

Review Article

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

Xinrui Tian,^{1,2} Zhuola Liu,² Bo Niu,³ Jianlin Zhang,^{1,4} Thian Kui Tan,¹
So Ra Lee,¹ Ye Zhao,¹ David C. H. Harris,¹ and Guoping Zheng¹

¹Centre for Transplantation and Renal Research, Westmead Millennium Institute, The University of Sydney, NSW 2145, Australia

²Department of Respiratory, Second Hospital of Shanxi Medical University, Shanxi, Taiyuan 030001, China

³Biotechnology Laboratory, Capital Institute of Pediatrics, Beijing 100020, China

⁴Department of Biochemistry and Molecular Biology, Shanxi Medical University, Taiyuan 030001, China

Correspondence should be addressed to Guoping Zheng, guoping.zheng@sydney.edu.au

Received 1 July 2011; Accepted 25 July 2011

Academic Editor: Sanford I. Bernstein

Copyright © 2011 Xinrui Tian et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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

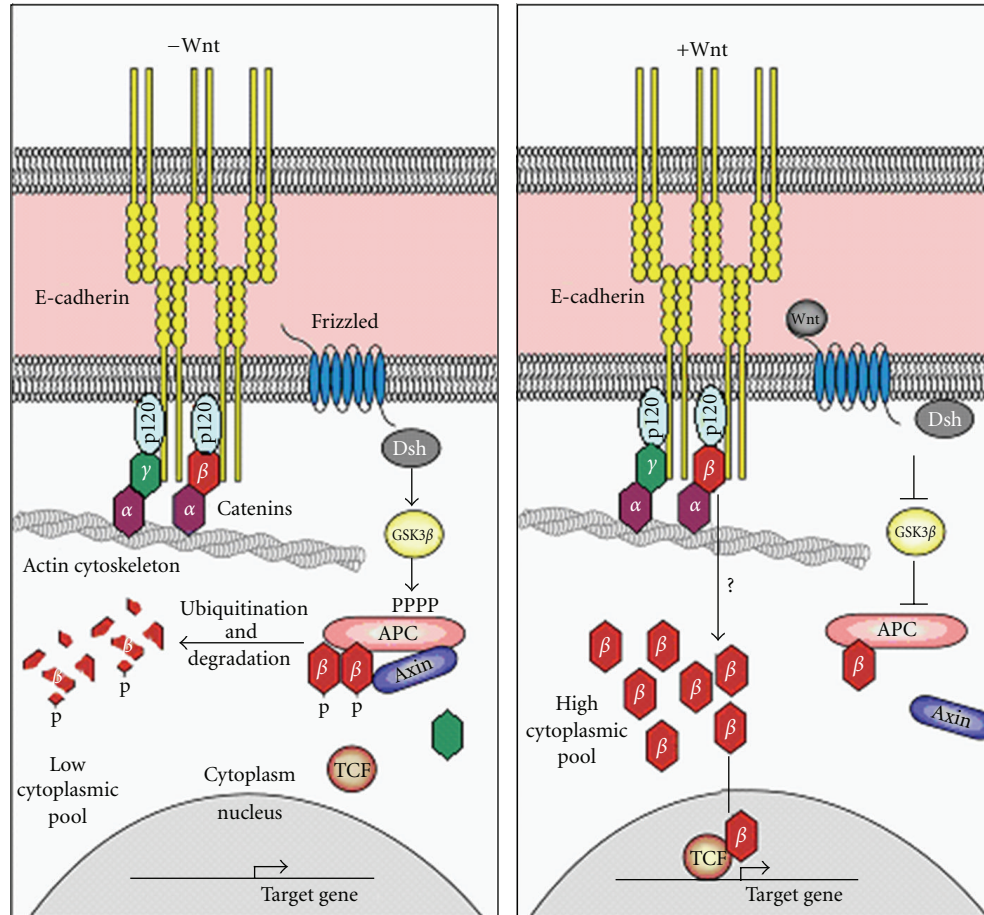


FIGURE 1: E-cadherin/ β -catenin complex in epithelial cell-cell adhesion and Wnt signaling.

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- β 1- and cell contact-dependent, synergistic induction of EMT [37]. In the absence of TGF- β 1, both E-cadherin and β -catenin are rapidly degraded following contact disassembly. However, TGF- β 1 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, hepatocellular, 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.

References

- [1] K. J. Green, S. Getsios, S. Troyanovsky, and L. M. Godsel, "Intercellular junction assembly, dynamics, and homeostasis," *Cold Spring Harbor Perspectives in Biology*, vol. 2, no. 2, p. a000125, 2010.

