The Notch signaling pathway has multifarious functions in the organization of the developing vertebrate embryo. One of its most fundamental roles is in the emergence of the regular pattern of somites that will give rise to the musculoskeletal structures of the trunk. The parts it plays in the early operation of the segmentation clock and the later definition and differentiation of the somites are beginning to be understood.

In one way or another, at one stage or another, almost every tissue in an animal body depends for its patterning on the Notch cell-cell signaling pathway [1]. The evidence from mutants is clear: disrupted Notch signaling entails disrupted pattern. The challenge is to define precisely what it is that Notch signaling does in any given case, and when it does it. This problem is posed in a particularly striking and curious way by the phenomena of somitogenesis - the process by which the vertebrate embryo lays down the regular sequence of tissue blocks that will give rise to the musculoskeletal segments of the neck, trunk, and tail.

These blocks of embryonic tissue, the somites, are arranged symmetrically in a neat, repetitive pattern on either side of the central body axis. Each somite is separated from the next by a cleft - the segment boundary; and each somite has a definite polarity, with an anterior portion and posterior portion expressing different sets of genes [2]. Mutations in components of the Notch signaling pathway play havoc with this whole pattern: although somites may eventually form, the segment boundaries are irregular and randomly positioned, and the regular antero-posterior polarity of individual somites is lost. Genetic screens for mutations that disrupt segmentation in this way chiefly identify Notch pathway components as the critical players. Notch signaling is clearly central to somitogenesis [3-6]. But precisely how?

Notch pathway components can be wired together in different ways for different outcomes

In general, the function of the canonical Notch pathway is to coordinate gene expression in contiguous cells. It does this in a particularly direct way. The signal-sending cell expresses a Notch ligand (belonging to either the Delta or the Serrate/Jagged subfamily) on its surface; this binds to the receptor, Notch, in the membrane of the signal-receiving cell and thereby triggers cleavage of Notch, releasing an intracellular fragment, the Notch intracellular domain (NICD); NICD translocates to the nucleus, where it acts as a transcriptional regulator [1,7] (Figure 1). The main - or at least, the best-studied - targets of direct regulation by NICD are the members of the Hairy/E(spl) family (Hes genes in mammals, her genes in zebrafish) [8,9]; these code for inhibitory basic helix-loop-helix (bHLH) transcriptional...
regulators, which can control many different secondary targets, including Notch ligand genes and the Hes/her genes themselves. The role of Notch signaling in pattern formation depends on the ways in which these components - and others that modulate their activity - are functionally connected into regulatory feedback loops [10]. Mathematical modeling highlights several possibilities. Thus, one type of linkage, where Notch activation leads to downregulation of Notch ligand expression in the signal-receiving cell, can lead to lateral inhibition, forcing neighboring cells to become different from one another [11] (Figure 2). An opposite linkage, whereby Notch activation stimulates ligand expression, can have an opposite effect, inducing contiguous cells to be similar [12]. Still other types of circuitry built from the same components can perform yet other tricks, including the production of temporal oscillations of gene expression [13,14]. And this brings us back to somitogenesis, where such oscillations are in fact seen.

