the lining between our bodies and the outside environment. The apical sides of these polarized cells face the topological exterior and the basolateral sides face the topological interior. The two compartments are kept separate by tight junctions and adherens junctions, which form seals between each cell in the epithelial sheet. These cell junctions prevent movement of ligands, nutrients and solutes across the epithelial sheet, such that the different sides of epithelial cells interact with different extracellular environments and have distinct cellular functions. Epithelial cells also secrete different types of lipids and transmembrane proteins to their apical and basolateral membrane domains, and the cell junctions keep the two membrane domains distinct by preventing lateral diffusion from the apical to the basolateral sides or vice versa.

Cdc42 and Rac1 have both been implicated in maintaining the polarity of epithelial cells. Both are members of the Rho family of small GTPases, which act as molecular switches to regulate diverse cellular events, such as organization of the actin cytoskeleton, regulation of cell-signalling pathways and formation of the cleavage furrow. Recent findings have shown that Cdc42 is involved in establishing epithelial polarity by regulating the fidelity of polarized transport of secretory vesicles. Rac1 is necessary for proper formation of tight junctions in epithelial cells, as expression of either a constitutively active or a dominant negative form of this protein results in disruption of the structure of tight junctions[6].

The excitement from the three recent papers has arisen because they indicate that there may be a link between Cdc42-mediated cell polarity and Par6-mediated asymmetric cell division. The recent results are also important because they help to fill gaps in our knowledge of how Cdc42/Rac1 and Par6 work, by identifying potential downstream effectors for Cdc42/Rac1 (the Par proteins) and potential upstream regulators of the Par proteins (Cdc42/Rac1).

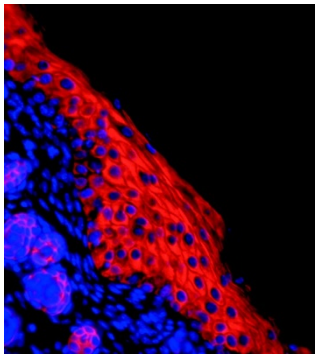
The authors of the three recent papers have independently reported the surprising finding that mammalian Par6 binds to both Cdc42 and Rac1. This result raises the exciting possibility of a mechanistic link between the maintenance of epithelial polarity (which involves Cdc42 and Rac1) and the setting up of asymmetry in a cell before cell division (which involves Par6). Cdc42 and

The consequences of incontinentia pigmenti

The link between well-studied signalling pathways and the causes of hereditary human disease is becoming stronger, especially with the advent of sequenced genomes and reverse genetics. One pathway that had not yet been implicated in a hereditary human disease was the NFκB signalling pathway. NFκB acts as either a homo- or heterodimer (of NFκB or Rel-family proteins), which is sequestered in the cytoplasm through interaction with an inhibitory molecule of the IκB family. Stimuli such as cytokines or viral infection lead to phosphorylation of IκB by Iκ kinase (IKK), which releases free NFκB to activate target genes. The IKK complex consists of many subunits, including two catalytic subunits, IKKα and IKKβ, and a regulatory subunit, IKKγ. Without the action of IKKγ, IKK is not activated, NFκB is not activated and cells will not generate an innate or adaptive immune response or resistance to apoptosis, especially that induced by tumour necrosis factor (TNF)-α.

Knockout mouse models of both IKKα and IKKβ have been generated, and despite their similar sequences the two catalytic subunits seem to have very different biological functions. IKKα-deficient mice have mild epithelial defects, whereas those lacking IKKβ have serious NFκB/IKK inflammatory-response phenotypes. Recently, two groups (Makris *et al.*, *Mol. Cell* **5,** 969–979, 2000; Schmidt-Supprian *et al.*, *Mol. Cell* **5,** 981–992, 2000) undertook the knock-out of IKKγ.

As it is encoded by an X-linked gene, male mice lacking IKKγ die in the uterus, whereas female heterozygous mice are born and immediately develop severe dermatopathy. This disease, which is caused by proliferation of keratinocytes, skin inflammation, hyperkeratotic lesions and increased cellular apoptosis, although physically scarring, is only transient (picture shows skin from IKKγ heterozygous females stained with the epidermal marker cK17; nuclei are stained in blue). IKKγ-heterozygous female mice recover and, despite retarded growth, go on to live relatively normal lives. The striking and transient nature of this phenotype led both groups to look for inherited human diseases that cause a similar phenotype in female sufferers. At the same time a different group was tackling this problem the other way around. The International Incontinentia Pigmenti (IP) Consortium was trying to identify the gene responsible for a female X-linked inherited disease that causes a variable, but transient, phenotype in adult females. The consortium discovered that female patients who have inherited,



K MARKIS

and recovered from, IP have mutations in the IKKγ gene. The group went on to show that in affected patients levels of IκB are increased and NFκB is not translocated to the nucleus. The genes downstream of NFκB that are essential for the immune response are therefore not activated and so the cells are very sensitive to pro-apoptotic signals.

But how can the lack of IKKγ cause this disease and why is it transient? As the IKKγ gene is present on the X chromosome, affected males die. Heterozygous females inherit one copy of each gene, and as somatic cells undergo random inactivation of X chromosomes, specific cells will become deficient for NFκB function. Makris and colleagues have proposed a model in which IKKγ-deficient cells in affected females undergo rapid hyperproliferation, leading to increased apoptosis and increased chemokine production in neighbouring NFκB-positive cells. Granulocyte infiltration increases in this area, causing the hyperproliferation and inflammation seen in affected patients. These cells undergo necrotic decay and release their contents, triggering an immune response and giving rise to the transiency of the disease.

In years to come it will be interesting to determine the full consequences of this disease and to obtain confirmation of the model proposed by Makris and colleagues; nevertheless, the implication of another known signalling pathway in an inherited human condition is an achievement in itself.

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