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Review Article

E-Cadherin/β-Catenin Complex and the Epithelial Barrier

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E-Cadherin/β-catenin complex plays an important role in maintaining epithelial integrity and disrupting this complex affect not only the adhesive repertoire of a cell, but also the Wnt-signaling pathway. Aberrant expression of the complex is associated with a wide variety of human malignancies and disorders of fibrosis resulting from epithelial-mesenchymal transition. These associations provide insights into the complexity that is likely responsible for the fibrosis/tumor suppressive action of E-cadherin/β-catenin.

1. Introduction

Cell-cell junctions are important to maintain cell and tissue polarity and integrity. In general, vertebrate animals possess three intercellular junction systems: gap junctions, which serve as intercellular channels that permit direct cell-cell transfer of ions and small molecules; tight junctions, the primary cellular determinant of epithelial barrier function; anchoring junctions, which includes desmosomes and adheren junctions (AJs) that associate with the cortical cytoskeleton to mediate cell and tissue behavior [1]. Among constituent structural molecules that assemble to form AJ, cadherin/catenin-based anchoring junctions organize and tether microfilaments to maintain cell adhesive properties and integrate intra- and intercellular signaling, including regulation of nuclear functions and transcription pathways [2, 3]. This paper focuses on the role of E-cadherin/β-catenin protein complexes in forming the epithelial barrier and discusses the effects of dysregulating the assembly of the E-cadherin/β-catenin adhesion complex in fibrotic diseases and cancer.

2. The Cadherin/Catenin Complex

Cadherins constitute a large family of cell surface proteins, including E (epithelial)-, N (neural)-, VE (vascular-endothelial)-, P (placental)-, R (retinal)-, and K (kidney)-cadherins [4]. Classical cadherins are single-pass transmembrane proteins which participate in Ca^{2+}-dependent cell adhesion that is necessary to form solid tissues [2, 5]. E-cadherin is functionally linked to the generation of a polarized epithelial phenotype [6, 7]. The extracellular region of E-cadherin extends from the cell surface and bind to cadherins present on adjacent cells [8] whereas its intracellular region contains binding sites to interact with catenins and other regulatory proteins (Figure 1) [9]. Immunoprecipitation of detergent-solubilised cell extracts with anticadherin antibodies identified major proteins involved in the formation of cadherin: p120-, α-, β-, and γ-catenin (plakoglobin) [10, 11]. P120 catenin acts to bind to the juxtamembrane portion, and β-catenin or plakoglobin binds to the carboxy-terminal 100 amino acids of the cadherin cytoplasmic region [12]. α-catenin links β-catenin to actin, which in turn has the ability to promote AJ protein clustering and stabilization of cell adhesion [13]. To allow for a continuous assembly of cadherin/catenin complexes in AJs, cadherins can be constitutively endocytosed and recycled to the cell surface [14, 15]. In *Drosophila* epithelial cells, exocyst components Sec5, Sec6, and Sec15 directly regulate the trafficking of E-cadherin to AJs via interactions with β-catenin [16]. Images from time-lapse microscopy using

