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Hox Genes: It's All a Matter of Context

Dispatch

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Recent studies provide compelling new evidence that Hox gene effects depend on fine-structure spatial and temporal information. Further, in a specific cell type, only one or a few downstream genes may mediate Hox morphogenetic functions. If this is generally true, it will have important implications for how Hox regulatory networks operate and evolve.

Hox genes play a major role in the morphological diversification of the anteroposterior body axis of animal embryos by switching the fates of segments between alternative developmental pathways [1]. In their role of controlling segment diversity, Hox proteins are responsible for many different morphological structures and cell types within a given segment. But it is still largely a mystery how a single *Hox* gene can determine a morphological trait at a specific location within a segment, and why that trait does not appear elsewhere in the same segment or in other segments. Two recent papers from Rozowski and Akam [2] and Brodu *et al.* [3] have approached this question in different ways.

The goal of the study of Rozowski and Akam [2] was to understand how the *Hox* gene *Ubx* modulates the mechanosensory bristle pattern in different *Drosophila* legs. The development of these mechanosensory mini-organs is initiated in imaginal discs through the formation of proneural cluster cells, all of which are competent to give rise to a bristle sensory organ [4]. A process of lateral inhibition within proneural cluster cells allows only one cell to develop into a sensory organ precursor, which then undergoes a series of stereotyped divisions. During bristle development, the first division generates two second-order precursors, one of which divides again to give rise to cells that construct the external aspects of the bristle, the shaft and the socket, whereas the other second-order precursor divides again to give rise to a glial cell and a neuron [5] (Figure 1).

Rozowski and Akam [2] focused on the development of the sternopleural and apical bristles, which normally appear only on the legs of thoracic segment T2, and not on T3 legs (Figure 1). The *Hox* gene *Ubx* is expressed in most cells of the T3 leg imaginal disc, but not in the T2 disc, and in *Ubx* mutants the sterno-pleural and apical bristles develop ectopically in T3. A naïve thought would be that the high-level segment identity control function provided by *Ubx* would prevent the initial formation of the T3 bristle. Not so. Rozowski and Akam [2] found that, in these two cases, *Ubx* acts directly on steps during sensory organ development, and not at an earlier, more general stage of pattern formation. In the T3 leg disc, the development of the sternopleural bristles aborts shortly after initiation of the proneural cluster (Figure 1), and this corresponds to the period during which *Ubx*'s repressive function on bristle development is required. In contrast, *Ubx* is required at two or more steps of the sensory organ division and specification pathway, in order to fully suppress apical bristle development on T3 legs (Figure 1).

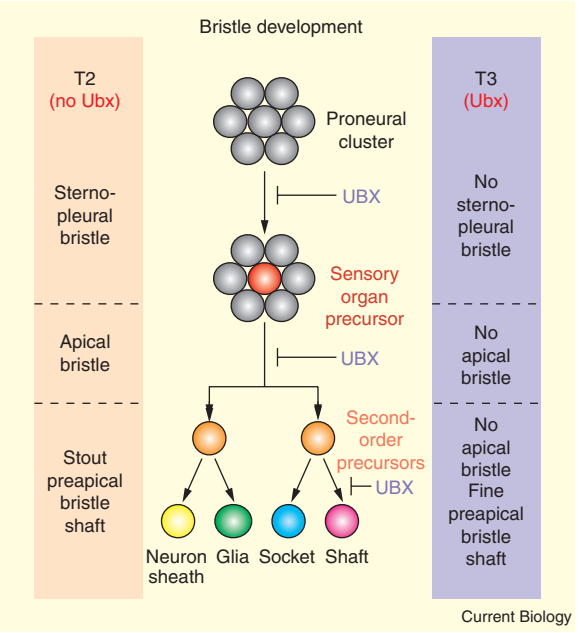

Figure 1. A schematic diagram of bristle differentiation during the development of *Drosophila*.