- [2] B. M. Gumbiner, "Regulation of cadherin-mediated adhesion in morphogenesis," *Nature Reviews Molecular Cell Biology*, vol. 6, no. 8, pp. 622–634, 2005.
- [3] H. Kurokawa and M. Ikura, "[Perspectives on structure elucidation of the cadherin-catenin complex]," *Seikagaku*, vol. 78, no. 7, pp. 595–600, 2006.
- [4] p. Hulpiau and F. van Roy, "Molecular evolution of the cadherin superfamily," *International Journal of Biochemistry and Cell Biology*, vol. 41, no. 2, pp. 349–369, 2009.
- [5] U. Tepass, "Genetic analysis of cadherin function in animal morphogenesis," *Current Opinion in Cell Biology*, vol. 11, no. 5, pp. 540–548, 1999.
- [6] M. J. Wheelock and p. J. Jensen, "Regulation of keratinocyte intercellular junction organization and epidermal morphogenesis by E-cadherin," *Journal of Cell Biology*, vol. 117, no. 2, pp. 415–425, 1992.
- [7] A. Jeanes, C. J. Gottardi, and A. S. Yap, "Cadherins and cancer: how does cadherin dysfunction promote tumor progression?" *Oncogene*, vol. 27, no. 55, pp. 6920–6929, 2008.
- [8] L. Shapiro and W. I. Weis, "Structure and biochemistry of cadherins and catenins," *Cold Spring Harbor Perspectives in Biology*, vol. 1, no. 3, p. a003053, 2009.
- [9] M. Perez-Moreno and E. Fuchs, "Catenins: keeping cells from getting their signals crossed," *Developmental Cell*, vol. 11, no. 5, pp. 601–612, 2006.
- [10] M. Ozawa, H. Barbault, and R. Kemler, "The cytoplasmic domain of the cell adhesion molecule uvomorulin associates with three independent proteins structurally related in different species," *EMBO Journal*, vol. 8, no. 6, pp. 1711–1717, 1989.
- [11] M. Ozawa and R. Kemler, "Altered cell adhesion activity by pervanadate due to the dissociation of α -catenin from the E-cadherin-catenin complex," *Journal of Biological Chemistry*, vol. 273, no. 11, pp. 6166–6170, 1998.
- [12] A. B. Reynolds and R. H. Carnahan, "Regulation of cadherin stability and turnover by p120ctn: implications in disease and cancer," *Seminars in Cell and Developmental Biology*, vol. 15, no. 6, pp. 657–663, 2004.
- [13] S. Hirano, N. Kimoto, Y. Shimoyama, S. Hirohashi, and M. Takeichi, "Identification of a neural α -catenin as a key regulator of cadherin function and multicellular organization," *Cell*, vol. 70, no. 2, pp. 293–301, 1992.
- [14] A. I. Ivanov, A. Nusrat, and C. A. Parkos, "Endocytosis of the apical junctional complex: mechanisms and possible roles in regulation of epithelial barriers," *BioEssays*, vol. 27, no. 4, pp. 356–365, 2005.
- [15] A. S. Yap, M. S. Crampton, and J. Hardin, "Making and breaking contacts: the cellular biology of cadherin regulation," *Current Opinion in Cell Biology*, vol. 19, no. 5, pp. 508–514, 2007.
- [16] J. Langevin, M. J. Morgan, C. Rossé et al., "Drosophila exocyst components sec5, sec6, and Sec15 regulate DE-cadherin trafficking from recycling endosomes to the plasma membrane," *Developmental Cell*, vol. 9, no. 3, pp. 365–376, 2005.
- [17] Y. Kam and V. Quaranta, "Cadherin-bound β -catenin feeds into the Wnt pathway upon adherens junctions dissociation: evidence for an intersection between β -catenin pools," *PLoS ONE*, vol. 4, no. 2, Article ID e4580, p. e4580, 2009.
- [18] H. Clevers, "Wnt/ β -catenin signaling in development and disease," *Cell*, vol. 127, no. 3, pp. 469–480, 2006.
- [19] T. Grigoryan, p. Wend, A. Klaus, and W. Birchmeier, "Deciphering the function of canonical Wnt signals in development and disease: conditional loss- and gain-of-function mutations of β -catenin in mice," *Genes and Development*, vol. 22, no. 17, pp. 2308–2341, 2008.
- [20] W. Luo and S. C. Lin, "Axin: a master scaffold for multiple signaling pathways," *NeuroSignals*, vol. 13, no. 3, pp. 99–113, 2004.
- [21] S. Amit, A. Hatzubai, Y. Birman et al., "Axin-mediated CKI phosphorylation of β -catenin at Ser 45: a molecular switch for the Wnt pathway," *Genes and Development*, vol. 16, no. 9, pp. 1066–1076, 2002.
- [22] J. Dixelius, M. Cross, T. Matsumoto, T. Sasaki, R. Timpl, and L. Claesson-Welsh, "Endostatin regulates endothelial cell adhesion and cytoskeletal organization," *Cancer Research*, vol. 62, no. 7, pp. 1944–1947, 2002.
- [23] S. Yanagawa, Y. Matsuda, J. S. Lee et al., "Casein kinase I phosphorylates the Armadillo protein and induces its degradation in Drosophila," *EMBO Journal*, vol. 21, no. 7, pp. 1733–1742, 2002.
- [24] H. Lickert, A. Bauer, R. Kemler, and J. Stappert, "Casein kinase II phosphorylation of E-cadherin increases E-cadherin/ β -catenin interaction and strengthens cell-cell adhesion," *Journal of Biological Chemistry*, vol. 275, no. 7, pp. 5090–5095, 2000.
- [25] S. Bek and R. Kemler, "Protein kinase CKII regulates the interaction of β -catenin with α -catenin and its protein stability," *Journal of Cell Science*, vol. 115, part 24, pp. 4743–4753, 2002.
- [26] J. Behrens, L. Vakaet, R. Friis et al., "Loss of epithelial differentiation and gain of invasiveness correlates with tyrosine phosphorylation of the E-cadherin/ β -catenin complex in cells transformed with a temperature-sensitive v-SRC gene," *Journal of Cell Biology*, vol. 120, no. 3, pp. 757–766, 1993.
- [27] M. L. Taddei, p. Chiarugi, p. Cirri et al., " β -catenin interacts with low-molecular-weight protein tyrosine phosphatase leading to cadherin-mediated cell-cell adhesion increase," *Cancer Research*, vol. 62, no. 22, pp. 6489–6499, 2002.
- [28] F. H. Brembeck, T. Schwarz-Romond, J. Bakkers, S. Wilhelm, M. Hammerschmidt, and W. Birchmeier, "Essential role of BCL9-2 in the switch between β -catenin's adhesive and transcriptional functions," *Genes and Development*, vol. 18, no. 18, pp. 2225–2230, 2004.
- [29] J. Rhee, T. Buchan, L. Zukerberg, J. Lilien, and J. Balsamo, "Cables links Robo-bound Abl kinase to N-cadherin-bound β -catenin to mediate Slit-induced modulation of adhesion and transcription," *Nature Cell Biology*, vol. 9, no. 8, pp. 883–892, 2007.
- [30] J. Hülsken, W. Birchmeier, and J. Behrens, "E-cadherin and APC compete for the interaction with β -catenin and the cytoskeleton," *Journal of Cell Biology*, vol. 127, no. 6, part 2, pp. 2061–2069, 1994.
- [31] M. p. Rastaldi, "Epithelial-mesenchymal transition and its implications for the development of renal tubulointerstitial fibrosis," *Journal of Nephrology*, vol. 19, no. 4, pp. 407–412, 2006.
- [32] p. Savagner, "Leaving the neighborhood: molecular mechanisms involved during epithelial-mesenchymal transition," *BioEssays*, vol. 23, no. 10, pp. 912–923, 2001.
- [33] N. Auersperg, J. Pan, B. D. Grove et al., "E-cadherin induces mesenchymal-to-epithelial transition in human ovarian surface epithelium," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 11, pp. 6249–6254, 1999.
- [34] E. D. Hay and A. Zuk, "Transformations between epithelium and mesenchyme: normal, pathological, and experimentally induced," *American Journal of Kidney Diseases*, vol. 26, no. 4, pp. 678–690, 1995.
- [35] A. Cano, M. A. Pérez-Moreno, I. Rodrigo et al., "The transcription factor Snail controls epithelial-mesenchymal

