Subdividing the metamere: one signal, two outcomes

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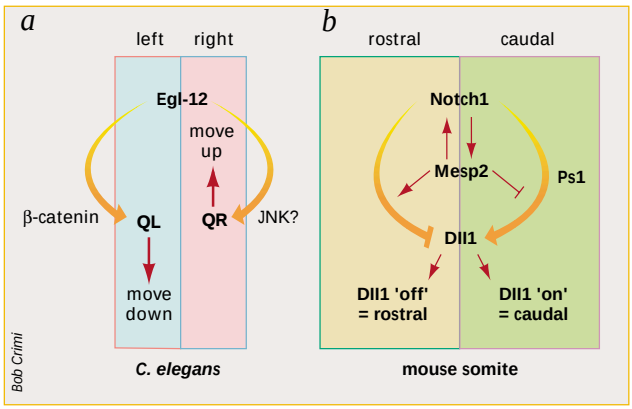
Each somite of the vertebrate embryonic body axis is subdivided into a rostral and a caudal half. Using elegantly designed mouse genetic experiments, a recent paper provides insight into the mechanisms that select between these two fates. Remarkably, both states require Notch activity, but the signal is transduced by a different pathway in each half.

The most obvious feature that defines the body plan of vertebrates, as well as some invertebrates, is a series of repeated elements (also known as 'metameres') along the length of the body axis, providing a highly effective device to ensure stability, rigidity and mobility. During vertebrate embryonic development, this pattern is generated by the sequential formation, in head-to-tail order, of spheres of cells called somites, each of which later gives rise to skeletal elements (such as vertebrae), voluntary muscle and dermis. The peripheral nervous system arises a little later in development, but is perfectly aligned with the somites. This alignment is achieved by an ingenious mechanism: each somite is divided into a rostral and a caudal half, of which only the former allows the passage of motor and sensory nerves[1,2].



Making the most of molecules. Different pathways downstream of a single signal can specify different cell behaviours. ***a***, An example[7] from the nematode *C. elegans*, where the same Wnt-like signal (Egl-12) determines whether QL and QR neuroblasts move posteriorly or anteriorly, respectively, according to the pathway activated in each half of the animal. ***b***, As demonstrated by Takahashi and colleagues[6], in the mouse somite two different pathways downstream of Notch1 mediate the maintenance of Dll1 expression (which specifies the caudal half) or the loss of Dll1 expression (which specifies the rostral half).

The mechanisms that regulate the orderly generation of somites and their subdivision during development are still largely unknown, even though some of the molecular players have recently come into focus. Among them are components of the Notch/Delta pathway. Mouse mutants defective in components of this pathway have defective segmentation or subdivision of somites[3–5], but their phenotypes are often so complex that it has been difficult to glean clues to the role of the encoded proteins in segmentation and how they relate to known events during this crucial time in development. For example, some of these mutations result in a loss of caudal identity and others, loss of rostral identity, raising the question of whether the Notch pathway is required to specify a particular identity within the somite or to regulate some other aspect of cell behaviour which in turn regulates identity. At the moment, we cannot even describe the events in cellular terms: we are still largely ignorant of which events occurring during segmentation are cell-autonomous (for example, those dependent on an intrinsic cellular clock) and which are controlled by signals flowing between adjacent cells.

A study[6] presented by Yu Takahashi and colleagues on page 390 provides welcome insight into how segementation is coordinated. The authors conclude that Notch signalling is required to specify both caudal and rostral identity—the deciding factor being the signalling route by which Notch regulates the expression of another component of this pathway, Delta-like-1 (Dll1), which is also a ligand of Notch. In cells that will give rise to the caudal half, Notch is proposed to act through the presenilin-1 secretase (Ps1) to activate Dll1, whereas in the rostral half it inhibits Dll1 expression by a Ps1-independent mechanism. Therefore, the cellular environment provides the switch between the two pathways. This type of mechanism had not been predicted by any of a large number of theoretical models of somite formation and rostral/caudal subdivision. It is, however, reminiscent of another, which governs the migration routes of two specific neuronal precursors in the nematode *Caenorhabditis elegans*[7] (see figure): the bilaterally symmetric neuroblasts QL and QR migrate in opposite directions in response to the same signal (conveyed by Egl-20, a homologue of the secreted factor Wnt). On the left, this signal is transduced by a β-catenin–dependent pathway, whereas on the right, it is transduced by an alternative mechanism, perhaps involving small GTPases of the rho/rac/cdc42 family[8].

The metastable metamere

The basic helix-loop-helix (bHLH) transcription factor Mesp2 provides a cell-autonomous switch between the two pathways downstream of Notch. Before somite formation, Dll1 is expressed in both halves of a presumptive somite. At this time, Mesp2 both inhibits the Ps1-dependent induction of Dll1 by Notch and enhances the inhibition of Dll1 by Notch. But Mesp2 expression is quickly extinguished in the prospective caudal half, releasing the Ps1-dependent induction of Dll1 in this half. In the rostral half, continued Mesp2 activity results in the down-regulation of Dll1. The expression of Dll1 beyond this point is proposed to provide the effector switch that specifies rostral/caudal identity: if Dll1 remains 'on', the cells acquire caudal character. Thus, just before segmentation, cells appear to be in a metastable state, simultaneously expressing signals that convey conflicting information. Tipping the balance in one direction or the other then initiates self-reinforcing mechanisms that lead to main-

tained Dll1 activity in the caudal half, and its repression in the rostral half.

But the most interesting biological questions remain unanswered. The decision between prospective caudal and prospective rostral cells must somehow be made before this stage, so that cells 'know' whether or not to switch off Mesp2 expression and which of the two pathways to activate. How is this achieved? How are cell populations apportioned so precisely to one or the other half, and to somites? The decision to become rostral or caudal has been causally linked to the formation of somite boundaries, such that boundaries arise at the point of confrontation between rostral and caudal halves; but then, why do somite boundaries initially arise at only one of these interfaces, and not also in the middle of each somite[9]?

Elegant genetics

In my view, the greatest value of this paper lies not so much in what it reveals about the mechanisms of somite formation and subdivision, but rather in the elegance of its approach. The introduction of techniques for targeted mutagenesis in the mouse (almost two decades ago) has made it possible at last to use reverse genetics to investigate whether a particular gene is essential for a specific biological process. But most papers limit themselves to reporting the phenotype of an individual mutation, and—as described above—the answers are not always as straightforward as might have been expected. The phenotype often differs in different genetic backgrounds (that is, mouse strains), and the analysis is not always sufficiently thorough to lead to new biological insights. It seems unlikely that a paper describing the phenotype effected by a new mutation in the nematode or fly would be published in a major journal unless it also contained information about gene function, or other new insight into biological process. Takahashi *et al.* have generated three carefully designed new mutations to answer a single question, and studied the interactions between the three in addition to their effects on downstream targets and on the process of segmentation. For once, if the name of the species were changed from 'mouse' to 'fly' or 'nematode', the paper would be just as significant. I hope that this is the shape of things to come, and that papers such as this one will lead us to question whether a description of a single mouse mutant or whether the results of a random 'functional genomics' approach should warrant high-visibility publication. □

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