Crums turns the corner

Crumbs (Crb) helps flies distinguish apical from basal in their epithelia. Now two new studies show that it is required for cell expansion independently of its specification of apical polarity. During cell expansion, the apical domain of photoreceptors elongates perpendicular to the apical–basal axis so that the domain can extend from the top to the bottom of the fly eye. The process may be conserved in humans, consistent with the recent finding that mutations in the human homologue, CRB1, lead to human retinitis pigmentosa.

In the maturing fly eye, the apical domains and rhabdomeres (containing visual pigment) are in the center of each cluster of photoreceptor cells. The rhabdomere is linked by the stalk membrane to the adherens junctions (AJs), which separate the apical and basolateral membranes.

The new studies by Ulrich Tepass (University of Toronto, Toronto, Canada) and colleagues and Kwang-Wook Choi (Baylor College of Medicine, Houston, TX) and colleagues demonstrate that the human and fly versions of Crumbs localize to corresponding domains of the apical plasma membrane in the stalk of the fly photoreceptor and the inner segment of mammalian photoreceptors. In this region, Crb appears to be carrying out two functions. First, it cements the AJs together so they form a continuous band from the top to the bottom of the eye. Crb is ideally suited for this job because, based on its function in determining cell polarity, it is already in the correct, apical part of the eye where the AJs are needed. Second, Crb contributes to the elongation of the rhabdomere during the rapid growth that drives expansion toward the base of the retina. Tepass hypothesizes that this may be a consequence of Crb binding a web of β1 Spectrin, which then reduces the general level of endocytosis.

Overexpression of corresponding domains of fly Crb and human CRB1 had similar effects, suggesting that the function of the protein is conserved between the species, despite marked differences in the light receptors. Further study of the system in flies may provide clues about why the retinal degeneration seen in humans is a relatively slow process.

References: Izaddoost, S., et al. 2002. Nature. 10.1038/nature720. Pellikka, M., et al. 2002. Nature. 10.1038/nature721.

A dual purpose antideath agent

Growth factor receptors can promote life, and now Reza Zarnegar and colleagues (University of Pittsburgh, Pittsburgh, PA) show they can also prevent death, via physical interactions with death receptors.

Hepatocyte growth factor (HGF) binds to and activates the receptor tyrosine kinase Met, which promotes cell survival by activating antiapoptotic programs such as the PI-3 kinase signaling cascade. The opposite result is triggered when Fas ligand (FasL) binds to the death receptor Fas, triggering its homotrimerization and the formation of a docking site for death-inducing factors, such as caspase-8. Aggregation of Fas independent of FasL is believed to be sufficient to initiate apoptosis, but under growth conditions is somehow prevented.

Zarnegar has now shown that Met directly associates with the majority of Fas, preventing self aggregation. Additionally, Met binding masks the FasL binding site on Fas, thereby preventing ligand-induced homotrimerization. Only high concentrations of Fasl will displace Met, allowing Fas to trigger the activation of caspases and the progression of cell death. In vivo, Met overexpression makes transgenic mice resistant to hepatic apoptosis induced by Fas.

Fas binding does not inhibit HGF binding of Met, so that HGF/Met signaling can still occur. But high concentrations of HGF can dissociate Met from Fas, sensitizing cells to death ligands. These results explain previous, seemingly paradoxical, reports that HGF could both prevent and induce cell death in culture.

The extracellular domain of Met alone is necessary to bind to and inhibit Fas. Thus, says Zarnegar, “Met acts as a double-edged sword against apoptosis from the outside and inside of the cell,” via its Fas-binding and antiapoptotic signaling activities, respectively. In cancerous cells, high levels of Met may down-regulate apoptosis by both methods, so cells are resistant to both extrinsic (death receptor) and intrinsic (DNA damage) apoptotic signals.

Reference: Wang, X., et al. 2002. Mol. Cell. 9:411–421.