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DEVELOPMENTAL BIOLOGY

Retinoic acid passes the morphogen test

Retinoic acid (RA) is one of several molecules that pattern vertebrate embryos by forming an anterior to posterior (A–P) concentration gradient. The issue of whether RA is a classical morphogen is controversial. Is it merely permissive for specifying cellular fates, or does it actually determine those fates? And how is the gradient modulated? Genetic and modelling studies have produced a more complete understanding of the RA gradient by describing how it is maintained and how it is coordinated with other pathways.

Classical morphogens specify cell fate in a concentration-dependent manner — cells read their position in the gradient and differentiate accordingly. Although there is evidence that this is true for RA, it has also been suggested that RA has only a permissive function: it merely gives cells a licence to differentiate into cell types that have already been specified by other means. White and colleagues sought to clarify these conflicting data by studying how the RA gradient patterns the zebrafish hindbrain.

The authors first examined the induction of either endogenous RA target genes or reporter genes placed under the control of RA-responsive elements and expressed when exogenous sources of RA are applied. The response was indeed graded along the A–P axis and dose-dependent. The fact that normal A–P patterning can occur even when embryos are bathed in a uniform concentration of RA (below a certain threshold) means that a mechanism is in place to maintain a stable RA gradient. The mechanism responsible is the activity of an RA-degrading enzyme, Cyp26a1, and the authors show that this gene is activated by RA itself. Why, then, does *cyp26a1* expression decline posteriorly, where RA concentration is in fact highest?

This paradox was resolved by invoking that *cyp26a1* is under another form of control. A candidate for modulating the relationship between RA and its degrading enzyme is fibroblast growth factor (Fgf) — indeed, when all Fgf signalling was eliminated from the embryo, expression of *cyp26a1* shifted posteriorly. These results suggest a model in which the RA gradient is under two opposing influences: a feedback relationship with a locally acting, RA-induced degradation enzyme, and a feed-forward one in which Fgf represses RA degradation.

To understand the implications of these relationships, the authors devised a mathematical model of RA dynamics in the gastrula embryo. Under biologically plausible concentrations of RA, the model revealed a robust RA gradient — in practice, this means that fluctuations in RA concentration would be buffered by its control of *cyp26a1*. The model also highlights the developmental importance of linking Fgf to RA degradation: thanks to this relationship, RA concentration can be coupled to the Fgf gradient as it expands when the embryo elongates.

So, is RA a classical morphogen? Yes, although a better way of looking at it would be to consider Fgf and RA as a single, integrated morphogen system. Given that RA and the Fgf pathway are also interrelated in other organs, it will be interesting to find out whether similar regulatory loops hold in other cell types and for other signalling pathways.

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ORIGINAL RESEARCH PAPER White, R. J. *et al.* Complex regulation of *cyp26a1* creates a robust retinoic acid gradient in the zebrafish embryo. *PLoS Biol.* **5**, e304 (2007)
FURTHER READING Tomlin, C. J. & Axelrod, J. D. Biology by numbers: mathematical modelling in developmental biology. *Nature Rev. Genet.* **8**, 331–340 (2007)