NEWS & VIEWS

EVOLUTIONARY BIOLOGY

Genomic hourglass

Comparative genomics studies reveal molecular signatures of the controversial 'phylotypic' stage — a time when embryos of members of an animal phylum all look more alike than at other embryonic stages. See Letters p.811 & p.815

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Most people would say that lizards and elephants bear little resemblance to each other. But not so the embryologist, for, at a particular stage in development, the embryos of very different species may look much the same. Elsewhere in this issue, papers by Kalinka *et al.*[1] and Domazet-Lošo and Tautz[2] offer a fresh perspective on this intriguing phenomenon.

This is a topic with a long history. In 1828, the German biologist Karl von Baer, one of the fathers of embryology, reported how very similar the early embryos of different species can be[3]: "I have two small embryos preserved in alcohol, that I forgot to label. At present I am unable to determine the genus to which they belong. They may be lizards, small birds, or even mammals." In fact, it was later observed that, over the course of development, the youngest embryos within an animal phylum often look very different, but progressively converge towards a similar form (described by von Baer and later dubbed the phylotypic stage), before they diverge again to achieve the tremendous diversity of adult forms.

This pattern of morphological divergence among species during embryonic development resembles an hourglass[4,5]. Its waist marks the phylotypic period during which the basic body plan of a given animal group is laid down. The existence and meaning of the hourglass model, however, have been the subject of heated controversy, in part because the model rests on subjective comparisons of animal likeness of shape[6–9]. The contribution of Kalinka *et al.*[1] and Domazet-Lošo and Tautz[2] is to report molecular signatures supporting the existence of the phylotypic stage in insects and vertebrates.

To test the hourglass model, Kalinka *et al.*[1] (page 811) reasoned that, because the development of shape is directed by the expression of genes, variations in morphological pattern among species might be reflected in the dynamic of gene expressions. The authors set out to test this idea by measuring differences in gene expression between various species of the fruitfly *Drosophila*. Using DNA microarrays, a technology that measures genome-wide gene expression, they first quantified levels of gene
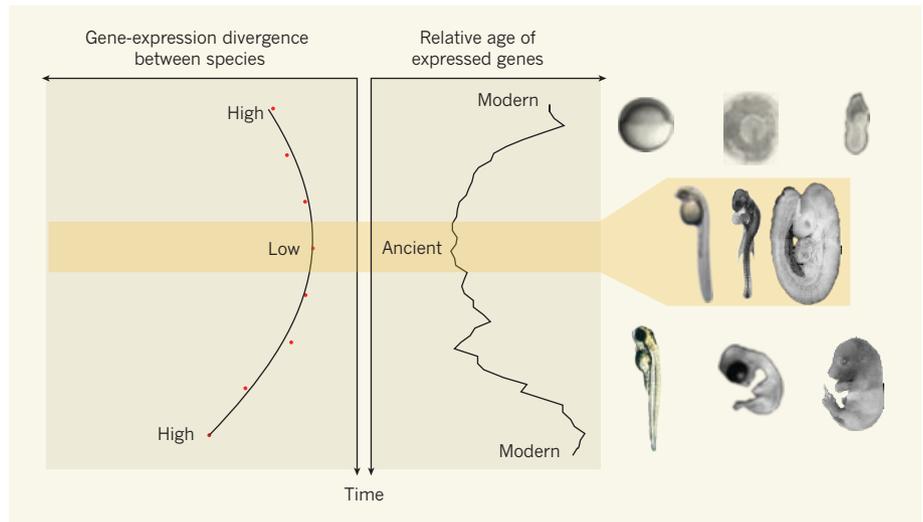

Figure 1 | The developmental hourglass, as revealed by comparative genomics. Mid-embryogenesis is marked by the phylotypic stage, a period of minimal anatomical divergence between species, as illustrated for vertebrate species by the orange band. This stage is now shown by Kalinka *et al.*[1] to display minimal gene-expression divergence between *Drosophila* species (left curve), and by Domazet-Lošo and Tautz[2] to express the oldest gene set of the entire life cycle (right curve). The species depicted, left to right, are zebrafish, chick and mouse. (Images reproduced from refs 12–14.)

expression throughout embryogenesis for six distinct species of *Drosophila*. Next, they compared the temporal expression profiles of all the genes across the six species.

A sophisticated statistical analysis of the data set revealed a pattern strikingly similar to the anatomical hourglass, in which the temporal gene-expression divergence among species is minimal around the 'extended germband' stage, which is classically regarded as the phylotypic stage in insects[10] (Fig. 1). That is, the expression of genes that are active during the extended germband stage is evolutionarily more stable than that of genes active earlier and later during development. Remarkably, the genes that mostly conform to an hourglass pattern are those involved in developmental processes, whereas genes involved in non-developmental functions show more variable expression profiles across species.

The detection of a phylotypic stage at the gene-expression level revives some long-standing considerations on the relationships between embryonic development (ontogeny) and evolution (phylogeny)[11]. Ontogeny clearly does not recapitulate phylogeny, yet these two

processes have intricate connections. It is precisely the nature of these connections that Domazet-Lošo and Tautz[2] (page 815) have explored.

