Ultrabithorax regulates genes at several levels of the wing-patterning hierarchy to shape the development of the Drosophila haltere

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Arthropods and vertebrates are constructed of many serially homologous structures whose individual patterns are regulated by Hox genes. The Hox-regulated target genes and developmental pathways that determine the morphological differences between any homologous structures are not known. The differentiation of the Drosophila haltere from the wing through the action of the Ultrabithorax (Ubx) gene is a classic example of Hox regulation of serial homology, although no Ubx-regulated genes in the haltere have been identified previously. Here, we show that Ubx represses the expression of the Wingless (Wg) signaling protein and a subset of Wg- and Decapentaplegic-activated genes such as spalt-related, vestigial, Serum Response Factor, and achaete-scute, whose products regulate morphological features that differ between the wing and haltere. In addition, we found that some genes in the same developmental pathway are independently regulated by Ubx. Our results suggest that Ubx, and Hox genes in general, independently and selectively regulate genes that act at many levels of regulatory hierarchies to shape the differential development of serially homologous structures.

[Key Words: Ultrabithorax; haltere; development; Drosophila; serial homology]

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Hox genes and serial homology

Figure 1. Ubx controls the differential development of the haltere. The wild-type wing (A) and haltere (B) differ in size, shape, and the presence of veins and margin bristles. (C,D) Antibody staining of third instar wing and haltere discs. (C) Ubx expression (red) in the wing disc is limited to the peripodial membrane and is not necessary for proper wing development (Struhl 1982). (D) Ubx expression fills the haltere disc, with strongest expression in the “pouch”, which will give rise to capitellar tissue (Beachy et al. 1985). Reduction of Ubx activity in the haltere leads to transformations toward wing identity. (E) Haltere from a Ubx<sup>CbxM1</sup> wing disc (Kerridge and Morata 1982), in which Ubx gene activity is <50% of wild-type (shown at the same magnification as B). A large number of ectopic margin bristles appear on the haltere, which is increased in size. (F) Total loss of Ubx activity in the developing haltere results in a complete transformation toward wing identity (Lewis 1978). Black scale bars, 0.25 mm; white scale bars, 0.2 mm.

nisms that govern the formation and patterning of the insect wing has created the opportunity to identify genes that are regulated differently between wings and halteres. In the Drosophila wing disc, growth and patterning are organized by the Decapentaplegic (Dpp) and Wingless (Wg) long-range signaling proteins (for review, see Serrano and O’Farrell 1997), which are produced by cells along the anteroposterior (AP) and dorsoventral (DV) compartment boundaries, respectively, and organize growth and patterning via the regulation of numerous downstream wing-patterning target genes. The expression of Dpp and Wg is regulated by the short-range signaling proteins Hedgehog (Hh) and Serrate (Ser), which are in turn regulated by the posterior engrailed (en) and dorsal ateruous (ap) selector genes (for review, see Burke and Basler 1997; Irvine and Vogt 1997; Neumann and Cohen 1997a).

We have investigated how Ubx modifies a wing field into a haltere field by focusing on these global signaling systems and their target genes. We discovered that Ubx regulates the expression of the Wg signaling protein, selected Dpp- and Wg-activated target genes or cis-regulatory elements, and genes that are further downstream of Ubx-regulated genes. We also examined whether the ectopic expression of these genes was sufficient to induce wing-like characters on the haltere. Our findings reveal that Ubx represses haltere development by independently regulating selected genes that act at different levels of the wing patterning hierarchy.

Results

The anteroposterior axis: Ubx represses selected Dpp target genes

The expression pattern of en is essentially the same in the haltere disc as in the wing disc (Fig. 2A,B), indicating that Ubx is not regulating haltere identity by altering the expression of this compartmental selector gene. Similarly, the expression of dpp in the developing haltere on the anterior side of the AP compartment boundary resembles that in the wing disc (Fig. 2A,B). Because these discs give rise to very different appendages, there may be genes downstream of the Dpp signal that are regulated by Ubx. To identify these, we examined how a number of genes involved in the development of specific wing characters are expressed and regulated in the developing haltere.