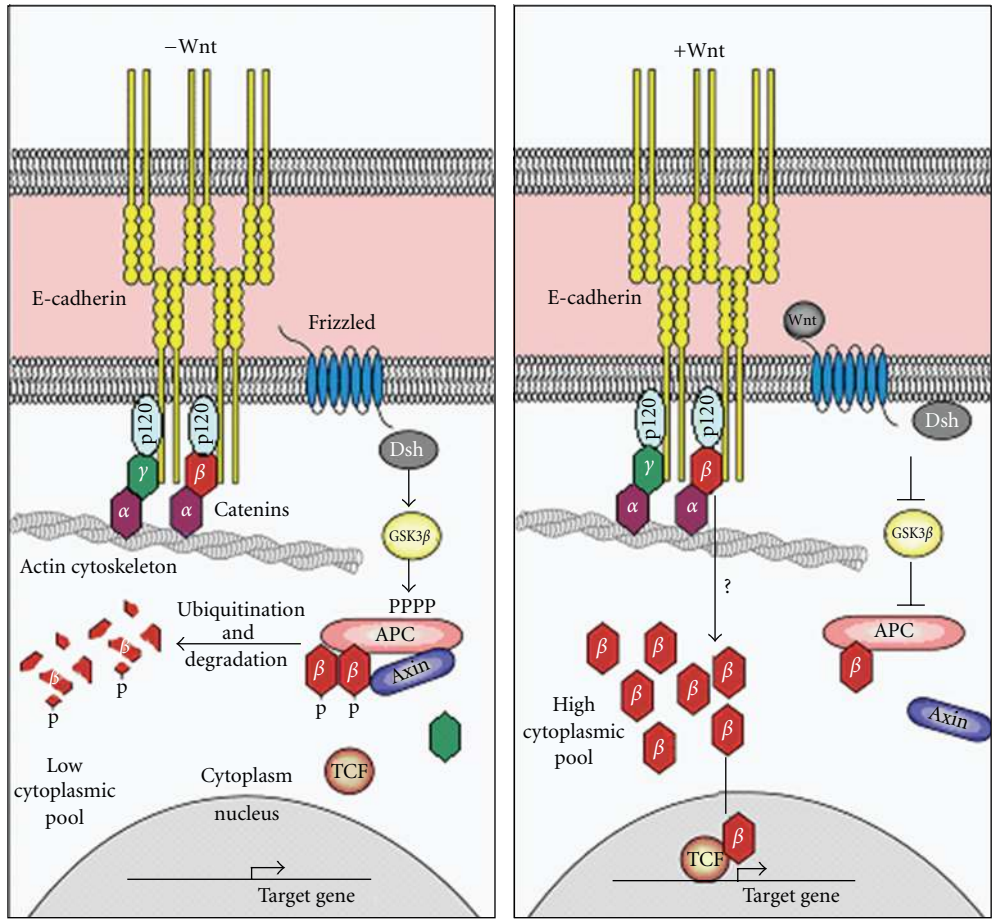

Figure 1: E-cadherin/β-catenin complex in epithelial cell-cell adhesion and Wnt signalling.

photoactivatable-GFP-tagged β-catenin in A431 cells show that β-catenin, internalised with E-cadherin, accumulates at the perinuclear endocytic recycling compartment (ERC) upon AJ dissociation [17].

3. E-Cadherin/β-Catenin-Mediated Signaling Pathways

Other than their structural role in stabilizing cell-cell contact, components of cadherin-catenin complex serve a role in activating several key signal transduction networks. β-catenin is a key regulator in the canonical Wnt signaling, where cytoplasmic β-catenin translocates to the nucleus and functions as an activator for T-cell factor (TCF)/lymphoid enhancer factor (LEF) transcription factors that result in a subset of cellular effects involving cellular adhesion, tissue morphogenesis, and tumor development (Figure 1) [18, 19]. In the absence of Wnt signals, a multiprotein destruction complex including axin and the adenomatous polyposis coli (APC) facilitates phosphorylation of serine residues in the N terminus of cytosolic β-catenin, which leads to its ubiquitination and proteosomal destruction (Figure 1) [20]. Wnt signaling inhibits this degradative process by binding to Frizzled receptors and signaling through the associated low-density lipoprotein-related proteins, LRP5/6, thereby allowing β-catenin to accumulate in the cytosol and enter the nucleus (Figure 1) [21–23]. Dissociation of AJ can influence E-cadherin endocytosis, β-catenin levels in the ERC, and β-catenin substrate levels available downstream for the Wnt pathway. One potential determinant in the structural integrity of the cadherin/β-catenin complex may lie in its phosphorylation status. Phosphorylation of E-cadherin or β-catenin by Ser/Thr kinase CK II stabilizes the complex [24, 25]. However, tyrosine 654 phosphorylation of β-catenin by an intracellular signaling event disrupts the E-cadherin/β-catenin complex and cell adhesion [26, 27]. The phosphorylation of β-catenin at tyrosine 489 or 142 strengthens Wnt signaling [28, 29]. Tyrosine phosphorylation can release β-catenin from E-cadherin, decrease cell-cell junction adhesion, and increase cell migration and invasiveness [30].

4. E-Cadherin/β-Catenin and Epithelial-Mesenchymal Transition (EMT)

E-cadherin/β-catenin protein complexes are involved actively in epithelial to mesenchymal (EMT) and mesenchymal to epithelial (MET) transitions, which play a particularly important role in embryo development, tissue fibrosis, and

cancer progression. The process of EMT is characterized by differentiated epithelial cells that undergo a phenotypic conversion that gives rise to the matrix-producing fibroblasts and myofibroblasts. Epithelial cells lose their marker proteins such as E-cadherin, zonula occludens-1 (ZO-1), and cytokeratin, and gain of a mesenchymal phenotype with expression of mesenchymal proteins including vimentin, α-smooth muscle actin (α-SMA), and fibroblast-specific protein-1 (FSP1), and production of interstitial matrix components type I collagen and fibronectin [31, 32]. Cell contacts are critical determinants of EMT. Loss of E-cadherin likely promotes β-catenin release and facilitates EMT, whereas the expression of E-cadherin can reverse the transformed phenotype [33–36]. β-catenin plays an important role in the TGF-β1- and cell contact-dependent, synergistic induction of EMT [37]. In the absence of TGF-β1, both E-cadherin and β-catenin are rapidly degraded following contact disassembly. However, TGF-β1 induces β-catenin dissociation from epithelial contacts and stabilizes β-catenin in the cytoplasm, making it available for nuclear import [38, 39]. So the loss of cell-cell adhesion triggers EMT and is associated with diseases involving EMT.

