Whither evo–devo?

Assessing the interplay between evolutionary and developmental processes.

From DNA to Diversity: Molecular Genetics and the Evolution of Animal Design
by Sean B. Carroll, Jennifer K. Grenier & Scott D. Weatherbee
Blackwell: 2001. 214 pp. £29.95, $44.95

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Did you ever wonder how snakes lost their necks and legs? Are you curious about why birds have feathers on their wings and scales on their legs? You will find the answers to these and many other intriguing questions in this excellent book, in which Sean Carroll, Jennifer Grenier and Scott Weatherbee describe the state of 'evo–devo' in an admirably lucid style.

The past ten years have seen a renaissance of interest in the connections between developmental and evolutionary biology and the rebirth of a biological discipline colloquially called 'evo–devo' (or 'devo–evo', depending on where you're coming from). Previous incarnations of this field by earlier generations of biologists lacked molecular genetics — now this discipline enjoys top billing. The most surprising result of this young and extremely fast-moving field (in which several new journals have been started and many universities have established professorships) has been the realization that a truly amazing developmental and genetic commonality underlies all the diversity of animal types.

With hindsight, perhaps, this conservation, which includes the almost universal sharing of genetic pathways specifying developmental processes, should not have been so surprising; it is almost trivial to state that the genome of a species contains a record of its entire evolutionary history and those of all its ancestors. But although this might sound like a truism, its implications are manifold and deep, and have led to a greater understanding of how animals develop, and how the commonality in their genomes and developmental mechanisms connect the very different sets of characteristics, or phenotypes, of distantly related phyla.

From DNA to Diversity is written for a general audience, including undergraduates, with an interest in developmental and evolutionary biology, and it is a joy to read. Using striking examples, the authors brilliantly summarize the current state of thinking on the interconnectedness between developmental genetics and evolutionary diversification.

For example, they describe how ideas about the evolution of eyes have been transformed by the new perspective. Eyes were thought to have evolved independently dozens of times, not only because some phyla that have eyes are more closely related to phyla without eyes than to other phyla that have them, but also because the structure of animal eyes is so varied. An astonishing example of evolutionary conservatism, however, involves the function of the *eyeless* gene in flies and *Pax6*, the corresponding gene in mice. Despite more than 600 million years of separate evolution of flies and mice, the introduction of the mouse gene into flies can induce new eye tissue — not of the camera-like eyes of mammals, but of the insect compound eye!

This conservation raises several important questions. How can such different structures, all serving to detect light, be made through the control exerted by essentially the same gene in different phyla? *Pax6/eyeless* sits near the top of a regulatory chain of genes involved in the development of all types of eyes, even those differing hugely in morphology. *Pax6* and its functions have been conserved throughout the Metazoa, and it was probably present in the genome of the ancestor of all bilaterians. Given that some phyla have never developed eyes, why were these genes not lost during evolution? The selective forces pushing genomes to be small and lean do not seem to be too strong. It is likely that this cascade of gene interactions was co-opted again and again into making eyes, having served other developmental functions in the (sometimes extremely long) evolutionary meantime. The repeated *de novo* assembly of this network, gene interaction by gene interaction, is implausible indeed.

Although not touched upon by Carroll *et al.*, this raises other important questions about homology, one of the central themes in biology. Do structures have to be simply either homologous or non-homologous, or can they be partly homologous, depending on whether or not their ancestors possessed these structures and/or whether a homologous or non-homologous developmental pathway is used to make them? It is becoming clear that there are different kinds of homologous relationships and that homology can exist at different levels of the biological hierarchy, from genes to structures. The distinctions between homology (similarity of structures due to evolutionary descent) and homoplasy (similarity due to similarity in function and not evolutionary descent) are becoming increasingly blurred.

Classic issues about convergence in phenotypes can now be studied at the genomic and developmental level to investigate whether evolution invented the wheel twice or found two different ways of making a similar wheel. It seems likely that, more often than not, the answer will be that old gene cascades are re-recruited, never having really been lost, to provide a similar phenotypic solution to a comparable ecological challenge. Evolution is a tinkerer that uses the tools at its disposal rather than repeatedly starting from scratch.

Morphology is the product of development, which is controlled by genetic regulatory programs — genetic toolkits, as Carroll *et al.* term them. Two major groups of gene products underlie these genetic programs — transcription factors, which regulate the expression of other genes, and signalling

Of scales, feathers and skin: the evo–devo toolkit that makes a snake a snake, and not a bird.

