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Tight junctions as regulators of tissue remodelling

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Formation of tissue barriers by epithelial and endothelial cells requires neighbouring cells to interact via intercellular junctions, which includes tight junctions. Tight junctions form a semipermeable paracellular diffusion barrier and act as signalling hubs that guide cell behaviour and differentiation. Components of tight junctions are also expressed in cell types not forming tight junctions, such as cardiomyocytes, where they associate with facia adherens and/or gap junctions. This review will focus on tight junction proteins and their importance in tissue homeostasis and remodelling with a particular emphasis on what we have learned from animal models and human diseases.

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Introduction

Cells interact with their neighbours and the underlying extracellular matrix via specialized protein complexes that mediate adhesion, maintain structure and transmit information to the cell interior about the environment. This information is essential for different aspects of tissue functions as well as for physiological and pathological remodelling. At the lateral membrane of epithelia and endothelia, junctional complexes include tight junctions (TJ) and adherens junctions (AJs), two adhesion complexes that are structurally and functionally intertwined (Figure 1). TJ form regulatable semipermeable paracellular barriers that control paracellular diffusion of solutes according to size and charge, and function as fences that restrict lipid diffusion between the apical and basolateral membrane domains (Figure 2). TJ also act as signalling hubs that guide epithelial proliferation, polarisation and differentiation. TJ-associated transmembrane proteins interact with different components of the TJ-associated cytoplasmic plaque. Although not fully understood, these interactions result in a protein network that controls multiple cell functions involved in tissue remodelling such as junctional dynamics, cell migration, proliferation and gene expression. TJ structure, composition and function have recently been reviewed [1,2]. Here, we will focus on TJ and their contributions to tissue remodelling with an emphasis on transmembrane proteins and RhoGTPase signalling.

Transmembrane proteins of TJ

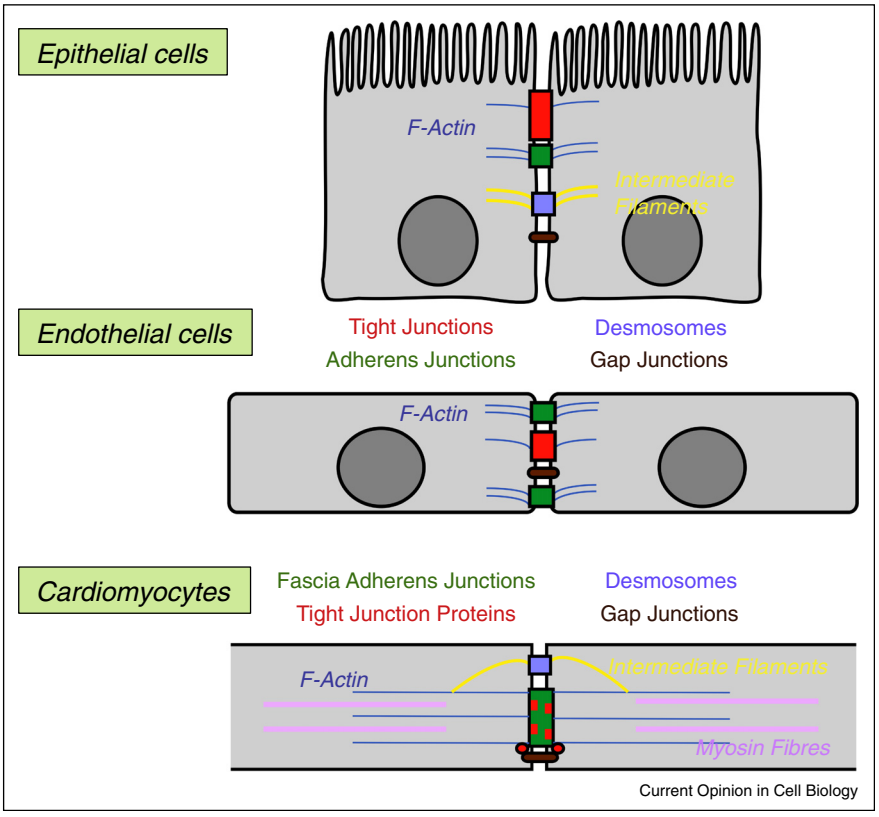
TJ contain a complex set of transmembrane proteins that includes the tetraspan proteins of the claudin family and occludin-related Marvel domain proteins, as well as multiple adhesion proteins with immunoglobulin-like domains. *In vivo* studies have linked these proteins to different types of physiological and pathological examples of tissue remodelling (Table 1).