Dpp acts as a morphogen from its source to organize wing growth, AP pattern, and to activate target gene expression over a distance. The optomotor blind (omb), spalt (sal), and spalt related (salr) genes are expressed in nested patterns centered on the Dpp stripe and are necessary for proper development of the central wing region including veins II–IV (de Celis et al. 1996; Grimm and Pflugfelder 1996; Lecuit et al. 1996; Nellen et al. 1996; Sturtevant et al. 1997). We examined the expression of these Dpp target genes in the haltere disc and found that although omb is expressed in the developing haltere pouch straddling the Dpp stripe as it does in the wing disc (Fig. 2C), sal and salr are not expressed in the haltere pouch (Fig. 2D; data not shown). These results show that the Dpp signal transduction machinery operates in the haltere disc but that selected wing target genes are not activated by the Dpp signal.

To determine whether Ubx represses salr expression in the haltere disc, we generated homozygous Ubx<sup>−/−</sup> clones. Indeed, salr is derepressed in Ubx<sup>−/−</sup> clones in the anterior compartment of the haltere disc. As in the wing disc, salr expression in these clones depended on their distance from the Dpp source (Fig. 2E). To determine whether Ubx is sufficient to repress salr, we examined salr expression in Cbx<sup>−/−</sup>/+ wing discs in which Ubx is ectopically expressed along part of the DV boundary. In these wing discs salr expression is repressed in a cell autonomous fashion (Fig. 2F). Because sal/salr are required for the induction of vein development (Sturtevant et al. 1997), the selective repression of salr by Ubx suppresses part of the Dpp-mediated AP wing patterning program in the haltere.

As with the spatial patterning of wing veins, the pattern of intervein tissue is also determined by specific
regulatory genes and critical for morphogenesis. The Drosophila Serum Response Factor (DSRF or blistered) gene is expressed in future intervein tissue and required for the adhesion of the dorsal and ventral surfaces of the flat wing (Montagne et al. 1996). The haltere, however, is more balloon-like and, interestingly, DSRF expression is absent from the halttere pouch except for two crescents at the extreme dorsal and ventral edges of the anterior compartment (Fig. 2G). This difference is caused by Ubx expression patterns are similar in the wing (A) and halttere (B). (C) om expression (blue, visualized by a lacZ reporter transgene) is found in the halttere disc (right) in a pattern similar to that found in the wing (left), indicating that Dpp signaling is not repressed by Ubx. (D–F) Antbody staining detecting Salr is shown in green; Ubx is shown in red. (D) Salr expression in a wing disc (left) and in a halttere disc (right). Salr is not expressed in the halttere pouch, indicating that this Dpp target gene is repressed by Ubx. (E) Ubx− clones close to the AP boundary shows cell-autonomous derepression of Salr expression (arrowhead). Ubx− clones more than eight cells anterior to the AP boundary and posterior clones do not show Salr derepression (not shown). (F) Ectopic Ubx expression in a Cbx431 heterozygous wing pouch represses Salr expression in a cell autonomous fashion (arrows). (G–I) antibody staining detecting DSRF is shown in green; Ubx is shown in red. (G, left), DSRF is expressed in the future intervein cells of the Drosophila wing imaginal disc. (right) Expression of DSRF in the halttere is limited to extreme ventral and dorsal crescents in the pouch, and is also present in pedicellar and notal portions of the disc. (H) Ubx− clone in the halttere (lack of red staining) showing DSRF derepression in the halttere pouch in a cell-autonomous manner. A winglike pattern forms in the clone, whereas the halttere expression pattern is still visible where Ubx is expressed (yellow overlap). (I) Ectopic Ubx expression in a Cbx431+/wing disc represses a portion (ventral intervein D) of the normal DSRF expression (arrow). Note that om expression does not extend into the posterior of the halttere nearly as far as it does in the anterior (Fig. 2C), and Salr expression is not derepressed in posterior Ubx− clones close to the AP boundary (not shown) which suggests that Dpp signaling may somehow be reduced in the posterior halttere disc.