Ubx alters the morphology of legs by interfering with the bristle specific program. If *Ubx* is present, as in T3 imaginal leg discs, it can suppress bristle development at any of the steps indicated, leading either to a complete block in development, as in the case of the sternopleural and apical bristles, or to a modified bristle morphology, as in the case of the preapical bristles. Whether and where in the hierarchy *Ubx* executes its function is critically determined by and completely dependent on the presence of other factors, like signaling molecules or other transcription factors. If *Ubx* is absent, as in T2 imaginal discs, then the default developmental program is able to generate the characteristic bristles on T2 legs.

In the cells that give rise to the preapical bristle, *Ubx* function plays a subtler role than the simple repressive action that it exerts in the cellular primordia of the apical bristle. Normally, the preapical bristle is stout on T2 and fine on T3, but in *Ubx* mutants the bristle is stout on both T2 and T3. By ectopically expressing *Ubx* in the sensory organ lineage, Rozowski and Akam [2] were able to transform the stout shaft of a normal preapical bristle on T2 to the much finer shaft of the preapical bristle of T3. When comparing the stout apical bristle versus the fine preapical bristle on the same T3 leg, one obvious possibility is that differences in amounts of Ubx protein between the T3 apical and preapical primordia might confer the

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difference between thick and thin bristle development. However, Rozowski and Akam's evidence [2] indicates that this different outcome is not due to a difference in *Ubx* protein levels. They find that the response of apical and pre-apical precursors to *Ubx* is intrinsically different, with *Ubx* subtly modulating the differentiation of the bristle shaft cell in a context-dependent manner (Figure 1).

Thus, it seems that specific effects of *Ubx* depend on local context and precise timing — on local fine-grain reading of patterning information from other transcription factors and signaling molecules, which modify bristle development by acting combinatorially on still unknown bristle cell-lineage target genes. Rozowski and Akam [2] also conclude that *Ubx* effects on bristle morphology do not appear to be constrained evolutionarily, or strongly canalized, as *Ubx* has evolved to repress bristle development by apparently using different mechanisms in two different regions of the leg disc.

Brodu and colleagues [3] also characterized a *Hox* function at single cell resolution: the control of larval oenocyte development by the *Hox* gene *abdominal A* (*abdA*). Oenocytes are specialized secretory cells restricted to the larval abdominal segments [6], which are recruited from the dorsal embryonic ectoderm by a local induction involving epidermal growth factor (EGF) receptor activation [7] (Figure 2). The ligand for EGF receptor, secreted Spitz (sSpi), is made by a chordotonal organ precursor, the C1 cell that lies adjacent to the presumptive oenocyte [6] (Figure 2). Brodu *et al.* [3] showed that oenocyte formation is selectively and transiently under the positive control of the *Hox* gene *abdA*, a function that could not be substituted for by the closely related *Ubx* gene.

The distinct functions of Ubx and AbdA in this instance are remarkable, as AbdA and Ubx proteins have highly overlapping functions during development — for example, they have equivalent biological activities in promoting haltere formation [8]. Although absolutely required for oenocyte development, *abdA* function is not required in oenocytes themselves. Brodu *et al.* [3] showed in a series of elegant misexpression and mutant rescue experiments that *abd-A* works by briefly prolonging the transcription of *rhomboid* (*rho*) in C1 cells (Figure 2). Rhomboid protein then provides local processing for the Spitz EGF receptor ligand [9]. Remarkably, the expression of *rhomboid* alone in C1 cells can rescue the oenocyte-inducing function of AbdA! Of course, the responding cells in the embryonic ectoderm also require localized factors to prime them to form oenocytes, and one crucial component of this prepattern is the zinc-finger transcription factor Spalt. In the absence of Spalt, sSpi signaling no longer induces oenocytes, but secondary chordotonal organs [7,10].