JEFF FOOTT/BBC WILD

proteins, which mediate short- and long-range interactions between cells. The best-known examples of developmentally important transcription factors are the family of Hox proteins, which are involved in, among many other things, specifying segmental identity along the antero-posterior axis. The interactions between the Hox genes themselves are extremely complex, involving at least six classes of regulatory elements, in addition to autoregulatory feedback mechanisms.

This tight regulatory coupling is probably one of the main reasons for the extreme evolutionary conservation of the architecture of the tightly linked *Hox* gene cluster. *Hox* genes lay down a ground plan in animals that translates amazingly well into major features — segments or modules — of their morphology. The universality of the *Hox* gene clusters has led to the — now often questioned — suggestion that the presence of a linked set of *Hox* genes is a defining characteristic of all animals, the so-called 'zootype'.

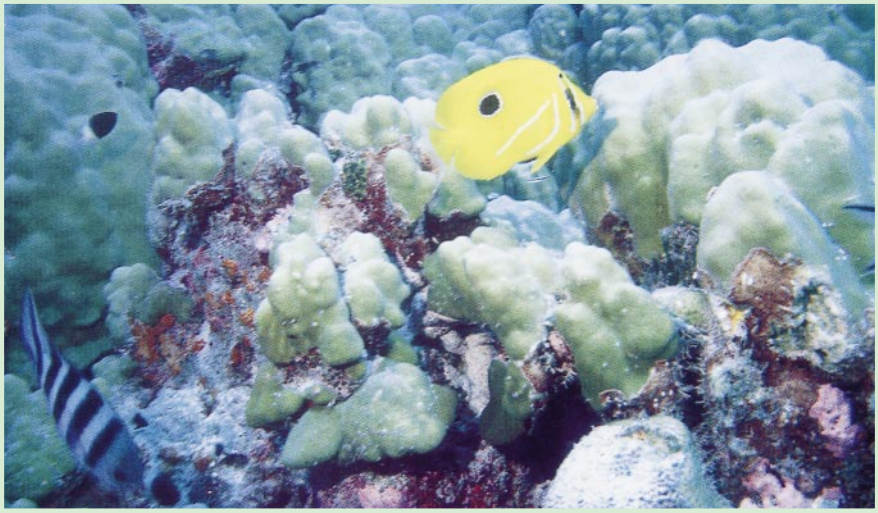
Evolution can select only for what is developmentally possible. The evo–devo field has matured, and now that we know conservation abounds, attention must focus on the big question — how does evolution make new and different things? Given the overwhelming similarity and stasis at many levels, ranging from genes and genomes to the interactions of genes in gene networks, how do differences between species arise? How can phenotypic differences be explained, and what, if any, are the rules of change? Carroll *et al.* argue that the answer probably lies largely in changes in the regulation of gene expression. I think that other kinds of molecular mechanism, such as alternative splicing, ribosomal RNA editing and gene duplication, will also be found to have major roles in explaining phenotypic diversification.

With regard to the influence of gene regulatory mechanisms in evolution, the *Hox* genes are prime examples of how selective and differential regulation of gene expression can confer distinct identities on body segments that were originally serially homologous. Such 'individuation' of segments, as Carroll *et al.* call it, results from the partial uncoupling of the underlying developmental program of each segment from the gene networks controlling the development of segments with other identities.

Carroll *et al.* describe how an increasing amount of work on the modular nature of the often extensive and complex regulatory regions of *Hox* and other developmental genes shows that it is neither accurate nor sufficient to try to explain the functions of a given evolutionary toolkit only in terms of the proteins it includes. The function of a protein always depends on the spatio-temporal context of its expression, which can be altered by changes in one or more of its gene's regulatory modules. A protein function can thus be dissociated from its original spatial and temporal pattern of expression, enabling the evolution of new gene and protein interactions, and thereby the evolution of phenotypic novelty or the individuation of particular segments and developmental modules.

