Deserts and Waves in Gene Expression

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Spalding *et al*. not only confirm that adult brain neurogenesis is restricted to the hippocampus, but the size of their data set (genomic DNA was isolated from hippocampal neurons from subjects 19 to 92 years of age) enabled the authors to attempt a quantitative estimate on the dynamics of the process. Based on a sophisticated modeling approach, they conclude that contrary to some expectations, humans have at least as much adult hippocampal neurogenesis as mice. They calculate a considerable turnover of neurons in the dentate gyrus portion of the hippocampus and put forth a model of how the composition of this hippocampal structure changes over the course of life. In the proposed model, "turnover" does not imply that specific neurons are renewed one-by-one. Rather, a subpopulation of neurons renews consistently and continually, whereas another population is nonrenewing. Spalding *et al*. estimate that one-third of adult hippocampal neurons are turning over. This amounts to 700 new neurons added per day, for an annual turnover rate of 1.75% (or 0.004% of dentate gyrus neurons). This turnover rate was not significantly different between men and women and declined only modestly with age. The author's modeling suggests that nonrenewing neurons in the hippocampus die without being replaced and account for the slow decrease in total neuron number throughout life. By contrast, adult-born neurons in the renewing population do not survive as long and are preferentially lost. The half life of the latter is about 7 years, 10 times shorter than that of the former.

The big question is whether adult-born neurons contribute to brain function. Indeed, other models already have suggested that such continual turnover is highly efficient for meeting some of the particular computational needs that the hippocampus has to face (*6*). It is the young, immature neurons that seem to play a critical role in the function of the dentate gyrus (*7*, *8*); essentially all long-term potentiation (which underlies learning and memory) measurable under normal conditions can be attributed to the newborn cells. Adult neurogenesis would not only provide plasticity but also add to stability because some new neurons are also integrated for a longer amount of time, presumably resulting in relatively long-lasting adaptations of the local network. Acute benefits from neurogenesis might be translated into lasting ones, depending on actual activity and cognitive demand.

At the behavioral level, adult neurogenesis adds a particular type of cognitive flexibility to the hippocampus (*8*). Adult neurogenesis does not appear to be required for hippocampal function per se, even though tampering with adult neurogenesis affects the efficiency of hippocampal functions such as "pattern separation" (which allows storing similar representations in a nonoverlapping manner) (*9*). Perhaps, the advantage of having a dentate gyrus, as mammals do, lies in the ability it provides to cope with change and novelty (*10*). Adult neurogenesis in this region might add a particular functionality not achievable by other types of plasticity. By staying "forever young," the dentate gyrus could command unique solutions to computational problems only found in the brain region central to learning, memory, and many higher cognitive functions considered essential for humans.

The evolutionary advantage attributable to the mammalian dentate gyrus compared to the analogous structures in other vertebrates might result from adult hippocampal neurogenesis and might even prominently contribute to the individualization of the brain and thus the shaping of personality (*11*). In such context, Spalding *et al*. provide a confirmation with the highest possible impact. Neurogenesis researchers can stop worrying and love the bomb.

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DEVELOPMENTAL BIOLOGY

Deserts and Waves in Gene Expression

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A gene cluster that regulates limb development is controlled in two phases by regulatory elements that flank the cluster and operate independently.

The homeotic genes, or *Hox* genes, encode transcription factors that are situated in tight clusters within the genome of broadly divergent taxa. In invertebrates and vertebrates, *Hox* genes specify differences along the anteroposterior body axis in the same order as their physical order in the cluster (*1*–*3*), but in the latter, this collinearity has also been co-opted for constructing secondary body axes such as the limb (*4*). On page 1195 in this issue, Andrey *et al*. (*5*) elucidate the complex regulatory mechanisms responsible for the collinearity of *Hox* genes in patterning such secondary axes.

Establishment of the primary body axis is attributable to the chromosomal organization of *Hox* genes in concert with two regulatory features. One is that the genes become accessible for transcription gradually from one end of the cluster to the other through chromatin derepression (see the figure). This mechanism, postulated over two decades ago (*6*), is supported by profiles of chromatin epigenetic marks that reflect changing states of gene expression (*7*). Another feature is that *Hox* genes activated at the lagging end of the cluster are functionally dominant over those activated at the leading end (*8*). To reemploy these genes for specifying the secondary body axes, however, new mechanisms are required.

In vertebrates, duplication of the *Hox* cluster has produced the *HoxA*, *B*, *C*, and *D* clusters. Of these, the *HoxA* and *HoxD* clusters pattern the limb buds (*4*). Within the limb, *HoxD* cluster expression is manifested in two discrete phases. In the early distal limb, when forearm elements are specified, *Hoxd1-9* are broadly expressed whereas *Hoxd10-13* are expressed in smaller spatial domains, similar to the collinearity that constructs the primary body axis (*9*, *10*). A second phase of expression arises in the late distal limb when the hand is specified, during which the order of collinearity is reversed—*Hoxd13* is