However, we found that Wg, which is expressed along both the anterior and posterior extent of the DV boundary in the wing disc (Fig. 3A), is not expressed in the posterior compartment of the halttere disc (Fig. 3B). Because Wg function along the DV boundary is required for growth and patterning of the wing disc (Couso et al. 1994; Diaz-Benjumea and Cohen 1995; Zecca et al. 1996; Neumann and Cohen 1997b), the absence of Wg in the posterior halttere disc probably contributes to its disproportionately smaller size in comparison to the anterior compartment. In posterior Ubx− clones in the halttere disc, Wg is expressed along the DV boundary (Fig. 3C), suggesting that Ubx represses the posterior portion of the Wg expression pattern. The activation of Wg along the DV boundary occurs via the Notch receptor signaling pathway (Diaz-Benjumea and Cohen 1995; Kim et al. 1995). This pathway also activates the “boundary” enhancer of the vg gene (Kim et al. 1996), which is activated along the entire anterior and posterior extent of the DV boundary in the halttere (Fig. 4A). These results demonstrate that the Notch pathway is active along the entire DV boundary but that Ubx selectively prevents Wg activation by this pathway in the posterior compartment.

The dorsoventral axis: Ubx represses Wg in the posterior compartment and selectively represses genes along the DV boundary

It has been long assumed that the global coordinate systems in homologous appendages are the same and, indeed, the ap selector gene is expressed in the dorsal compartment of the halttere disc as in the wing (Fig. 3A,B).
Wg is expressed in the anterior compartment of the haltere disc, yet its phenotypic effects are markedly different than in the anterior of the wing disc. The most conspicuous difference is that in the wing, Wg activity along the DV boundary induces the formation of the prominent triple and double rows of bristles along the wing margin, whereas in the haltere it does not. The formation of margin bristles is regulated by Wg via the induction of the proneural \textit{achaete} (\textit{ac}) and \textit{scute} (\textit{sc}) target genes (Fig. 3D) and also requires the Cut transcription factor (Couso et al. 1994; Neumann and Cohen 1996). In the haltere disc, Cut is expressed along the anterior DV boundary (data not shown), whereas \textit{ac} and \textit{sc} are not induced (Fig. 3D).

To determine if Ubx represses \textit{ac/sc} activation by Wg, we examined \textit{Ubx-} clones. In the haltere disc, \textit{sc} expression is derepressed in clones that touch or cross the anterior portion of the DV boundary (Fig. 3E). Conversely, \textit{sc} expression is lost in anterior wing disc cells that ectopically express Ubx (Fig. 3F). This repression by Ubx is sensitive to the dosage of Ubx activity as ectopic \textit{ac/sc} expression is observed in \textit{Ubx}+/− haltere discs (data not shown). This ectopic expression corresponds with ectopic bristles found on the halteres of \textit{Ubx}+/− adults.

**Figure 3.** Ubx represses selected genes along the DV boundary of the haltere disc. (A–C) Antibody staining detecting Wg (green); Ap (purple), Ubx (red). (A, B) Ap and Wg are expressed in a similar domain in the haltere (B) as in the wing (A), but Wg expression is absent from the posterior haltere (bracket). (C) Haltere disc with several Ubx− clones (lack of red staining). A posterior clone, located along the DV boundary (arrow) shows derepression of Wg expression. (D–H) Antibody staining detecting Sc (green); Ubx (red). (D) Wild-type expression of Sc in the wing (left) and haltere (right) disc pouches. The double row of expression in sensory organ precursors along the future wing margin (asterisks) is absent from the haltere disc. In the haltere disc, Sc is also expressed in unique patterns including the pedicellar region (arrowhead). (E) Haltere disc with two dorsal Ubx− clones that each touch the DV boundary. The anterior (arrow) clone shows derepression of Sc expression; the posterior (arrowhead) clone shows no Sc expression as in the posterior of the wing. (F) Ubx expression along the DV boundary of a Cbx+/+ wing disc represses Sc expression along the presumptive anterior wing margin (arrows). (G) Ubx+/−/+ haltere disc showing ectopic Sc expression along the anterior DV boundary. (H) Ubx− clone (arrow) crossing into the pedicellar region of the haltere disc (see arrowhead in D) fails to activate the normal Sc expression there indicating that Ubx is necessary for activation of Sc in the pedicellar region of the haltere.
ther reductions of Ubx function in haltere discs causes greater derepression of sc on the DV boundary (Fig. 3G) and a corresponding emergence of triple row bristles on the adult haltere (Fig. 1E).

