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Review

Tight junctions and the regulation of gene expression

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ABSTRACT

Cell adhesion is a key regulator of cell differentiation. Cell interactions with neighboring cells and the extracellular matrix regulate gene expression, cell proliferation, polarity and apoptosis. Apical cell–cell junctions participate in these processes using different types of proteins, some of them exhibit nuclear and junctional localization and are called NACos for Nuclear Adhesion Complexes. Tight junctions are one type of such cell–cell junctions and several signaling complexes have been identified to associate with them. In general, expression of tight junction components suppresses proliferation to allow differentiation in a coordinated manner with adherens junctions and extracellular matrix adhesion. These tight junction components have been shown to affect several signaling and transcriptional pathways, and changes in the expression of tight junction proteins are associated with several disease conditions, such as cancer. Here, we will review how tight junction proteins participate in the regulation of gene expression and cell proliferation, as well as how they are regulated themselves by different mechanisms involved in gene expression and cell differentiation.

Contents

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1. Introduction

For the development and function of epithelial tissues, the interactions of epithelial cells with each other and the extracellular matrix via specialized adhesive structures play a critical role. Therefore, during the last years a key area of cell and developmental biology has been to understand how epithelial cells interact with their neighbors and the extracellular matrix, to regulate intracellular signal transduction, as well as transcriptional and translational regulatory mechanisms of gene expression involved in the control of cell proliferation and differentiation. The apical epithelial intercellular complex consists of tight junctions (TJs), adherens junctions, and desmosomes. As reviewed in other chapters of this series, adherens junctions and desmosomes are adhesive junctions that are linked to the actin and intermediate filament cytoskeleton, respectively [1–3]. TJs also interact with the actin cytoskeleton and function as selective barriers that restrict paracellular diffusion – the gate function – as well as apical/basolateral intramembrane diffusion of lipids — the fence function [4–7]. A fourth type of intercellular junctions are gap junctions, which allow cell to cell communication via the exchange of small diffusible molecules [8,9]. At the basal membrane, epithelial cells adhere to the extracellular matrix mainly via integrins and syndecans [10]. All of these adhesion complexes consist of particular sets of transmembrane proteins that interact extracellularly with ligands and intracellularly with generally large multimeric protein complexes consisting of cytoskeletal linkers, signal transduction proteins as well as factors involved in DNA transcription and RNA processing.

The transmission of signals from adhesion complexes occurs according to two different principles: regulation of signaling cascades that transmit signals via several intermediates, and regulation of specific proteins that shuttle between sites of adhesion at the plasma membrane and the nucleus, a class of proteins we have previously proposed to call NACos [11–17].

We have previously reviewed how epithelial TJs and cell adhesion use these dual localization proteins to regulate gene expression in the context of G1/S phase transition and crosstalk with Ras signaling [11,18,19]. Here, we will provide an update on the role of TJs in the regulation of gene expression and review some recent observations on how the expression of TJs proteins can be controlled at the transcriptional level.

2. Tight junction associated proteins

The identification of TJ associated proteins has been a key area of cell biology during the last twenty years. Occludin, claudins, tricellulin, JAMs (Junction Adhesion Molecules), CRB-3 (a human homologue of *Drosophila* Crumbs) and Bves (blood vessel/epicardial substance) are the TJ-associated transmembrane proteins that have been identified [7,20–25]. We are only just starting to understand how each of these transmembrane proteins interacts with components of the cytoplasmic plaque and how these interactions affect cell functions.

The cytoplasmic plaque associated with TJs is formed by multiple adaptor and scaffold proteins (e.g., ZO-1/2/3, PATJ, Pals1, PAR-3 and PAR-6) as well as different types of signaling components such as GTP-binding proteins, protein kinases and phosphatases as well as transcriptional and post-transcriptional regulators [6,19,26,27]. Cytoplasmic plaque components interact with the membrane proteins as well as each other, resulting in a protein network that controls paracellular permeability, gene expression, junctional dynamics, proliferation and polarity. Although we start to know more about particular proteins and their interactions and functions, how these proteins work in the normal cellular context and which of their interaction partners are relevant for particular functions are still poorly understood.