5. The Role of E-Cadherin/β-Catenin in Fibrosis

Fibrosis is an active extracellular matrix (ECM) biosynthetic process and represents the final pathway of chronic failure of many organs. Evidence of EMT has been reported in kidney, lung, liver, eye, and serosal membranes suggesting that EMT can be closely associated with the pathogenesis of fibrotic disorders in those organs [40]. E-cadherin downregulation responsible for the loss of cell-cell adhesion and β-catenin upregulation for the subsequent transcriptome program of EMT are two important changes in the process of fibrosis. Iwano et al. found that 36% of renal fibroblasts, the main effector cells in kidney fibrosis responsible for ECM production, originate from renal tubular epithelial cells via EMT [41] despite conflicting evidence about the relative importance of various sources of myofibroblasts was reported [42]. Decreased expression of E-cadherin and early expression of EMT-related markers as well as β-catenin cytoplasmic translocation have been detected in kidney specimens from patients with glomerulonephritis and diabetic and chronic allograft nephropathies [43–46]. Similar changes appear in lung epithelial cells of patients with idiopathic pulmonary fibrosis and usual interstitial pneumonia [47, 48], and in biliary epithelial cells of patients with primary biliary cirrhosis, primary sclerosing cholangitis and alcoholic liver disease [49]. The transition of retinal pigment epithelial cells into myofibroblasts is observed in patients with proliferative vitreoretinopathy, and peritoneal mesothelial cells from fluid effluents of dialyzed patients show a mesenchymal phenotype with reduced E-cadherin expression [50–52]. Nuclear β-catenin immunoreactivity suggests aberrant activation of Wnt/β-catenin signaling and subsequent EMT in the pathogenesis of a number of fibrotic disorders. In addition to the nuclear translocation of β-catenin, we previously reported that matrix metalloproteinase (MMP)-mediated E-cadherin disruption led directly to tubular epithelial cell EMT via Slug and that MMP-9 secreted by macrophages is capable of initiating tubular cell EMT by disruption of the E-cadherin/β-catenin complex [45, 53].

6. The Role of E-Cadherin/β-Catenin in Cancer

EMT is an important mechanism for the cancer development and initial step of metastasis [54, 55]. Disruption of E-cadherin/β-catenin might contribute to tumor aberrant morphogenetic effects. Loss of E-cadherin expression or loss of its normal localization at cell-cell contacts is consistently observed at sites of EMT during tumor progression. E-cadherin expression level is often inversely correlated with the tumor malignancy [56–58]. Cases of invasive lobular carcinoma have been associated commonly with the loss of E-cadherin expression as a result of E-cadherin gene mutation and promoter hypermethylation [59, 60]. Evidence from animal models has shown that conditional deletion of E-cadherin in p53-deficient mouse mammary epithelium promoted tumor initiation and progression to invasion and metastasis [61]. β-catenin is a critical element in the canonical Wnt signaling of tumorigenesis. Activating mutations of β-catenin or inactivating mutations of APC or Axin have been found to be associated with a wide variety of human malignancies, such as colorectal, ovarian endometrial, heptocellular, desmoid and pancreatic tumors [62, 63]. Cancer studies suggest that deregulated β-catenin signaling promotes tumorigenesis by inducing expression of oncogenes such as *c-myc* and *cyclin D1* [64–66]. Stabilizing mutations in the β-catenin N-terminal sequence have been found in 25% of metaplastic breast cancers [67]. Increased cytoplasmic and nuclear β-catenin levels have been observed in 40% of primary breast cancers and correlated with poor prognosis and worse patient survival [68–73].

7. Concluding Remarks

Taken together, these data show that in addition to their adhesive functions, the E-cadherin/β-catenin complex also plays a crucial role in modulating Wnt signaling. E-cadherin/β-catenin complex maintains integrity of epithelial cell-cell contact and keeps Wnt/β-catenin signals in check. Loss of cadherin-mediated cell adhesion can promote β-catenin signaling. The E-cadherin/β-catenin complex is very important in maintaining epithelial morphology, and high-affinity E-cadherin/β-catenin interaction can be disrupted during oncogenesis and fibrosis. This complex is dysregulated in response to mediators of inflammation, including MMPs, growth factors, and cytokines, suggesting that dysregulation of E-cadherin/β-catenin association holds promise as a new target for therapy of fibrotic disorders and cancer.

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