Development 1989 Supplement, 1–2
Printed in Great Britain © The Company of Biologists Limited 1989

The molecular basis of positional signalling: introduction

R. R. KAY[1] and J. C. SMITH[2]

[1]*MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK*
[2]*Laboratory of Embryogenesis, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK*

The importance of cell–cell interactions in embryonic development was first described by Driesch (1891), who showed that any of the blastomeres of the 2-cell or 4-cell sea-urchin embryo is capable of forming a complete embryo if cultured in isolation; this implied that in normal development each blastomere is aware of the other and will only form a half- or quarter-embryo, as appropriate. And it was only ten years later that Spemann (1901) discovered the phenomenon of embryonic induction, recently reviewed by Gurdon (1987) and defined as an interaction in which the differentiation of one group of cells is affected by a signal from an adjacent group. Thus the significance of cell signalling during development has been appreciated for almost a century, but, as has frequently been remarked, progress in the molecular analysis of the phenomenon has been slow compared with that in the younger disciplines of, for example, immunology and molecular biology. This slow progress no doubt discouraged younger workers from entering the field, so that by the late 1960s only a few stalwart research groups continued the struggle.

In retrospect, one can see that the reason progress was so slow is simply that the problem of cell signalling in development is so difficult; indeed, as we see in this volume, techniques derived from immunology and molecular biology are required for its solution. But it was not the emergence of these new techniques that was responsible for the revival of interest in cell–cell interactions that occurred in the 1970s and which has led to the current state of optimism. Instead, one spur was the concept of positional information, introduced by Wolpert (1969), and also discussed by Stumpf, Lawrence and Crick. Positional information suggested new ways to design and interpret experiments on organisms as diverse as hydra, slime-moulds, chicks, insects and amphibia – all of which species are discussed in this book. Another spur was provided by genetic studies on *Drosophila* and, more recently, on *Caenorhabditis elegans*. This work identified 'fields' in which positional information might be established and, latterly, has identified genes required for various steps in cell signalling processes. Examples of these genetic studies are also included in this volume.

Although the work of the 1970s identified few signalling molecules (one of the exceptions is discussed in this volume by Schaller), it did predict what such molecules had to do, where they should be, and when they should act. This in turn guided the design of biological assays to detect signalling molecules and in the last five years several candidate morphogens have been identified.

Because mechanisms of pattern formation in different organisms could all be described by the same formal language of gradients and positional information, it was once thought that there might be only one, or just a few, biochemical mechanisms of positional signalling. We now know enough to see that this view was wrong, although we do not know how wrong. One loose way of classifying positional signalling processes, that we have used in arranging this book, is according to the range and location of the signal. The different classifications might imply different mechanisms of signal transmission and localization, and they include: interactions within a single cell (as in the early *Drosophila* embryo, where interaction with cytoskeletal elements might be important for localizing the signal), short-range interactions (as in the *Drosophila* eye, where the signals might be cell-bound) and finally long-range interactions (as in the *Dictyostelium* aggregate or the chick limb) where diffusible signals are involved. Another distinction that might be drawn concerns the type of information passed between and within cells and the way this is interpreted. On the one hand, a signal may consist of the instruction to differentiate as a particular cell type (as occurs in the *sevenless* system,) or even to continue mitotic, rather than meiotic, cell divisions (as in the *Glp-1* system). Although the intracellular machinery required to interpret this information is undoubtedly complicated, it is unlikely to be as complicated as when different concentrations of factors cause different outcomes, as occurs, for example, in the chick limb. In this case, cells may require several thresholds, and the signalling system might be viewed in terms of positional information, with cells first having their position defined with a coordinate system and then using their positional values to decide how to differentiate.

At present the best-understood example of a multithreshold system is in the anteroposterior axis of the *Drosophila* egg, where the genes *X* and *hunchback* respond to different concentrations of *bicoid* protein. However, this interaction occurs within a single cell, and the *bicoid* protein probably acts directly on the *X* and *Hb* promoters. The situation is different in multicellular systems, where it is not even clear whether single cells have many thresholds or whether thresholds represent a cell population effect. As Gurdon (1987) has pointed out, the answer to this question will depend

on being able to analyze single cells, in the absence of cell division. This may require improvements in our cell culture techniques, as well as the development of early markers of response to cell signalling. Such culture systems and markers are now available in the slime mould *Dictyostelum discoideum*.

It is clear that much remains to be done if we are to understand how cell–cell signalling establishes the correct spatial pattern of cellular differentiation in even the simplest organisms. However, the identification of signalling molecules, the essential first step, is now being achieved. This book describes this work and points the way towards analyzing how the factors might act.

As organizers, we should like to thank everyone involved in making the St Andrews meeting such a success. We are particularly grateful to John Tucker, the local organizer, and to the Company of Biologists and American Airlines for financial support.

References

Driesch, H. (1891). Entwicklungsmechnische Studien. I. Der Werth der beiden ersten Furchungszellen in der Echinodermenentwicklung. Experimentelle Erzeugung von Theilund Doppelbildungen. *Z. wiss. Zool.* **53**, 160–178, 183–184.

Gurdon, J. B. (1987). Embryonic induction: molecular prospects *Development* **99**, 285–306.

Spemann, H. (1901). Uber Korrelationen in der Entwicklung des Auges. *Verh. Anat. Ges., 15 Vers. Bonn (Anat. Anz.* **15**), 61–79.

Wolpert, L. (1969). Positional information and the spatial pattern of cellular differentiation. *J. theor. Biol.* **25**, 1–47.