ZO-1, the first TJ protein identified [28], can serve as a typical example. It is an adaptor protein that belongs to a family of proteins that contain different types of protein/protein interaction domains such as three PDZ and an SH3 domain, a domain homologous to yeast guanylate kinase (GUK domain) and an alternatively spliced large C-terminal domain that interacts with the actin cytoskeleton [29–31]. Other family members include PSD-95 (post-synaptic density-95) and DlgA (Discs large A), a *Drosophila* tumor suppressor. ZO-1 interacts with many different TJ proteins and at least some of these interactions are mutually exclusive; hence, ZO-1 seems to participate in distinct protein complexes that also might have distinct functions. Functionally, ZO-1 has been linked to both, assembly of functional junctions as well as signal transduction [26,32–34]. This is not restricted to vertebrate cells, the *Drosophila* homologue of ZO-1, Tamou/Polychaetoid, associates with adherens junctions and regulates dorsal closure, epithelial migration, and cell fate determination in sensory organs [35,36], and is required for cell specification and rearrangement during *Drosophila* tracheal morphogenesis [37]. In agreement, knockout of ZO-1 in mice has recently also been shown to cause an embryonic lethal phenotype associated with defects in yolk sac angiogenesis and apoptosis of embryonic cells [38].

3. ZO-1 and ZONAB in the control of cell proliferation and gene expression

Several of the TJ-associated adaptor proteins have been linked to the regulation of epithelial proliferation, and two of them, ZO-1 and ZO-2, have been shown to regulate transcription factors (Fig. 1). In the case of ZO-1, reduced expression correlates with increased proliferation of epithelial cells and/or transformation. For example, in proliferative cells, during corneal wound repair and in colorectal epithelial cells transformed by overexpression of beta-catenin, ZO-1 is downregulated [39,40]. Similarly, ZO-1 is downregulated in breast cancer tissues[41], in primary and metastatic pancreatic cancer [42], in brain microvascular endothelial cells from human brain tumors [43] as well as several models of epithelial mesenchymal transition [44–47]. In agreement, increased expression of ZO-1 in MDCK cells reduces cell proliferation [48].

The mechanism by which ZO-1 regulates proliferation may involve nuclear translocation as ZO-1 has been reported to accumulate transiently in the nucleus of proliferating cells. However, the role of nuclear ZO-1 is not clear as not all investigators have found it in the nucleus, suggesting that additional unknown parameters might affect its nuclear distribution [49–54]. In fact, ZO-1 inhibits cell proliferation outside of the nucleus by cytoplasmic sequestration of the Y-box transcription factor ZONAB, which interacts with the cell cycle regulator CDK4 and controls expression of cell cycle regulators such as cyclin D1 and PCNA [48,50,55]. ZO-1 also interacts with the NaCo ubinuclein, a protein that interacts with viral transcription factors in the nucleus and ZO-1 at epithelial TJs [56]. Little is known about the functional relevance of the interaction between ZO-1 and ubinuclein; however, it may play a role during differentiation as their interaction is cell density dependent, similarly to the one with ZONAB.

ZONAB is a Y-box transcription factor, a class of multifunctional regulators of gene expression and cell proliferation [57,58]. The Y-box factor family includes DbpA/ZONAB, DbpB/YB-1 and DbpC/contrin. DbpA and DbpB were originally identified as DNA binding proteins of the promoters of EGF receptors and MHC II [59,60]. DbpB/YB-1 is the most extensively studied Y-box factor. Overexpression of DbpB/YB-1 increases the expression of genes involved in proliferation, including cyclin A, cyclin B1, EGFR and erbB2 [61–63]. Although DbpB/YB-1 does not seem to associate with cell junctions as DbpA/ZONAB does [50] (Matter and Balda, unpublished), the two Y-box factors seem to be functionally redundant to some extent. Knockout experiments in mice have shown that ZONAB/MSY3-deficient animals develop normally but, if combined with a DbpB/YB-1 knockout, die earlier than animals with a DbpB/YB-1 knockout alone [64]. Nevertheless, the molecular basis for this redundancy is not known.

ZONAB localizes to TJs, where it binds to the SH3 domain of ZO-1, and can be in the nucleus where it participates in the regulation of gene expression [48,50]. In MDCK cells, ZONAB's nuclear distribution is