**A gene-expression oscillator marks out the periodic pattern of body segments**

Somites derive from the unsegmented presomitic mesoderm (PSM) at the tail end of the embryo. PSM cells are specified by the combined action of Wnt and fibroblast growth factor (FGF) signaling molecules, which are produced at the tail end of the PSM and spread anteriorly to generate a morphogen gradient. At the point where the level of Wnt and FGF falls below a threshold value, somites form. Thus, as the PSM grows caudally, extending the embryo, one pair of somites after another is budded off from the anterior end of the PSM in a regular head-to-tail sequence. Each species generates its characteristic number of somites at its own pace, ranging from one new somite pair approximately every 30 minutes in zebrafish to one pair every 2 hours in mice. This rhythmic process involves coordinated patterns of cell behavior not only in space but also in time: it depends on an underlying gene expression oscillator - the *segmentation clock* - that ticks in the cells of the PSM and dictates the rhythm of somite formation, with each oscillator cycle corresponding to the production of one additional somite [15]. The genes that were first found to oscillate in the PSM and that show this cyclic expression in all vertebrates belong to the Notch signaling pathway; these oscillatory genes include, specifically, certain members of the Hairy/E(spl) gene family of bHLH transcriptional regulators - in particular *Hes1* and *Hes7* in mice, *her1* and *her7* in zebrafish, and *hairy1* and *hairy2* in chick [15-22] - and (in zebrafish) the Notch ligand DeltaC, whose expression is controlled by them. These, and certain other oscillatory genes, display a characteristic pattern of expression that can be seen in fixed specimens stained by *in situ* hybridization. In the posterior part of the PSM, the level of expression may be high or low, depending on the phase of the oscillation cycle at the moment when the embryo was fixed. In the anterior part of the PSM, meanwhile, one sees a stripy pattern, in which bands of cells that express the oscillatory gene strongly alternate with bands of cells that do not (Figure 3). This pattern reflects the gradual slowing of the oscillations as cells approach the point of exit from the PSM, beyond which oscillation is halted: cells in more anterior positions are thus delayed in phase relative to more
posterior cells, with the consequence that one sees laid out along the antero-posterior axis of the PSM an ordered array of cells in different phases of the oscillator cycle [15,23]. Disturbances of oscillator behavior are thus clearly displayed in a disturbed spatial pattern of gene expression in the anterior PSM - a great convenience for experimental analysis.

**Notch signaling keeps cell clocks synchronized**

Since, as we noted earlier, any mutation that blocks Notch signaling leads to disrupted somite segmentation, an obvious suggestion is that the oscillation depends on Notch signaling and fails to occur when Notch signaling fails. However, the detailed consequences of mutations in the Notch pathway do not quite fit this simple explanation. A different interpretation is instead suggested by a closer examination of the behavior of one of the oscillatory genes, coding for the Notch ligand DeltaC, in zebrafish with mutations in the Notch pathway [24]. The individual PSM cells in these mutants still express DeltaC, but in an uncoordinated way: tissue fixed for analysis by in situ hybridization shows a pepper-and-salt mixture of cells expressing DeltaC at different levels, as though the cells are still oscillating individually, but no longer in synchrony with their neighbors (Figure 4). Moreover, both in zebrafish and in mice, the first few somites of embryos with Notch pathway mutations develop almost normally [25-27], implying that Notch signaling is not absolutely necessary for somite segmentation and that the consequences of failure of Notch signaling make themselves felt only gradually, after the onset of somitogenesis. These findings led to the suggestion that the primary function of Notch signaling is not to drive the oscillations of individual cells, but only to coordinate them and keep them synchronized; and that the cells begin oscillation in synchrony at the start of somitogenesis, and take several cycles to drift out of synchrony when Notch signaling is defective [24]. This proposal - that Notch signaling from cell to cell in the PSM serves to maintain synchrony but is not necessary for oscillation of individual cells - has been supported by several subsequent experiments. For example, zebrafish embryos can be treated at different stages of somitogenesis...
with the inhibitor DAPT, which inhibits the enzyme that releases NICD from the membrane (Figure 1) and thus blocks Notch signal transmission. When Notch signaling is prevented in this way, somite defects ensue, but always with a delay that corresponds to a gradual disordering of the pattern of oscillator gene expression [28,29]. Other evidence comes from experiments where PSM cells are transplanted into a wild-type zebrafish embryo from an embryo in which the expression of the oscillatory her genes [28,29] is defective. The transplanted cells then cause abnormal segmentation behavior in their neighbors; but they fail to exert this effect if they are prevented from expressing the Notch ligand DeltaC [30]. The oscillatory behavior of individual PSM cells and the influence of Notch signaling can also be demonstrated through study of cells from the PSM of a transgenic mouse embryo containing a luminescent Hes1 reporter. These cells show oscillating expression of the reporter gene even when they are dissociated and thus unable to communicate via Notch [31], but in that condition the oscillations are much less regular than in the intact tissue.

