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Like Poles Repel: Molecular Mechanisms of Dendritic Tiling

To cover the entire sensory field once and only once, dendrites of some sensory system neurons avoid crossing other dendrites from the same type of neurons. In this issue of *Cell*, Emoto et al. (2004) provide first insight into the molecular mechanisms of dendritic tiling.

To represent the sensory world effectively and precisely, some sensory system neurons deploy a strategy in which dendrites of the same type of neurons cover the sensory field as complete as possible with minimal overlaps. This dendritic behavior is referred to as "tiling" with analogy to tiling of kitchen floors. The best-described dendritic tiling occurs in dendrites of rabbit retinal ganglion cells (RGCs), which are grouped into at least 11 types based on their morphological and physiological properties (DeVries and Baylor, 1997; Rockhill et al., 2002). Dendrites from neurons of a given type cover the entire retina with little or no overlap with dendrites of the same type but overlap with dendrites of different types. How is this type-specific tiling achieved? When patches of ganglion cells are removed during a critical postnatal period, dendrites of the same neuronal types adjacent to the depletion site invade into the vacated territory. These observations suggested homotypic repulsion between dendrites of the same types of neurons to avoid crossing between homologous dendrites (reviewed in Jan and Jan [2003]).

Drosophila dendritic arborization (da) neurons have recently been used as a model system for studying dendritic development including tiling (Jan and Jan, 2003). da neurons can be grouped into four classes based on dendritic morphology. Among them, the dendrites of classes III and IV exhibit the tiling property: they cover the body wall once and only once (Grueber et al., 2002). Homotypic repulsion among the like dendrites has also been suggested for class IV dendritic tiling: ablation of class IV neurons results in dendritic invasion from adjacent class IV neurons, whereas generation of supernumerary class IV neurons causes reduction of dendritic territory for each neuron so that the body surface is again covered once and only once (Grueber et al., 2003; Sugimura et al., 2003). So far, little is known about molecular mechanisms by which such tiling is achieved. In this issue of *Cell*, Emoto et al. identified Furry (Fry) and Tricornered (Trc) kinase in regulating tiling and dendritic branching.

Fry and Trc proteins are evolutionarily conserved from yeast to mammal. Fry is a large protein known to act with Trc to regulate epithelial cell morphology (reviewed in Adler [2002]). Emoto et al. found two major dendritic phenotypes in null mutants for *fry* and *trc*. Excessive dendritic branching was observed where the numbers of terminal dendritic branches in all classes of neurons were increased. Defective dendritic tiling was also observed, where the class IV neuron dendritic branches often overlapped with the dendrites of the same neuron (iso-neuronal tiling defects) and with dendrites from other neurons of the same class (hetero-neuronal tiling defects). Timelapse imaging studies showed that when class IV dendrites get close to branches of same neurons or other class IV neurons, they make a turn to avoid crossing them in wild-type animals; *fry* mutant dendrites could not turn away from homologous dendrites, resulting in dendritic branches crossing each other with straight trajectories. Mosaic analysis indicated that Trc and Fry act cell autonomously to regulate dendritic branching and tiling. The kinase domain of Trc is essential for both activities, and Fry positively regulates Trc kinase activity in an as yet unidentified manner.

Since *trc/fry* mutants exhibit tiling and overbranching defects, the tiling defect could be a secondary consequence of overgrowth. Two lines of evidence argue against this possibility. First, a hypomorphic allele of *fry* showed only tiling but not branching defects. Second and more interestingly, when exploring connections with other molecular pathways in dendritic development, Emoto et al. found that Trc forms a complex with and negatively regulates Rac GTPase, previously known to be important for dendritic morphogenesis. Genetic interaction studies indicated that only the Trc regulation of dendritic branching, but not tiling, is affected by manipulating Rac activity.

Is the Trc/Fry signaling pathway functionally conserved to control dendritic tiling? In a recent issue of *Neuron*, Gallegos and Bargmann (2004) reported that Sax-1 and Sax-2, homologs of Trc and Fry in *C. elegans*, are also essential for tiling of neurites of two neurons, ALM and PLM. Both contribute to mechanosensation for the anterior and posterior half of the animal, respectively. Interestingly, tiling of ALM and PLM uses a different strategy than class IV da neurons in *Drosophila*.

