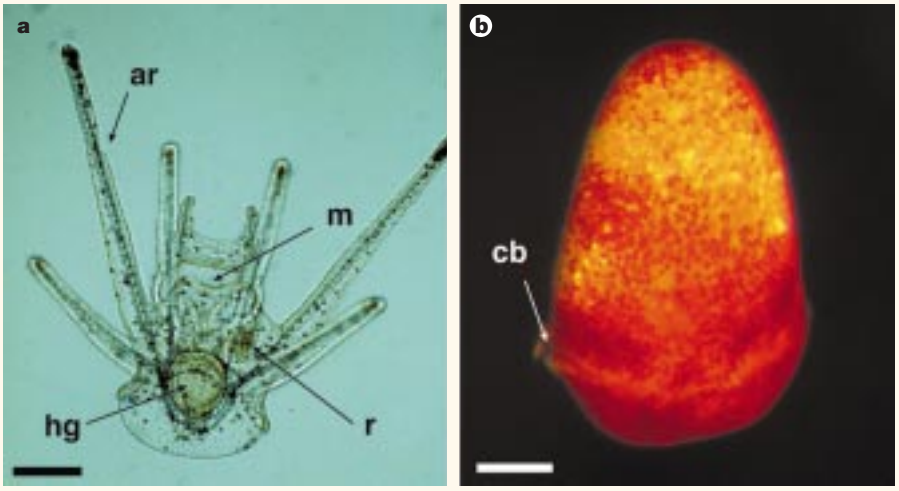

Figure 3 | **Evolution of developmental mode in closely related species. a** | Ventral view of an eight-armed pluteus larva of the indirect-developing sea urchin, *Heliocidaris tuberculata.* Arms (ar), hindgut (hg) and mouth (m) are all features of the feeding larva. The rudiment (r) represents the developing juvenile adult. **b** | Larva of *H. erythrogramma*. A ciliary band (cb) is present, but no mouth or larval gut. Most of the body in this larva corresponds to the juvenile rudiment, and feeding larval features have been discarded in favour of a highly modified direct development of the adult form. Scale bar, 100 μm. (Reprinted with permission from *Development* (REF. 40) © (1999) The Company of Biologists Ltd.)

BILATERIAN animal was small, but possessed an adult-like body plan. Planktonic larvae would have evolved later, perhaps as part of the CAMBRIAN 'EXPLOSION'.

The debate is not merely an exercise in speculative zoology. Both views require that extensive convergent evolution has taken place. Either embryonic forms evolved convergently in several lineages, or complex features of adult body plans and what are generally regarded as shared, deeply embedded developmental regulatory gene systems, evolved independently with the invention of set aside cells. This latter hypothesis seems less probable, particularly in the light of convergent evolution of larval forms. The issue is still unresolved.

A controversial debate surrounds the divergence times of phyla[7]. Typically these have been extrapolated from the differences in gene sequence between taxa for which divergence times are known. Extrapolations deeper into time estimate phylum divergence times that range from 600 to 1,200 million years ago, which is too broad to be useful. Once again, there is hope that the fossil record will resolve the argument by providing some unexpected data. Microfossils, thought to represent marine animal embryos, are emerging from late Precambrian rocks, and if they turn out to be widespread in time and diverse in preserved forms, they may show us what ancient larvae looked like and provide a better minimal date for the origins of animal development[33].

Evolution biased by development

As in developmental biology, much of research in evolutionary developmental biology is empirically driven. This is not surprising given the lack of a general theory of development, and the diversity of developmental patterns. However, development may make a crucial contribution to evolutionary theory. Modern evolutionary biology has focused on the role of natural selection, which operates external to the organism, and views organisms as unconstrained in variation. Micro-evolutionary processes are considered sufficient to explain macro-evolutionary history[4]. However, developmental processes are emergent, and not predictable from the properties of genes or cells; therefore, starting with a particular ONTOGENY, some phenotypes might be readily achieved and others impossible. Developmental mechanisms are crucial, both to large-scale evolutionary changes, and also to small-scale evolutionary processes.

The evolution of body shape poses the difficult problem of how the scaling of body parts is regulated during development. Potential constraints in interactive or co-varying systems during development highlight the mechanistically definable limitations that development imposes on the micro- and macro-evolution of body form. In insects, the growth of body features, such as horns, is linked to body size through common regulation by juvenile hormone (FIG. 2), suggesting mechanisms for evolutionary variation[34]. Experimentally varying the resource allocation to one body part affects the size of other parts, indicating that interactions occur that control relative growth and may provide developmental constraints. Scaling of body parts also can be greatly changed in response to artificial selection, providing a link between micro-evolution and development.

It remains unclear how genotype maps to phenotype. It is crucial to discover internal constructional features imminent in developmental processes that constrain variation and determine how selection affects organisms. Constraints have been suggested to lie in the function of regulatory genes and in interactions among elements of a developing regulatory system[3,35]. The emerging unifying theme is that developing systems are composed of genetically discrete modules that interact EPIGENETICALLY with each other during development. Modules include individual elements of a developing system, such as the oral ectoderm of the sea urchin larva, or the limb field of a vertebrate embryo. A modular structure generates constraint because some interactions between modules may be difficult to de-couple. Paradoxically, modularity also allows marked evolutionary change, because many inter-modular interactions can be dissociated in timing (heterochrony), or in other ways that allow viable, albeit changed patterns of development[3,36]. The link between the traits identified in selection studies and the modules that seem to be units of development still needs to be clarified. The traits used in selection studies can be complex characters composed of several underlying modules. For example, selection on tail length in mice would potentially involve several constituent developmental modules, such as SOMITES. Experimental systems (such as butterfly wing patterning), in which a link has been found between the units of micro-evolution and developmental modules (and their regulation), provide a crucial link between development and studies of selection[37].

The genetic mechanisms that permit such dissociations probably lie in the combinatorial structure of eukaryotic promoters, which allow gene expression to be modified in various ways, and to be readily co-opted to new functions. The developmental mechanisms of inter-modular dissociation are not well understood. So we have the amazing but unexplained observation that different developmental pathways can converge on similar outcomes. For example, changes in embryonic modules produce different pathways during early development of similar sea urchins (FIG. 3)[38], and induction of the

eye lens in some frogs depends on induction by the optic cup in some species, but not in others[39].

Modularity is a characteristic of multicellular life, and modules themselves must have evolved. Individual developmental modules initially may have arisen by integration of genetic processes that regulated separate events. Later, as more complex ontogenies evolved, more individualized modules may have arisen by packaging elements from within larger integrated units into separate modular entities, each an independent target of selection[36].

Challenges

The synthesis of the sciences of biological change promises new and powerful solutions to long-standing problems, and a new understanding of the basis of evolution. Along with the controversies listed in BOX 1, a number of crucial fundamental challenges remain. These include: gaining an understanding of how regulatory gene networks govern ontogeny; what makes developing systems robust enough to tolerate mutations that change the course of development so that developmental evolution is possible; and how the rules that govern ontogeny constrain the production of new variation in phenotypes. Developmental genetics, comparative developmental biology, palaeontology and genomics are adding a vast number of new data sets. Questions on the nature of homology (a subject made even more rich and strange by the emergence of evolutionary developmental biology), the origins of novelties and ultimately a complete understanding of evolution lie before this young discipline.

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Links

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ENCYCLOPEDIA OF LIFE SCIENCES

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