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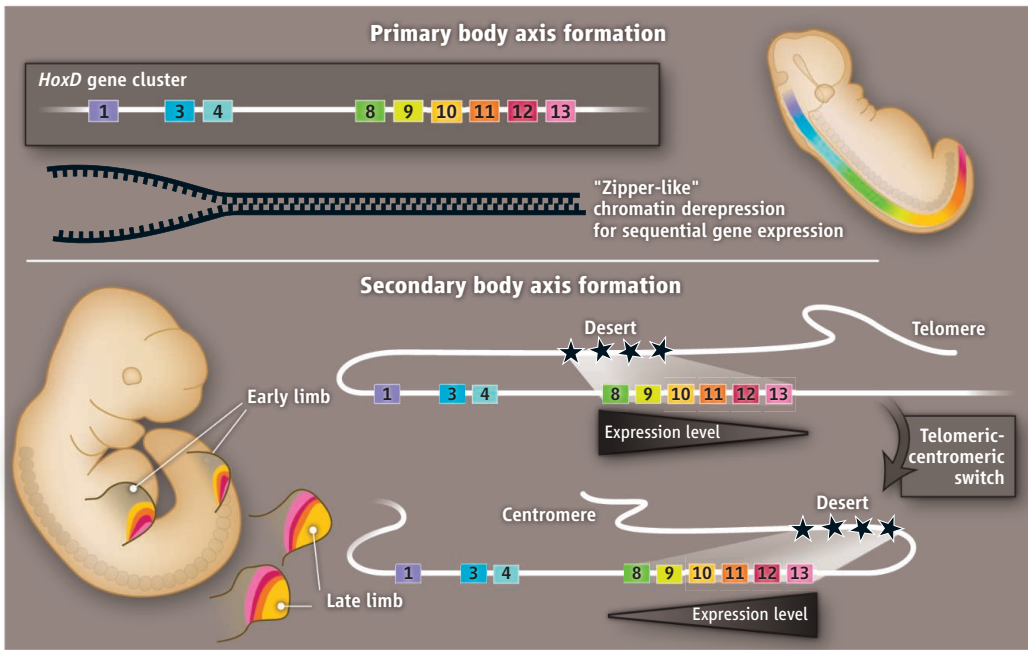

Controlling collinearity. Genes in the *HoxD* cluster are expressed from one end to the other, through sequential opening of the chromosome, to construct the vertebrate primary body axis (mouse embryo shown). Later in development, when limbs emerge (secondary body axes), the same cluster is redeployed through a different regulatory mechanism. During early limb development, a regulatory region flanking one end of the cluster (telomeric enhancers) controls *HoxD* gene expression. As limb development progresses, the telomeric enhancers are switched off while centromeric enhancers flanking the other end of the cluster are switched on.

expressed most broadly, whereas *Hoxd12-10* are expressed in smaller domains (*9*, *11*).

To articulate how the second wave of *Hox* gene expression follows the first, it is necessary to know where in the genome the responsible regulatory regions lie. The main sources are likely the gene-poor yet highly conserved regions ("gene deserts") that flank both sides of the *HoxD* cluster (*12*). To pinpoint specific regulatory elements within these large (~1 MB) gene deserts, Andrey *et al*. used chromosomal capture, transient transgenic, and genomic deletion techniques, approaches that previously identified a series of enhancer elements in a neighboring telomeric gene desert that controls *Hoxd* gene expression in the presumptive digits of the late limb (*13*). Focusing on *Hoxd9* in the mouse, which is transcribed in the first phase of expression, the authors observed that the gene is not in physical contact with the telomeric desert but contacts a centromeric desert on the opposite end of the cluster, where two enhancers robustly drive expression in the early limb bud.

Are individual genes within the cluster regulated by only one or both of the two distinct regulatory landscapes? Andrey *et al*. found that genes at the extremes of the cluster only contact the deserts they are adjacent to, regardless of developmental stage or transcriptional activity. By contrast, genes within the center of the cluster (*Hoxd9-11*) have a more dynamic interaction profile. During the early phase of limb development, these central *HoxD* genes contact the centromeric gene desert; both regions possess chromatin marks of active enhancers and genes, indicating that their interaction results in early-phase *HoxD* expression. During the late phase of limb development, *Hoxd9-11* no longer contact the centromeric desert but contact the telomeric desert instead. This shift in contact also correlated with the presence of active chromatin marks on the telomeric desert.

Intriguingly, the centromeric desert is shut down at the appropriate time, when the switch normally takes place, even if the telomeric desert is deleted. Hence, Andrey *et al*. conclude that the two deserts are functionally independent. However, even if the repressive epigenetic marks can be laid down on the centromeric desert in the absence of the telomeric desert, the signaling input that causes the centromeric desert to shut down could be the same as that which activates the telomeric desert. The nature of the signals orchestrating the switch remains an important open question.

Another interesting aspect of *Hoxd* gene regulation is the gap that lies between the forearm domain, where the *Hoxd* genes are under the control of the centromeric desert, and the distal domain, where they are regulated by telomeric enhancers. The chromatin state in this gap, where *Hoxd* genes are inactive, is not known. The cluster may continue to make centromeric contacts without maintaining expression, or it may have switched to telomeric contacts without activating transcription. Regardless of the mechanism, this gap in *Hoxd* expression seems important as it corresponds to the domain of the future wrist, which appears to be specified either in response to low *Hoxd* activity, or through the directed action of *Hoxa13* (which is expressed there) in the absence of *Hoxd13* input (*14*). Another unique *Hox* code is found in the region of the presumptive thumb, where *Hoxd13* is expressed but *Hoxd11* and *Hoxd12* are silent. Perhaps this too is regulated at the level of the specific chromatin contacts in the telomeric desert.

In addition to the *HoxD* cluster, the *HoxA* cluster also has been coopted to regulate limb patterning. *Hoxa11* and *Hoxd11* are roughly coexpressed in the proximal limb and *Hoxa13* and *Hoxd13* overlap extensively in the distal limb. It will be interesting from a comparative standpoint to unravel the chromosomal mechanisms used in the *HoxA* context.

The serial duplication of *Hox* genes potentiated a simple mechanism for their collinear expression along the main body axis. Andrey *et al*. have revealed how this organization also allowed new regulatory mechanisms to be superimposed on the clusters to direct collinear expression in new secondary locations and under new controls.

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