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NEWS AND COMMENTARY

Evo-devo

Relaxed constraints on Hox gene clustering during evolution

B Galliot

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A new study of Hox genes in *Oikopleura* reveals these developmental genes to be scattered across the genome, rather than clustered, as found in most animals.

Hox genes were initially identified in *Drosophila* as grouped regulatory genes, known as homeotic genes. They encode positional information during development following the colinearity rule, that is, their physical location in the cluster parallels the physical order of their expression along the anterior to posterior (AP) axis of the developing embryo (Lewis, 1978). Some years later, their molecular characterisation in both *Drosophila* and vertebrates proved that they code for proteins that bind DNA through the homeodomain, a domain of 60 highly evolutionarily conserved amino acids. Furthermore, mammals have the same clustered chromosomal organisation, where four copies of the *Hox* cluster, homologous to that of *Drosophila*, were found. Transcriptional analyses performed on sectioned and whole-mount embryos subsequently demonstrated the conservation of the colinearity rule (McGinnis and Krumlauf, 1992). So it seemed that Hox genes might provide a common molecular representation of the body plan at an early stage of the development of all animals. This is referred to as the phylotypic stage, during which embryos from distinct species tend to resemble to each other (Slack *et al*, 1993). Consequently, it was expected that the Hox gene cluster might have had this crucial developmental role even in the common ancestor of all bilaterally symmetrical animals.

However, in vertebrates, the spatial colinearity rule turned out to be only part of the story. In mammals, it was shown that the temporal order of activation of the Hox genes during development also corresponds to the order that these genes are arrayed in the genomic cluster (Kmita and Duboule, 2003). This temporal regulation is not observed in *Drosophila* embryos, where Hox genes are split into two half-clusters and are activated simultaneously. Genetic manipulations in mice show that the clustered organisation of Hox genes is required to implement such a tight temporal control. In contrast, Hox clustering is not necessary to achieve a proper spatial expression in other numerous cases (see in Kmita and Duboule, 2003).

So what factors determine whether Hox genes need to be clustered or not? Only a detailed analysis of the organisation, function and regulation of Hox genes in diverse phyla where the clustered organisation of Hox genes has obviously been disrupted, such as in the nematode *Caenorhabditis elegans*, is likely to definitively answer this question. In the case of *C. elegans*, several Hox genes have been lost and homeodomain sequences have significantly diverged (Aboobaker and Blaxter, 2003). These disruptions correlate with the fact that Hox genes in *C. elegans* no longer deliver positional information along the AP axis.

In a recent paper, Seo and co-workers (Seo *et al*, 2004) describe a similar disintegration of the Hox complex in the tunicate *Oikopleura dioica*, where the nine Hox genes actually do not represent a complete Hox cluster. Two belong to the two most anterior groups (labial/PG-1, pb/PG-2), one might have diverged from the Hox genes that specify the trunk (Dfd/PG-4 to PG-7) and six are related to the most posterior groups (PG-11 to PG-13). *Ciona*, another tunicate species, has also lost the central Hox genes, which indicates that this evolutionary event might have occurred in a common tunicate ancestor, this group diverged from the lineage that led to vertebrates. In contrast, amplification of the posterior Hox genes in *Oikopleura* might correlate with the evolution of the tail, a chordate-specific feature. This situation is thus similar to that seen in worms, but occurs in a chordate phylum distinct, yet not far away from vertebrates. Surprisingly, even without genomic clustering of Hox genes, the authors report an apparent spatial colinearity, although temporal colinearity is nevertheless not observed. However, as expression of these Hox genes is restricted to the tail region, with some of them exhibiting a strict tissue and cell specificity, a clear function of *Oikopleura* Hox genes in delivering positional information along the AP axis is as yet to be proven. In other words, these genes may serve a rather different task in such a derived animal. In any case, these results support the link between clustering of Hox genes and temporal colinearity.

The time at which spatial and temporal colinearities emerged during evolution remains an open question. On the one hand, Hox genes might be dispensable for embryonic development but not for adult body plan formation, as demonstrated in species undergoing an indirect development, where the adult body plan derives from a limited portion of the larva (Peterson *et al*, 2000). In such cases, expression of Hox genes was detected not during larva formation but subsequently in larval tissues that go on to form the adult body plan. But there again, rules seem to vary according to the context: in the polychaete annelid *Chaetopterus variopedatus* larva, Hox genes seem to follow both the spatial and temporal colinearity rules, while in the sea urchin *Strongylocentrous purpuratus* larva, colinearity is restricted to mesodermal derivatives (Arenas-Mena *et al*, 2000). On the other hand, clustering of Hox as well as non-Hox homeobox genes likely corresponds to a very ancestral event (Holland, 2001). Whether or not this ancestral clustering was dependent on transcriptional control remains to be examined. In cnidarians, a phylum that predated bilaterians, Hox-related genes are expressed as developmental genes (Finnerty *et al*, 2004), hence a systematic and comparative analysis of their chromosomal organisation, function and regulation in this phylum could help identifying the common original theme among the numerous bilaterian variations.

B Galliot is at the Department of Zoology and Animal Biology, University of Geneva, 30, quai Ernest-Ansermet, Geneva 4, Switzerland.

e-mail: brigitte.galliot@zoo.unige.ch

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Further Reading

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