The haltere has several types of sense organs, including the proximally located pedicellar sensillae, that are not present on the wing. Correspondingly, sc is expressed in the presumptive pedicellar portion of the haltere disc but not in the equivalent part of the wing disc (Fig. 3D, arrowhead). Importantly, we found that in Ubx− clones in this region of the haltere disc, sc expression is lost (Fig. 3H). Therefore, Ubx is required to positively regulate sc in this unique pattern in the haltere disc. Together with the repression of sc along the DV boundary of the haltere, these observations suggest that Ubx acts upon two independent domains of the sc expression pattern, presumably via specific cis-regulatory elements controlling each aspect of sc gene expression.

The proximodistal axis: Ubx selectively represses one enhancer of the vestigial gene

We first examined the effects of ectopic expression of the vg gene in the haltere and other tissues under the control of the GAL4/UAS system (Brand and Perrimon 1993; Kim et al. 1996). Whereas vg expression in all other appendages and tissues causes wing-like outgrowths (Kim et al. 1996), in the haltere we did not observe any significant change in adult appendage size or morphology. We did, however, observe striking differences between the morphology of the outgrowths formed on the second and third thoracic legs (Fig. 5). The former had clear wing-like morphology (Fig. 5A), whereas the latter had haltere-like morphology (Fig. 5B). The failure of ectopic vg expression to significantly alter haltere morphology and the distinct haltere-like character of the outgrowths formed in third thoracic legs suggests that Ubx acts on genes that are downstream of or parallel to vg in the genetic hierarchy.

To test whether Ubx regulates genes downstream of vg, we first searched for candidate genes whose expression depended upon Vg. We found that the sal (Fig. 5C, D) and DSRF (not shown) genes that are normally not expressed in leg imaginal discs are ectopically induced in first and second thoracic leg imaginal discs as a response to targeted expression of Vg and may thus be activated in the developing wing through some mechanism that is dependent upon Vg. The patterns of ectopic induction of sal and DSRF (not shown) in T1 and T2 leg discs are reminiscent of their normal expression patterns in wing discs (cf. Figs. 5D and 2D). In contrast to T3 leg discs, which also express Ubx, the central domains of ectopic induction of Sal and DSRF expression are suppressed (cf. Fig. 5E with Figs. 5D and 2D). These results demonstrate that downstream targets of Vg are also regulated by Ubx, independent of the Ubx regulation of Vg itself. The repression of these and other targets by Ubx would then suggest why the deregulation of Vg expression in the
developing haltere is insufficient to reprogram haltere development towards wing development and to alter the morphology of the adult haltere.

Similarly, ectopic expression of the DSRF (not shown) or Sal (M. Averof, pers. comm.) transcription factors also do not alter haltere size, shape, or cell morphology. These results imply that there are genes downstream of DSRF and Sal whose expressions are necessary for the realization of a phenotype but which are repressed by Ubx in the haltere disc.

In contrast, ectopic expression of the sc gene in the developing haltere is sufficient to induce ectopic sensory organs (Fig. 5F). Interestingly, near the DV boundary, large bristles resembling those of the wing margin are induced (Fig. 5, cf. K with F and I), whereas in more proximal regions, sense organs characteristic of the haltere form (Fig. 5, cf. J and H). This result suggests that the repression of sensory organ formation by Ubx at the DV boundary is largely at the level of the sc gene, whereas the character of the proximal sense organs is modified by Ubx action downstream of or parallel to scute. Thus, all three outcomes outlined above are obtained in these ectopic expression experiments which reveal that Ubx acts independently upon the five genes we have identified as well as upon genes further downstream of or parallel to these regulators in the wing patterning hierarchy.