During development they transiently overlap their territories, which is later resolved through regulation of relative growth of body and neurites. Neurite-neurite repulsion is unlikely used here, as removal of ALM does not affect growth extent of the PLM neurite. Despite these differences, the same molecular machinery is used to achieve the same eventual purpose—in the case of ALM and PLM tiling, Sax-1/Sax-2 appear to regulate neurite termination as compared to Fry/Trc regulating terminal branch turning.

Even in the case of the mammalian retina, where dendrite-dendrite interaction has been strongly implicated in tiling, other mechanisms may also contribute. Indeed a recent study using genetic mutations in mice that remove a large fraction of RGCs showed that characteristic dendritic arbors can form without homotypic dendritic contacts (Lin et al., 2004). Tiling is likely achieved through sequential steps. Neurons of a given class may be generated in a defined space pattern; each class of neurons may have an autonomous program to decide roughly how large the dendritic tree should be; dendrite-dendrite interactions may then be used at the end stage of dendritic growth to achieve the eventual tiling.

For the first time, an evolutionarily conserved pathway for dendritic tiling involving Trc/Fry (Sax-1/Sax-2) has been identified. These findings of Emoto et al. and Gallegos and Bargmann raise several new questions. For example, what proteins on the dendritic surface of class IV da neurons sense the like dendrite and transduce the signal to Trc/Fry? Is homotypic dendritic repulsion mediated by direct contact or short-range diffusible molecules? Do Sax-1/Sax-2 transduce signals from the extracellular environment or are they part of an intrinsic developmental program? How does Fry regulate Trc? What are the downstream effectors regulating dendritic tiling? Are mammalian homologs of these molecules essential for RGC dendritic tiling? Finally and perhaps the most enigmatic of all, what allows dendrites of different neuronal types to distinguish self from nonself?

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A Nuclear Strike against *Listeria*—The Evolving Life of LXR

LXRs are members of the nuclear receptor superfamily and function as master regulators of cholesterol metabolism. In the macrophage, they control cholesterol efflux and inhibit the transcription factor NF-κB-mediated proinflammatory responses. In this issue of *Cell*, Joseph et al. (2004) discover surprising, protective functions for LXRα in innate immunity.

Liver X receptors (LXRs) are members of the nuclear receptor superfamily that bind oxysterol metabolites and heterodimerize with retinoid X receptors (Repa and Mangelsdorf, 2002). They emerged as key mediators of cholesterol homeostasis following the discovery that LXRα null mice develop enlarged, cholesterol-laden livers and elevated serum cholesterol levels upon exposure to high-cholesterol diets. Indeed, LXRs function as cholesterol sensors, coordinately regulating target genes for cholesterol efflux, bile acid production, and lipid transport to maintain cholesterol homeostasis. The α isoform is relatively restricted to liver, macrophages, kidney, adipose tissue, and the intestine, whereas the β isoform is more broadly expressed. To date, this difference in distribution has been the major distinction between LXR isoforms, which have appeared functionally indistinct.

The role of LXRs in macrophage biology, where LXRα and LXRβ are coexpressed, has been an area of significant progress. Work has particularly focused on the function of LXRs in atherosclerosis, a chronic inflammatory disease driven by the foam cell macrophage. LXRα/β dual agonists potently inhibit atherogenesis in animal models, and, conversely, transplantation of bone marrow devoid of both LXR isoforms substantially hastens atherosclerosis in mice (Joseph et al., 2002; Tangirala et al., 2002; Terasaka et al., 2003). Taken together, data suggest that LXR may protect against vascular disease not only through peripheral effects on cholesterol metabolism but via direct activities within the atherosclerotic lesion. LXR drives cholesterol efflux from the macrophage through upregulation of the reverse cholesterol transport protein ABCA1, and, unexpectedly, LXR mitigates macrophage inflammation via repression of NF-κB signaling (Figure 1) (Joseph et al., 2003; Venkateswaran et al., 2000).

In this issue of *Cell*, new studies deepen the ties between LXR and inflammation by uncovering a protective role for LXR in immunity to *Listeria monocytogenes*, a gram-positive bacteria implicated in serious food-borne human illness, including gastroenteritis, meningitis, and intrauterine fetal demise (Joseph et al., 2004). *Listeria* infects by escaping the phagolysosome to enter the cell cytosol, where it multiplies and can spread directly from cell to cell. In experimental listeriosis, bacteria injected via the tail vein are routed to the liver and spleen, where most are destroyed by resident macrophages (Vazquez-Boland et al., 2001). Surviving bacteria grow and infect hepatocytes but are initially countered by the innate antimicrobial defenses of macrophages and neutrophils