Developmental Patterning of the Vertebrate Limb

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A COMPARISON OF REACTION DIFFUSION AND MECHANOCHEMICAL MODELS FOR LIMB DEVELOPMENT

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Several theoretical models have been proposed to attempt to elucidate the underlying mechanisms involved in the spatial patterning of skeletal elements in the limb. Here, I briefly compare two such models - reaction diffusion (RD) and mechanochemical (MC) - and highlight their properties and predictions.

Although similar mathematically, these models are based on fundamentally different biological approaches. RD theory asserts that a chemical prepattern is first set up in the limb by a system of reacting and diffusing chemicals (Turing, 1952). Cells then respond to this prepattern by differentiating wherever the concentration of one of the chemicals lies above a threshold value (Wolpert, 1969, 1981). Thus, the spatial pattern of chemical concentration is reflected by the spatial pattern of cell differentiation.

The MC theory (Oster et.al., 1983, Oster et.al., 1985) proposes that the mechanical and chemical interactions of cells with their external environment - the extracellular matrix - leads to a spatial pattern in cell density. The cells in the aggregates thus formed differentiate. Thus, the spatial pattern of cell differentiation overlies the spatial pattern of cell density.

The spatial patterns predicted by both RD and MC theory, from linear analysis, are essentially the eigenfunctions of the Laplacian operator (Maini and Solursh, 1990). The more complex tensor form of the MC model may lead to a richer set of structures than those exhibited by RD models. This possibility has yet to be analysed. Thus, at the moment, one cannot distinguish between these models on a purely mathematical basis.

The similarity of the mathematical formulation of the above hypotheses does, however, enable one to make some general predictions on the properties of the skeletal pattern in the limb independent of the biological basis of the model. For

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example, both models suggest that there are only a limited number of ways in which elements may arise and bifurcate. This has lead to a more precise formulation of the idea of developmental constraints on vertebrate limb evolution (Oster et.al., 1988, Oster and Murray, 1989).

Both models predict that the complexity and form of spatial pattern is dependent on scale, geometry and boundary conditions. For example, they predict that decreasing limb bud width will result in a loss of elements. This agrees with experimental observation (Alberch and Gale, 1983).

Recently it has been shown that if two stage 19 anterior chick limb halves are combined, the recombinant forms two humeral elements (Wolpert and Hornbruch, 1990). As the recombinant has the same size as a normal limb, both the above models would predict a single humerus. The observation suggests that the anterior stage 19 limb half contains cells that have already differentiated yet, at this stage, there is no visible aggregation of cells. This is inconsistent with the MC approach but may be consistent with the RD approach assuming that the prepattern is laid down and stabilised before stage 19. However, another interpretation of the result is that during normal development a prepattern may divide the early limb bud into domains in which cells are either competent or incompetent to differentiate into cartilage. Such a prepattern may be set up by a gradient in homeobox gene expression or in retinoid distribution (Maini and Solursh, 1990). The recombination experiment would then be seen as combining two such cell populations and, in effect, doubling the domain width. The eventual developmental fate of cells could then be determined by either of the above models.

This scenario suggests that pattern formation is a hierarchal process wherein each mechanism provides the initial condition for subsequent processes. This possibility warrants further experimental and theoretical investigation.

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