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DEVELOPMENT

Mutual collaboration

Hox proteins have been described as the 'master regulators' of body patterning, but how they selectively activate or repress target genes in different tissues is poorly understood. New work reveals how Hox proteins might achieve this through 'collaboration'— co-regulation of a target gene without a direct interaction — with cofactors such as Smads.

Ultrabithorax (UBX) is the sole Hox protein that controls differentiation in the fly haltere imaginal disc, where its loss results in transformation into a wing. *spalt* (*sal*, also known as *spalt major*) is directly repressed by UBX in the haltere disc; by contrast, it is activated in the wing disc through decapentaplegic signalling, which requires the Smad protein Mothers against decapentaplegic (MAD). However, *sal* was shown to be expressed in the haltere discs in some *Mad* mutant clones, suggesting that *sal* is normally repressed by MAD in the haltere.

MAD interacts directly with its co-Smad, Medea (MED), and together they recruit a co-repressor, Schnurri (SHN), to target genes. *sal* was also derepressed in *Med* and *shn* hypomorphic clones, indicating that all three are essential for *sal* repression in the haltere.

Examination of the *sal cis*-regulatory element (CRE), *sal*1.1, revealed a putative MED–MAD binding site located close to two UBX binding sites. Point mutations in this MED–MAD site reduced the binding of a MAD–GST fusion protein. Furthermore, derepression of a *sal*1.1–lacZ reporter in transgenic flies correlated with the reduction in MAD–GST binding for each point mutation.

Mutations in the MED–MAD or UBX binding sites, or both, caused equivalent derepression of the *sal* CRE, and loss of binding of either component did not affect that of the other — so MED–MAD and UBX are equally required, rather than acting additively. However, there was no evidence for a physical interaction between MED–MAD–SHN and UBX, and moving the UBX binding sites away from the MED–MAD site similarly abolished repression of *sal*1.1. Comparison of the *sal* CRE between *Drosophila* species revealed a perfectly conserved 37-bp region encompassing the binding sites — striking evidence that this strict topology has been evolutionarily conserved.

The authors suggest that, rather than being master regulators, Hox proteins might generally rely on collaborations with cofactors that are actually responsible for directing gene expression, a mechanism that could be far more widespread previously thought.

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ORIGINAL RESEARCH PAPER Walsh, C. M. & Carroll, S. B. Collaboration between Smads and a Hox protein in target gene repression. *Development* **134**, 3585–3592 (2007)