**Discussion**

The differentiation of the *Drosophila* haltere from the wing through the action of the Ubx gene is a classic example of Hox regulation of serial homology, and has served as the paradigm for understanding the nature of homoeotic gene function (Lewis 1963; Garcia-Bellido 1975; Morata and Garcia-Bellido 1976; Lewis 1978). This study reveals several features of the control of haltere development by Ubx which, in principle, are likely to apply to the Hox-regulated differential development of other serially homologous structures in other animals. Specifically, we have shown that Ubx acts: (1) at many levels of regulatory hierarchies, upon long-range signaling proteins, their target genes, as well as genes further downstream, (2) selectively upon a subset of downstream target genes of signals common to both wing and haltere, and (3) independently upon these diverse targets. Below, we discuss these features of the Ubx-regulated gene hierarchy in the haltere and how they expand our general understanding of the Hox-regulated development of homologous structures.

The architecture of the Ubx-regulated gene hierarchy in the haltere

Ubx acts at many levels of wing patterning hierarchy. Unexpectedly, Ubx does not act solely on genes...
that are downstream of the global coordinate systems, but also regulates the expression of at least one global organizing signal. Along the DV boundary, Ubx represses the expression of the Wg signal in the posterior of the haltere field (Fig. 6). Ubx also regulates genes downstream of Wg, for example, the sc proneural gene, and downstream of the Dpp signal including salr and the vg quadrant enhancer (Fig. 6). Ubx must also control genes downstream of or parallel to Vg, DSRF, and Sal because the ectopic expression of these genes is not sufficient to alter haltere size or cell morphology (Fig. 6).

Ubx acts on a selected subset of genes downstream of the global organizing signals. We found that the Wg, Dpp, and Notch signal transduction pathways are active and competent throughout the haltere field and that Ubx selectively prevents activation of targets of these pathways. For example, Ubx prevents Notch-mediated Wg activation but not vg boundary activation on the DV boundary in the posterior of the haltere. Similarly, Ubx represses Dpp-mediated activation of salr and the vg quadrant enhancer, but not of the omb gene. Repression is therefore gene or enhancer-specific, not pathway-specific.

Ubx acts independently on target genes at different levels of the wing patterning hierarchy. The picture emerging from this work is that there are different tiers of target genes that are regulated by Ubx independently of each other. For example, Ubx represses the expression of the vg quadrant enhancer and two downstream targets of Vg, salr and DSRF, in the haltere. However, the repression of salr and DSRF is independent of the repression of vg because ectopic expression of Vg cannot induce salr or DSRF when Ubx is present (Fig. 5). Similarly, the repression of scute in the anterior of the haltere is independent of the repression of Wg.

The independent regulation of these five genes or enhancers by Ubx may be either direct or indirect. Several observations are more consistent with direct control by Ubx. First, we have shown that the long-range signals and/or signal transduction pathways that are the activators of these genes operate in the haltere. The simplest explanation for the repression of Wg, salr, DSRF, sc, and the vg quadrant enhancer is that Ubx is directly blocking their activation by these pathways. Second, the cell autonomy of the derepression of these target genes in Ubx− clones in the haltere and of their repression by ectopic Ubx in the wing disc show that Ubx is both necessary and sufficient for the differential regulation of these genes in individual cells. And third, the effects of reduced Ubx gene dosage on ac/sc and vg quadrant enhancer expression demonstrate that repression of these genes is operating near a threshold, which is also consistent with a direct control.

Regardless of whether Ubx regulation of any individual gene is direct or not, the independent regulation of these target genes by Ubx has several important implications. First, because there is independent regulation of genes at different levels of the same pathway, it reveals that Ubx is not acting on just a few genes at the top of regulatory hierarchies. Second, it explains why the deregulation of any individual Ubx target gene may be insufficient to transform particular haltere characters towards the wing. That is, it is difficult to break the grip of Ubx repression of wing characters because repression is operating on genes at multiple levels. And third, for repression to operate at these different levels, it implies that the evolution of the haltere progressed through the accumulation of a complex network of Ubx-regulated interactions.