Marvel domain proteins

TJ contain three Marvel domain proteins: occludin, tricellulin or MarvelD2, and MarvelD3. MARVEL domains are motifs based on four transmembrane helices and are found in proteins involved in membrane–membrane aposition. Although the three proteins are related, they have distinct functions. Occludin knockout mice have a complex phenotype, which includes hyperplasia and chronic inflammation of the gastric epithelium, calcification in the brain, testicular atrophy, loss of cytoplasmic granules in striated duct cells of the salivary gland, and thinning of compact bones. The underlying mechanisms are not known. However, manipulation of occludin in culture affects the junctional barrier functions with its N-terminal domain being important for the regulation of neutrophil transmigration. Occludin depletion also inhibits Rho activation required for extrusion of apoptotic cells from monolayers. It is thus possible that defects in leukocyte transmigration and cell extrusion lead to chronic inflammation and hyperplasia of epithelial tissues *in vivo*.

Occludin depletion leads to junctional remodelling with tricellulin, normally concentrated at tricellular corners, becoming more equally distributed along the cell periphery. Tricellulin is essential for sealing tricellular corners and for hearing in human and mice; hence, occludin deficiency in mice also leads to deafness as the normal tricellulin localization is disrupted in the hair cells of the inner ear [3•]. The underlying mechanisms are not well understood. However, tricellulin has recently been shown to regulate RhoGTPase signalling by recruiting the guanine-nucleotide-exchange factor (GEF) Tuba (ARHGEF36) and, thereby, modulating Cdc42 activation and tension generated at tricellular corners [4]. Whether the

Figure 1



Intercellular junctions in epithelia, endothelia and cardiomyocytes. Schematic representation of main intercellular junctions in vertebrate cell types discussed in this review. Epithelia and endothelia form tight and adherens junctions that are often closely associated and linked to the actin cytoskeleton. Mature tight and adherens junctions are morphologically and biochemically distinct but form from a primordial junction that contains tight and adherens junctions. In epithelia, tight junctions generally form the apical/lateral border and, hence, are localized more apically than adherens junctions. In endothelia, the two junctions can be intercalated. Cardiomyocytes do not form tight junctions but form a variant of adherens junctions, fascia adherens junctions, that also contains proteins associated with tight junctions in epithelia. Gap junctions, which form small channels allowing cell–cell communication, are expressed in all three cell types and also recruite tight junction proteins in some cell types. Epithelia and cardiomyocites also form desmosomes that link the junctional complex to intermediate filaments.

Tuba/tricellulin interaction is indeed related to hair cell degeneration and deafness is unknown.

The third Marvel protein, MarvelD3 regulates cell migration and proliferation in cells in culture, and MarvelD3 overexpression in pancreatic cancer cells inhibits tumour growth *in vivo* in mouse xenographs [5•]. MarvelD3 modulates JNK activation by inhibiting MEKK1, an upstream component of the JNK pathway. This regulatory function is also important during osmotic stress-induced cytoskeletal remodelling, as MarvelD3-mediated tuning of JNK signalling is required to maintain junctional integrity and support cell survival. Further studies will need to address the role of MarvelD3 in tissue remodelling *in vivo*.

Claudins

Claudins are part of the paracellular diffusion barrier and mediate ion-selective paracellular diffusion by constituting conductive paracellular pores [6]. Knockout studies in mice support this role and report phenotypes related to barrier formation and paracellular ion diffusion. Barrier defects often lead to inflammatory responses and, consequently, tissue remodelling. Examples include knockouts of claudin-2, which leads to increased colorectal inflammation and gallstones; claudin-4, which provokes acute lung inflammation; and claudin-7, which induces intestinal inflammatory remodelling (Table 1) [7•,8,9]. Given the barrier defects, however, it is generally assumed that the inflammation is an indirect response caused by increased tissue permeability rather than reflecting a direct role in inflammatory signalling. An exception is claudin-18. Although its deletion also leads to lung remodelling, it is also required to activate NF-κB in response to RANKL-stimulated osteoclast differentiation [4,10•,11,12].

A different example is provided by claudin-1. Claudin-1 (−/−) mice have an abnormal skin structure and function. Claudin-1 is expressed in the stratum granulosum of the