Starting from the notion that developmental novelties might be enabled by the evolution of new genes, these authors sought to correlate the emergence of new genes (or gene families) with novelties in the anatomical development of a species — zebrafish, in their case. They used 'phylostratigraphy', an approach they had developed previously, to parse the genome into classes of genes according to their evolutionary origin in the history of life ('phylostrata'). For instance, the zebrafish genome includes genes that date back to the origin of cells, others that date to the evolution of animals and yet others that date to the evolution of vertebrates. Then, using DNA microarrays, the authors measured the relative contribution of each phylostratum to global gene expression (the 'transcriptome') at different time points in the zebrafish life cycle, thereby estimating the relative age of the transcriptome at each time point.

It turns out that genes of different evolutionary origins are expressed at different time

points (Fig. 1). Strikingly, the stage classically viewed as the phylotypic stage in zebrafish is marked by the expression of the evolutionarily oldest transcriptome set, whereas earlier and later stages (including adult stages) express comparatively younger transcriptomes. Importantly, the authors identified a similar pattern in published microarray data for other organisms (fruitfly, mosquito and nematode), suggesting that their findings are generally applicable.

By revisiting the subjective anatomical comparisons of classical embryology using quantitative genomics, these two studies[1,2] have revived the concept of the phylotypic stage with much-needed objectivity. Although they take very different approaches, it is remarkable that both studies identify genomics signatures of the phylotypic stage — in short, the phylotypic stage sees expression of the oldest gene set, which is maximally conserved across species. These results reinforce the notion that animal body plans emerged using novel signalling and regulatory genes that arose at the inception of multicellular animal life, and that, once established, the gene-expression patterns underlying the specification of the different body plans have remained fairly invariant.

This newly acquired molecular legitimacy does not, however, explain what establishes and maintains the hourglass pattern. Kalinka *et al.*[1] found that the hourglass pattern of gene-expression variation is best explained by the action of natural selection. This echoes the proposition that mechanistic constraints pertaining to the building of a shared body plan might explain the conservation observed at the phylotypic stage[4,5].

A body plan is a particular organization of anatomical rudiments. The early embryonic specification of these rudiments, independently of one another, might take different evolutionary roads. But the assembly of these elements into a functional body plan might require a tight and constrained orchestration of gene expression, reflected in the hourglass waist. Once coherently assembled, the connected elements make a stable evolutionary substrate for an organism to explore new morphogenetic directions within the realm of the established body plan.

With this work[1,2], new avenues open up in addressing a long-standing debate. Future comparative studies of the gene-regulatory networks and developmental events underlying the phylotypic stage will certainly shed light on the *raison d'être* of this peculiar embryonic period. ∎

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QUANTUM PHYSICS

Hot entanglement

Quantum entanglement has been observed at low temperatures in both microscopic and macroscopic systems. It now seems that the effect can also occur at high temperatures if the systems are not in thermal equilibrium.

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Quantum physics is usually thought to apply to small systems at low temperatures. A standard example would be the quantum dynamics of an electron in a hydrogen atom. Atomic orbits of electrons are roughly an ångström in size — that is, comparable with electronic de Broglie wavelengths, which characterize the extent over which electrons display a quantum wave-like behaviour. More importantly, at low temperatures, the typical energies characterizing electronic jumps are hundreds of times larger than the thermal energy of the environment to which the system is exposed. This, in turn, means that the noise due to the environmental temperature is negligible compared with the typical electronic-jump energies, and therefore that the noise does not spoil the system's quantum behaviour. Writing in *Physical Review Letters*, Galve *et al.*[1] show that, contrary to the common view, a macroscopic system at high temperatures can also sustain quantum features.

It is interesting that similar considerations about the restriction of quantum phenomena to small systems at low temperatures can be made about the most quantum of all quantum effects: quantum entanglement. The term entanglement was coined by Erwin Schrödinger, who described it as "the characteristic trait of quantum mechanics". It refers to a state of two or more quantum systems in which the systems are so intertwined that they behave like one — it is actually a mistake to think of the subsystems separately. Quantum systems become entangled when they interact with one another. In the past decade, extensive theoretical and experimental research[2] has shown that, no matter what systems we look at, a general rule says that if the interaction strength between the subsystems is larger than the thermal energy due to their coupling to the environment, entanglement should exist between these subsystems provided that they are in thermal equilibrium with the environment.

Now Galve *et al.*[1] prove that this relationship between temperature and entanglement is not valid for systems that are not in thermal equilibrium. Here, in fact, the news is very good for entanglement. The authors predict that nanomechanical oscillators can be entangled at much higher temperatures than previously thought possible.

The basic intuition behind this result is as follows. When a system is not in thermal equilibrium, the temperature no longer provides the relevant energy scale against which to compare the system's quantum behaviour. What matters instead is an effective temperature, which can be much lower than the absolute one. This effective temperature is obtained by multiplying the absolute temperature by the rate at which the system approaches equilibrium divided by the driving frequency, the frequency of the signal with which the system is made to oscillate. Galve and colleagues demonstrate that this new condition for entanglement — that the interaction between subsystems should be compared with the thermal energy at the effective temperature — holds quite generally and is intuitively pleasing. It says that if we can drive the system to oscillate within a shorter timescale than the time it takes to reach thermal equilibrium, then an entangled steady state can be attained at higher temperatures than the absolute one.

The actual system that Galve *et al.* investigate — two macroscopic (harmonic) oscillators coupled to each other — is important because a number of laboratories are currently working with similar systems. For instance, Aspelmeyer and colleagues[3] have created quantum states