A common thread linking these two studies [2,3] is that morphological and transcriptional responses to *Hox* genes can be highly local, sometimes only in a single cell, allowing one *Hox* gene to control a cavalcade of different traits within one segment and between different segments, depending on the information present. Another important lesson that we can learn

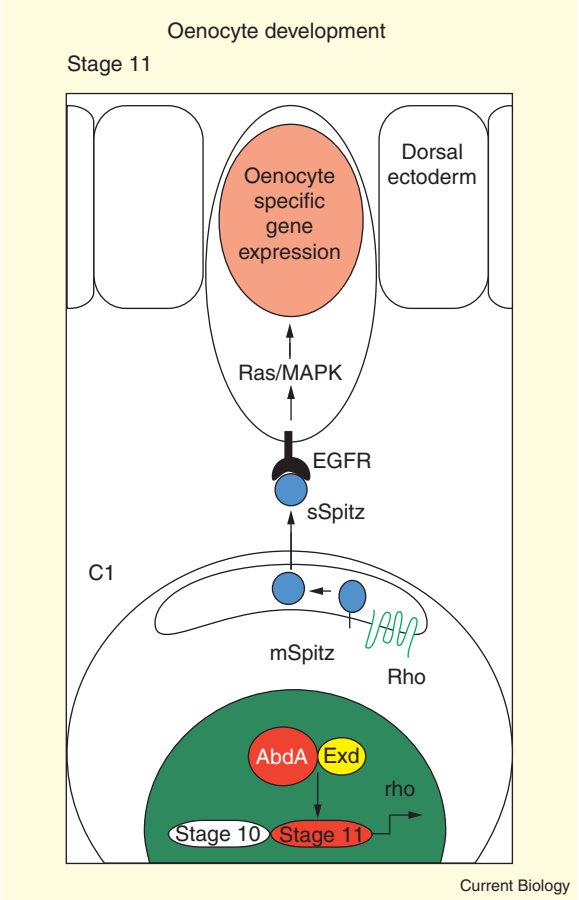

Figure 2. *abd-A* is necessary for the development of oenocytes in the abdomen of *Drosophila* embryos.

abd-A and *exd* genetic functions are required to maintain transcription of *rhomboid* (*rho*) in the chordotonal organ precursor (C1) past stage 10, thus keeping secreted Spitz (sSpi) available to activate the EGF receptor in the responding dorsal ectoderm, leading to the activation of the oenocyte specific gene expression in a competent, *spalt*-expressing ectodermal cell. (Adapted from [3].)

from the papers of Rozowski and Akam [2] and Brodu *et al.* [3] is that, during development, *Hox* genes act at all levels in the developmental hierarchy. If they act very far down in the hierarchy, as in these two cases, then the output is subtle, with *Hox* genes acting as cell-type switches rather than as major developmental pathway switches. If they are acting (apparently) far up in the hierarchy, then the fate switch is more dramatic, which is most beautifully demonstrated in the famous four-winged fly [11]. But even at this general level, context is still crucial: loss of *Ubx* in the haltere does not generate a leg, but a wing.

Finally, Brodu *et al.* [3], extrapolating from their finding that *abdA* needs only the *rhomboid* target gene to effect its oenocyte inducing function, make a sweeping and provocative proposal. That most or all functions of *Hox* genes, at the level of one or a few cells, are mediated by only one or a few critical target genes, which would then execute a specific response, which may be dramatic or subtle depending on where

in the developmental hierarchy the *Hox* target gene lies. This notion is not completely without precedent [12], but differs from the usual idea that hundreds of genes are targeted by *Hox* genes in a given tissue [13]. In the view of Brodu *et al.* [3], most of the previously observed downstream complexity would largely arise from cell-to-cell heterogeneity and from indirect regulation through cell signaling. If this turns out to be generally true, the use of genome-wide approaches like microarrays to identify biological relevant target genes of *Hox* genes using whole animals, or even specific tissues, might be extraordinarily limited.

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