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DEVELOPMENT

Deciphering the Wingless gradient

A key principle of developmental biology is that during pattern formation, a cell detects the local concentration of a morphogen within a gradient, which guides the cell down the appropriate differentiation pathway. But how can such simple information reliably activate the range of intricate signalling pathways required to pattern a complex structure?

A recent study by Piddini and Vincent shows that, in *Drosophila melanogaster*, the Wingless (Wg) morphogen does more than just trigger gene expression in a dose-dependent fashion. It also activates two non-autonomous inhibitory pathways that modulate the reaction of surrounding cells to the Wg signal, thereby enhancing their ability to recognize their position within the Wg gradient.

The authors used models in which the Wg signal was disrupted in all or parts of the *D. melanogaster* imaginal disc and looked at the expression of Wg target genes. These targets included *dll* (which is induced by mid to low Wg levels at the first to second instar) and *sens* (which is induced by high Wg levels at the third instar).

When the Wg signal was gradually depleted across the whole imaginal disc, so that it was absent by the end of the third larval instar, *dll* expression was largely unaffected. This shows that, once it is established, *dll* expression is maintained in the absence of Wg. However, expression of *sens* was fully depleted in these models, showing that *sens* expression requires continuous Wg signalling.

The authors also looked at what happened when Wg signalling was overactivated in a mosaic fashion. In discs with small patches of high-signalling cells among wild-type (WT) cells, *dll* expression was expressed normally in most WT cells; however, *dll* expression was reduced in WT cells directly adjacent to cells undergoing high Wg signalling activity. In mosaic discs with large patches of high-signalling cells, *dll* expression was reduced in most WT cells and *sens* expression was completely absent in all WT cells. Excess Wg signalling inhibited the expression of *dll* and *sens* in neighbouring WT cells, indicating that these Wg target genes are sensitive to a non-autonomous negative-feedback mechanism that is activated as a result of Wg signal transduction.

One candidate for this negative signal was Notum, a phospholipase that is an inhibitor of Wg signalling. The authors used the same mosaic disc model described above, but the Wg-overexpressing cells were also depleted of Notum through RNA interference. *sens* expression was restored in WT cells, showing that Notum is required to suppress *sens* expression. However, *dll* expression was not restored in the WT cells: an additional signal must therefore be responsible for the observed *dll* suppression. The authors suggest that this second signal could be mediated by a secreted protein or by a more subtle influence, such as mechanical tension.

This study highlights one case in which the final cellular response to a patterning signal is modulated by secondary cell interactions. Such mechanisms may operate in other developmental scenarios to achieve the striking precision observed in patterning processes.

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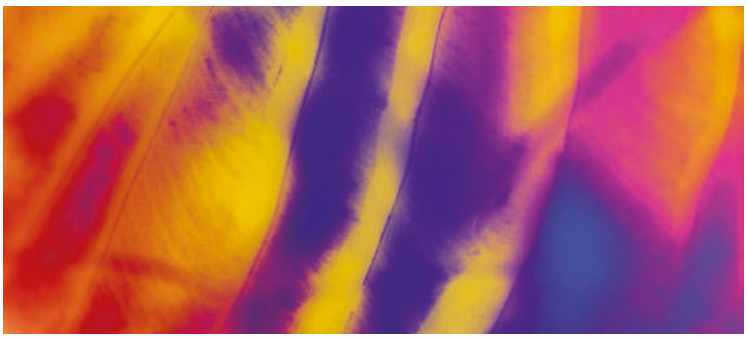

ORIGINAL PAPER Piddini, E. & Vincent, J.-P. Interpretation of the Wingless gradient requires signaling-induced self-inhibition. *Cell* **136**, 396–307 (2009)
FURTHER READING Hausmann, G. *et al.* Helping Wingless take flight: how WNT proteins are secreted. *Nature Rev. Mol. Cell Biol.* **8**, 331–336 (2007)