Individuation of a module, such as the conversion of the gill arches of fish into functionally new structures such as jaws, or the conversion of arthropod segments used in locomotion into segments used for feeding structures, antennae or genital structures, is the stuff of evolutionary novelty. Modularity

The shrinking world of corals



Australia's Great Barrier Reef hosts the elegance coral, *Catalaphyllia jardinei*, shown above. The picture comes from *Corals of the World* by J. E. N. Veron (3 vols; Australian Institute of Marine Science, A$265). In the Indo-Pacific, the Bennett's butterflyfish, *Chaetodon bennetti* (right), feeds primarily on coral polyps, and is among the species affected by the mass coral mortality — from *World Atlas of Coral Reefs* by Mark D. Spalding, Corinna Ravilious and Edmund P. Green (University of California Press, $45, £29.95), which details the state of the world's coral reefs.

and repetition of parts coupled with individuation is the emerging principle of phenotypic organization, and is reminiscent of the organization of genes and the structure of genomes. Are there generalities, or even rules, of evolutionary change to be discovered here? Carroll *et al.* contend that these findings can explain why modularly organized animal phyla such as arthropods are among the most diverse in terms of numbers of species and morphological diversity.

'Hopeful monsters' — the hypothetical outcome of a major change in morphology at a single step — are fated to be evolutionarily stillborn. Macroevolutionary innovation must have its roots in microevolutionary variation in development at the population level, and this is going to be a major area of future research in the evo–devo field. All this and more is described in this eminently readable book, which is illustrated with beautiful colour figures. Any new graduate student in either developmental or evolutionary biology should read it. The book has the potential to inspire the next generation of biologists to use the developmental and genomic tools now available to address some of the most exciting questions in biology.

To paraphrase the Apple Powerbook commercials: "You so gonna want this book." ■

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More on evo–devo

Cycles of Contingency: Developmental Systems and Evolution
edited by Susan Oyama, Paul E. Griffiths & Russell D. Gray
MIT Press, $50, £34.50

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No easy answers

Human Trials: Scientists, Investors, and Patients in the Quest for a Cure
by Susan Quinn
Perseus Publishing: 2001. 295 pp. $26, £18.99

Xavier Bosch

Until the early 1950s, the effectiveness of a clinical therapy was judged largely by doctors' opinions rather than by statistically rigorous observational evidence. The modern clinical trial has been essential for the movement to a type of medicine where treatment is expected to be based on firm evidence of benefit rather than opinion. Although far from perfect, present-day clinical trials follow a strict scientific methodology to find out whether a new treatment option is safe, effective and a better alternative to current treatments.

BRIGHAM AND WOMEN'S HOSPITAL

Weiner at work: his research into autoimmunity led to a clinical trial for treating multiple sclerosis.

In *Human Trials*, Susan Quinn gives us a readable and authoritatively written insight into what is at stake when a determined and talented scientist puts his ideas on the line in a clinical trial. She relates the efforts of Howard Weiner, Harvard University neurologist and scientist, to find a useful treatment for multiple sclerosis (MS). In this relapsing, and often eventually progressive, autoimmune disorder of the central nervous system, the myelin sheaths surrounding nerve-cell axons become the target of immunological attack.

Weiner's proposed treatment turns on an approach known as oral tolerance, a relatively 'natural' and logical therapy aimed at suppressing an immune response to a given antigen by previous administration of the identical or similar antigen by the oral route. The scientific rationale behind the idea is that, by stimulating the immune mechanisms in the gut-associated lymphoid tissue (GALT) of the small intestine, it is possible to suppress and interrupt the autoimmune disease process. Because the ingested antigen is naturally derived — it is a natural component of the body — and undergoes the normal digestive processes, the approach would seem to be remarkably safe. And it has the great advantage that the antigen can be given simply in the form of a pill.

Quinn describes how and why the oral-tolerance idea, discredited and regarded almost as homeopathy by some, was put into practice to find out whether it works in multiple sclerosis and rheumatoid arthritis. After successful results in laboratory mice given an oral myelin preparation, and in a small group of MS patients, Weiner carries out a phase-I clinical trial to test safety and then decides to test the efficacy of his treatment on a large group of MS patients in a phase-III multicentre clinical trial throughout North America.

Weiner's enthusiasm and faith in the natural, oral approach is transmitted to his colleagues in the laboratory and the clinic and also to venture capitalists, who help him to found a biotech start-up company, which goes public. The optimism, strengthened after publication of the preliminary findings in prestigious journals with notable media impact, is also passed on to the patients, who face enormous prognostic uncertainty and have few therapeutic options. Quinn conducted extensive interviews with patients and scientists during the course of the trials, observed meetings at the company and read Weiner's personal diaries.

Although encouraged by the initial results of the MS trial, Weiner has reservations about the doses used and the type of antigen administered. There is also some concern that, because of time constraints, a phase-II trial had been skipped to enter phase III directly. Phase-II trials involve a larger group of patients than phase I and