What is the ultimate pacemaker of the segmentation clock?
All these findings support the view that Notch is needed to maintain synchrony between the oscillations of the individual cells, which are somewhat noisy and imperfect timekeepers when left to their own devices. But what is generating the cell-intrinsic oscillations? According to one view, the core oscillator - the pacemaker of the whole process - is a delayed negative feedback loop in the auto-regulation of the oscillatory Hes/her genes - Hes7 in mammals, her1 and her7 in the zebrafish [13,32] (Figure 5). Loss of Hes7 in the mouse, or of her1 and her7 in the zebrafish, disrupts segmentation all along the body axis; and it has been shown experimentally that these genes are indeed subject to negative regulation by their own products [22,23,32,33]. The idea that this Hes/her negative feedback loop is the core oscillator has been articulated in quantitative mathematical terms and is supported by many pieces of evidence, but it still lacks firm proof [34]. In mouse and chick, the PSM cells also show oscillating expression of various other genes, including (in the mouse) genes in the Wnt and Fgf pathways [35-37], some of which appear to continue their oscillation even when the Hes7 oscillations fail [35]. Thus, the nature of the ultimate generator and pacemaker of the oscillations is still under debate, especially for mouse and chick [38-40].

The need for Notch signaling may extend beyond the control of the clock
Failure of synchronization is sufficient to explain the disruption of segmentation in Notch pathway mutants. But that is not necessarily the end of the story. To acknowledge that Notch signaling has this critical function, and that that is enough to explain the mutant phenotypes, is not the same as saying that synchronization is the only function of...
Notch signaling in somitogenesis. At least two additional functions have been proposed. One is in the final step at which a segment boundary is created by physical separation of one nascent somite from the next; the other is in creating or maintaining the difference between anterior and posterior halves of each somite. Each of these possible further roles for Notch signaling - in boundary formation and in segment polarity - seems attractive on the basis of analogies with other systems. Thus, in the Drosophila wing disc, Notch signaling plays a critical part in organizing the dorso-ventral compartment boundary [41]; and in the vertebrate hindbrain, likewise, it is involved in organizing the boundaries between rhombomeres [42]. As for segment polarity, the creation of a difference between the cells of the anterior and posterior parts of each somite could be seen as similar to the creation of differences between adjacent cells through lateral inhibition - a well known function of Notch signaling in many different systems [1].

**Notch signaling is dispensable for boundary formation in zebrafish**

It is in the anterior part of the PSM, where the oscillation of cyclic genes slows down and then halts, that cells are assigned to anterior or posterior somite compartments and clefts form, finally demarcating one somite from the next. Thus, the formation of the segment boundary and the specification of antero-posterior polarity are both processes that occur relatively late in the history of each somite, after its precursor cells have graduated to the anterior part of the PSM from the posterior as the embryo grows and extends. If the early function of Notch signaling in maintaining synchrony in the posterior PSM is disrupted, any failure in these later functions is likely to be imperceptible amid the general chaos. One can, however, test for the later functions by imposing a block of Notch signaling part way through somitogenesis. For example, one can take a zebrafish that has already formed five somites and immerse it in a DAPT solution to block Notch signaling from that time point onwards. The result is striking: the next approximately 12 somites proceed to form in the normal way, with regularly spaced boundaries, and only after that does one begin to see segmentation defects [28,29]. This shows that Notch signaling is not needed, in the zebrafish at least, for the creation of somite boundaries, and it quantitatively matches predictions based on the proposition that the only function of Notch signaling is to maintain synchrony in the posterior PSM [29].

