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Apical junctional complexes and cell polarity

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Recent studies have greatly expanded our knowledge of initial events that lead to epithelial cell polarity. Epithelial polarity is defined, in part, by apical cell–cell tight junctions that separate the plasma membrane into the apical domain and the basolateral domain, as well as the zonula adherens that mediate intercellular adhesion. The process of epithelial polarization is closely coupled to the biogenesis of these junctions. Studies in mammalian epithelial cells and lower organisms have identified two evolutionarily conserved junctional complexes as important epithelia polarity regulators: the Crumbs complex and the partitioning defective complex. Disruption of the components of the two complexes leads to a disorder of epithelial cell polarity and defects in junction formation or maintenance. Recent discoveries have revealed more details of how the two junctional polarity complexes function to establish epithelial polarity. They also raised the question about the relationship between polarity and adhesion. Although it is widely accepted that cell–cell adhesion provides a landmark from which polarity can proceed, there are results pointing to the possibility that polarity complexes can regulate cell–cell adhesion. It seems likely that proteins that control cell adhesion and cell polarity work intimately together to establish final epithelial polarity.

Kidney International (2007) **72,** 1448–1458; doi:10.1038/sj.ki.5002579; published online 3 October 2007

KEYWORDS: epithelial polarity; tight junctions; adherens junctions; CRB complex; PAR complex; EMT

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Received 19 June 2007; revised 17 August 2007; accepted 21 August 2007; published online 3 October 2007

The bodies of Metazoa enclose numerous highly organized cavities and compartments that are lined by sheets of epithelial cells. To protect the integrity of these cavities and compartments, epithelial cells have developed various intercellular junctions so that they are tightly packed and strongly adherent to one another. These junctions include the tight junctions (TJs) and the zonula adherens (ZA), which together comprise the apical junctional complexes. In addition to the protection function, epithelial cells are highly polarized and they mediate diverse polarized activities including absorption, secretion, transcellular transport, and sensation. The polarization of epithelial cells is reflected by the asymmetric distribution of proteins and lipids into the apical and basolateral surfaces. The apical domain faces the lumen while the basolateral domain consists of the basal domain that contacts the basement membrane and the lateral domain that contacts the neighboring cells. The process of apical–basal polarization is closely coupled to the establishment of the apical junctional complexes.

The TJ, also referred to as the zonula occludens, is the apical most structure of the intercellular junctional complex. It carries out two important functions: first, it forms tight seals between epithelial cells and creates a selectively permeable barrier to diffusion through the intercellular space, namely the barrier function;[1] second, it physically separates the apical and basolateral membranes and prevents the intermixing of the components of the two membrane domains, namely the fence function.[2] TJs are revealed to be the tight apposition of neighboring epithelial cells in conventional electron micrographs, while in freeze-fracture electron micrographs, they appear as a continuous network of parallel and interconnected strands that circumscribe the apex of lateral membranes.[3] TJs are composed of three families of transmembrane proteins: occludin, claudins, and junctional adhesion molecules. They reach across the intercellular space and connect the membranes of adjacent epithelial cells (reviewed in Shin *et al.*[4]). The functional equivalent structure in *Drosophila* epithelia is the septate junction, which lies basal to the ZA and has a different molecular composition.[5]

The adhesion between epithelial cells is primarily contributed by the ZA, which is also called the adherens junction in vertebrates. It is an adhesive belt that encircles the cell just below the apical surface, and it lays basal to TJs in mammalian epithelial cells. Cadherins represent the primary structural component of ZA and their calcium-dependent

trans-dimerization provides the adhesion between neighboring epithelial cells. Cryo-electron microscopy of the adherens junction reveals rod-like structures extending from the extracellular surface into the intercellular space, and it is suggested that they represent the extracellular domains of E-cadherin.[6] Other adherens junction transmembrane components include Nectins and nectin-like molecules, and they *trans*-interact in a calcium-independent manner.[7]

The apical junctional complexes are dynamic structures. They undergo dramatic rearrangement and redistribution during embryonic development. The cytoplasmic domains of the junctional structural components are associated with various adaptor proteins as well as signaling elements, and they are linked to the cytoskeleton. These connections integrate the dynamics of cell–cell junctions with a number of cellular processes such as migration, proliferation, differentiation as well as pathological processes that include tumor cell metastasis, infiltration, and microbial infections.

