Discovery of a morphogen

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A new morphogen

In 1967, Theo Konijn, a young staff scientist at the Hubrecht Laboratory, and John Bonner of Princeton University and their colleagues, published a collaborative discovery which identified one of the first signal molecules (morphogen), regulating multicellular organisation during a developmental process (Konijn et al., 1967, 1969).

This breakthrough was antedated by initial identifications of nerve growth factor and of epidermal growth factor in 1956 and 1962 respectively (Cohen and Levi-Montalcini, 1956; Cohen, 1962), but potential morphogens in early metazoan embryos were not identified until 1987 when b-FGF was identified as a putative regulator of mesoderm induction in the early Xenopus embryo (Slack et al., 1987).

Using classical chemical separation methods, and a novel bioassay (see Fig. 2), these groups identified a chemoattractant for cells of the cellular slime mould Dictyostelium discoideum (purified initially from an Escherichia coli extract, see Konijn et al., 1967) as 3'5' cyclic AMP (c-AMP).

These groups proceeded to demonstrate that c-AMP mediates a chemotactic aggregation process (Konijn et al., 1969), via which Dictyostelium achieves multicellularity. They and others later showed that it regulates morphogenesis and patterned cell differentiation throughout the multicellular developmental cycle of this organism.

Weyer’s turbine

Aggregating Dictyostelium cells show waves of chemotactic movement. These waves reflect the fact that Dictyostelium cells not only chemotact, but also relay c-AMP in an oscillatory fashion; secreting a c-AMP pulse in response to a c-AMP signal and then transiently entering an insensitive, adapted state. This property generates movement waves which are either expanding concen-
Fig. 2. (A) Small drop assay. Dictyostelium cells in a small drop on an agar surface are attracted towards a neighbouring drop of c-AMP.

(B) Spiral wave in a population of Dictyostelium cells. By courtesy of C.J. Weijer. (C) Three dimensional spiral wave (torus scroll wave) deduced from cell movement vectors in a doughnut shaped Dictyostelium aggregate (Durston et al., 1978).

Fig. 3. Life cycle of Dictyostelium with spiral waveforms. The aggregating cells stream into mounds and these develop into cylindrical structures (first finger, slug), which contain a 3-dimensional spiral (scroll) wave. This scroll wave becomes twisted along its axis due to a frequency difference between anterior and posterior cell types (see text). The twisting provides a turbine effect which drives morphogenesis. Eventually, the structure becomes a fruiting body via mechanisms not discussed here. (By courtesy of C.J. Weijer).

Fig. 4. Close up of two variants of the turbine wave in slugs of two different Dictyostelium species. (By courtesy of C.J. Weijer).

Recent findings by Kees Weyer, who obtained his Ph.D. on Dictyostelium in the Hubrecht Laboratory in 1985, demonstrate the power of these relayed signals. The multicellular life cycle (developmental sequence) of Dictyostelium consists of a sequence of radially symmetrical structures, built on a cylindrical plan, which are each controlled by an apical organising region (tip).

Pursuing a line of work which was initiated in the Hubrecht Lab in the 1970s (Durston et al., 1978; Weyer et al., 1984), Weyer showed that these structures are organised by a variant of the 3-D transformant of the spiral wave: the scroll wave (Siegert and Weyer, 1992; Steinbock et al., 1993; Bretschneider et al., 1999). He discovered that multicellular Dictyostelium structures contain an axial scroll wave which is twisted. Twisting occurs because these later structures contain two basic cell types with different excitability properties: Weyer showed during his Ph.D. years that anterior (tip) cells are relatively excitable, with a high oscillation frequency (Weyer et al., 1984). They therefore generate a rapidly rotating spiral. Posterior cells are less excitable, and generate a slower rotating spiral. The twist to the scroll generates a turbine waveform which ultimately breaks up into backward directed plane waves, powering forward chemotaxis and providing the driving force for morphogenesis.

References