**Cleft formation correlates with the appearance of sharp boundaries of gene expression**

Findings in the mouse, however, are not so clear, and there are differing schools of thought. In a series of papers [43-49], Saga and colleagues have argued that Notch signaling is indeed needed to create a sharp boundary of gene expression that is necessary to mark the future cleft between one nascent somite and the next [43,44]. Their conclusions emerge from study of a pair of transcriptional regulators - Mesp2, and the less well characterized Mesp1 - that are expressed in the anterior PSM. They seem to operate as orchestrators of the process by which the output of the somite oscillator is translated into the spatially repeating pattern of the somites [45] - a process that is disrupted in Mesp2 mutants [46]. Mesp2 is expressed dynamically in each forming somite, beginning as a one-somite-wide stripe, rapidly narrowing to a half-somite-wide stripe (which marks the future anterior compartment of the somite), then disappearing completely as the somite buds off from the PSM. In the brief window during which it is expressed, Mesp2 seems to be responsible for allocating anterior or posterior identity to the cells of the somite through activation or repression of various targets that distinguish the anterior from the posterior cells, and for regulating some of the genes required for border formation [47,48]. In particular, somite boundaries form at interfaces where cells with high expression of Mesp2 but low Notch activation confront cells in an opposite state, with high Notch activation but no expression of Mesp2. These observations strongly suggest that some sort of feedback loop involving Mesp2 and Notch signaling organizes the formation of an interface between cells with high Notch activation and cells with low Notch activation, and that this interface is necessary to define the segment boundary. Moreover, the same studies suggest that Notch signaling is involved in the restriction of the Mesp2 expression domain from the whole presumptive somite to just its anterior half [48,49], and thus essential for the establishment of the anterior-posterior polarity of each new somite. However, these observations do not amount to firm proof: correlation need not imply causation, and Mesp2, acting independently of Notch activity, could be the critical factor. The pattern of Mesp2 expression is indeed altered in Notch pathway mutants [43], but it is hard to be sure whether this reflects a function of Notch signaling in the anterior PSM where Mesp2 is expressed, or merely the aftermath of the disorder created by prior failure of Notch signaling in the posterior PSM.

**Notch signaling is required to give each somite its antero-posterior polarity**

Feller et al. [50] tested the role of Notch signaling in the mouse PSM in a different way and came to a somewhat different view. When they artificially expressed NICD, the intracellular transcriptional regulator domain of Notch, throughout the entire PSM, they found that many somite boundaries still formed, despite the absence of any interface...
between cells with differing levels of Notch activation; these boundaries, however, were irregularly spaced, and the resulting irregular blocks of somite tissue lacked the normal anterior-posterior polarity. The same was seen when Notch signaling, instead of being artificially activated, was inactivated by mutations in Notch1, or Dll1 (Delta1), or Pofut1 (coding for an enzyme that fucosylates Notch and is required for Notch function). In fact, a similar outcome is seen in zebrafish Notch pathway mutants - clefts eventually appear in the mesoderm, dividing it up into somites, but these clefts form later than normal and are crooked and irregularly spaced. The somitic mesoderm, it seems, has a propensity to split up into tissue blocks and will do so even if the segmentation clock is broken and Notch signaling defective. The role of the clock is to control the pattern of this splitting, ensuring that the clefts are regularly spaced, and to confer on each somite a regular anterior-posterior polarity. For this last step, it seems that Notch signaling is required directly and not merely to keep the segmentation clocks of the individual cells ticking synchronously in the run-up to overt segmentation; for in the mice where NICD is expressed throughout the tissue, each somite has a double-posterior character, whereas when Notch fails each somite has a double-anterior character [50].

**Notch signaling is used repeatedly in the somite cell lineage**

The formation of the somites is not the end of the involvement of Notch signaling in the development of the somitic cell lineage. For example, skeletal muscle tissue, which arises from the somites, also depends on this pathway to control the differentiation of myoblasts and satellite cells and their incorporation into multinucleate muscle fibers [51-54]. Like that other ubiquitous communication device, the mobile phone network, the Notch signaling pathway has been recruited for many different purposes - for the simple delivery of instructions from one individual to another, for competitions and collaborations, for the synchronization of individual actions, and for the playing of the tunes to which cells dance.

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