APICAL POLARITY COMPLEXES

The formation of junctional complexes is intimately linked to cell polarization. Recent studies in mammalian systems and lower organisms have revealed several evolutionarily conserved protein complexes that regulate cell polarization. The complicated interplay among these complexes and their orderly function regulate the establishment of epithelial cell polarity and the cell–cell junctions. Studies of the apical membrane domain have focused on two major complexes, the Crumbs (CRB) complex and the partitioning defective (PAR) complex.[8] These complexes are important in recognizing the initial polarization cues, and they play a pivotal role in regulating the establishment of apical junctional complexes.

Work in both the mammalian and *Drosophila* systems have demonstrated that the CRB complex and the PAR complex have a conserved function in the establishment and maintenance of apical–basal polarity. In this review, the composition and function of these complexes will be summarized, with an emphasis on recent literature that highlight novel aspects of their structure and function.

CRB complex

The CRB complex is composed of three proteins: CRB, protein associated with Lin Seven 1 (PALS1), and PALS1-associated tight junction protein (PATJ) (see Figure 1). In *Drosophila*, CRB is localized to the apical membrane and the subapical region. The subapical region represents a spot where the apical membrane ends and the lateral membrane begins. In mammalian cells, this is the site of the TJ, but in *Drosophila* no junction is localized at this point. In *Drosophila*, CRB is an important apical membrane determinant, as the plasma membrane-associated expression of CRB is necessary and sufficient to confer apical character on a membrane domain, and overexpression of CRB results in an expansion of the apical plasma membrane with concomitant reduction of the basolateral domain.[9] *Drosophila* CRB is a transmembrane protein with 30 EGF-like and 4 laminin A G-domain-like repeats in its extracellular domain. The exact function of this large extracellular domain is not clear, since a truncated form of CRB devoid of the entire extracellular domain is sufficient to rescue the CRB mutant *Drosophila* embryo.[9] The short cytoplasmic domain of CRB contains two functionally important motifs.[10] The 4.1/ezrin/radaxin/moesin (FERM) domain-binding motif of zebrafish CRB binds an FERM protein Moe, and it has been shown recently that Yurt, the *Drosophila* ortholog of zebrafish Moe, interacts with the *Drosophila* CRB FERM-binding motif.[11,12] This interaction is conserved between the mammalian Yurt orthologs YMO1 and EHM2 and the mammalian CRB proteins, and it may be part of a negative feedback loop that regulates CRB activity.[12] The C-terminal postsynaptic density/discs large/zonula occludens (PDZ) domain-binding motif, on the other hand, is recognized by the PDZ domain of Stardust, the *Drosophila* homolog of PALS1.[13,14] The CRB–Stardust interaction is important for the biogenesis of the ZA, which is a pivotal step in the establishment of epithelial integrity.[15,16]

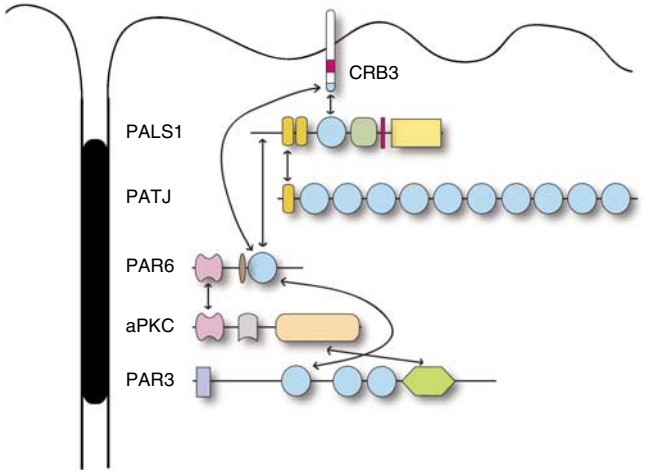

Figure 1 | Domain structures of components of the CRB complex and the PAR complex. Protein domains are represented by filled shapes. Note that CRB3 is depicted larger in proportion to other proteins, and the red and blue fills represent the FERM-binding motif and the PDZ-binding motif respectively. Protein–protein interactions are indicated by double-headed arrows.

Three mammalian CRB proteins have been identified, all of which consist of a transmembrane domain and an intracellular domain with the conserved FERM- and PDZ-binding motifs. CRB1 is the human ortholog of *Drosophila* CRB, and it is expressed primarily in the eye and brain. Mutations in CRB1 cause various diseases including Leber congenital amaurosis and retinitis pigmentosa.[17,18] CRB2 has not been extensively characterized to date. CRB3 is expressed ubiquitously in epithelial tissues, and unlike *Drosophila* CRB and the other two mammalian CRB proteins has a very short extracellular domain. CRB3 is localized to the apical membrane of mammalian epithelial cells and concentrated to TJs, where it interacts with PALS1 with its C-terminal