**Regulatory hierarchies and evolution**

One unpredictable and very informative finding of this work was that the ectopic expression of certain Ubx-regulated genes that have fairly dramatic effects on other tissues did not perturb haltere development. One con-
clusion that might be drawn from these results is that the repression of these genes is not significant for haltere development. Yet, there is no doubt that the Ubx-regulated genes we have identified are developmentally significant in that they are required for the formation or patterning of major wing characters. Furthermore, the repression of their expression in the haltere disc correlates with the differences in size (Wg in the posterior, Vg in the "pouch"), venation (Sal-r), shape (DSRF), and sensory organs (Sc) between the Drosophila forewing and haltere. An alternative to the interpretation that the regulation of these genes is insignificant to the haltere is that some developmental pathways in the haltere are "canalized". This concept, forwarded by Waddington in the 1940s (Waddington 1941, 1956, 1960), recognized that regulatory interactions in developmental processes may constrain the extent or direction of morphological change in response to environmental or genetic perturbation. In evolutionary terms, canalization is an example of "developmental constraint" for which there has been considerable comparative but relatively little experimental evidence (Maynard-Smith et al. 1985).

An explanation for the canalization of certain developmental pathways in the haltere may lie in the evolution and architecture of the Ubx-regulated hierarchies. The evolution of the haltere was a gradual transformation of a full-sized hindwing into a balancing organ, involving the modification, reduction, or elimination of many characters. If we consider just one feature, such as the relative size of the flight appendage, we can extrapolate from mutational studies to infer that there were many genes and pathways upon which selection could act to reduce the size of the hindwing. It is likely that the reduction of hindwing cell number and volume involved changes in the regulation of multiple genes acting at different developmental stages (with the vg and wg genes being two of many potentially affected genes). If Ubx regulation thus evolved at many loci, then we should find that perturbation of single genes in these networks may have no overt effects. Although it is not obvious why Ubx regulation would be maintained on targets whose derepression has no clear consequences, we must acknowledge that our resolution in these experiments is relatively low and we may not be able to perceive minor effects. Over evolutionary time selection against even the slightest deleterious effects that may arise from derepression of target genes would stabilize Ubx repression throughout a hierarchy.

Materials and methods

Clonal analysis and immunohistochemistry

The null allele (Kerridge and Morata 1982) Ubx(6-28) was used to make mitotic clones in developing halteres. In Figures 2 and 3 clones were generated by heat-shock induction of FLP recombinase (Ku and Rubin 1993) in hsFLP122; P[ry⁺, hs-neo, FRT] 82B, Ubx(6-28)/P[ry⁺, hs-neo FRT] 82B, P[mini-w⁺, hsM] 87E flies. The Ubx⁺ clones in Figure 4 were generated by exposing vg(w¹¹^ey) / Ubx(6-28)-fly to γ-rays (4000 rads). Antibodies were provided by M. Affolter (DSRF) (Biozentrum, Basel, Switzerland), R. Barrio (Sal-r) (EMBL, Heidelberg, Germany), S. Cumberledge (Wg) (University of Massachusetts, Amherst), N. Patel (En) (University of Chicago, IL), J. Skeath (Sc) (Washington University, St. Louis, MO), and R. White (Ubx) (Cambridge University, UK). Immunohistochemistry was performed as previously described (Carroll et al. 1995).

Targeted expression of regulatory genes

Vg and Sc were ectopically expressed by means of the GAL4 system (Brand and Perrimon 1993). Using a Distal-less (DII)-GAL4 driver that directs ectopic expression in a large area of the developing leg including the region distal to the presumptive tibia ectopic, Vg expression was examined in developing leg discs. Ectopic expression of Sc in the wing and haltere was targeted by the Decapentaplegic (Dpp)-GAL4 driver that directs ectopic expression along the AP boundary of imaginal discs.

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