- transitions by repressing E-cadherin expression," *Nature Cell Biology*, vol. 2, no. 2, pp. 76–83, 2000.
- [36] K. Vleminckx, L. Vakaet, M. Mareel, W. Fiers, and F. Van Roy, "Genetic manipulation of E-cadherin expression by epithelial tumor cells reveals an invasion suppressor role," *Cell*, vol. 66, no. 1, pp. 107–119, 1991.
- [37] A. Masszi, L. Fan, L. Rosivall et al., "Integrity of cell-cell contacts is a critical regulator of TGF- β 1-induced epithelial-to-myofibroblast transition: role for β -catenin," *American Journal of Pathology*, vol. 165, no. 6, pp. 1955–1967, 2004.
- [38] A. Masszi, C. di Ciano, G. Sirokmány et al., "Central role for Rho in TGF- β 1-induced α -smooth muscle actin expression during epithelial-mesenchymal transition," *American Journal of Physiology*, vol. 284, no. 5, pp. F911–F924, 2003.
- [39] Y. C. Tian, D. Fraser, L. Attisano, and A. O. Phillips, "TGF- β 1-mediated alterations of renal proximal tubular epithelial cell phenotype," *American Journal of Physiology*, vol. 285, no. 1, pp. F130–F142, 2003.
- [40] M. Guarino, A. Tosoni, and M. Nebuloni, "Direct contribution of epithelium to organ fibrosis: epithelial-mesenchymal transition," *Human Pathology*, vol. 40, no. 10, pp. 1365–1376, 2009.
- [41] M. Iwano, D. Plieth, T. M. Danoff, C. Xue, H. Okada, and E. G. Neilson, "Evidence that fibroblasts derive from epithelium during tissue fibrosis," *Journal of Clinical Investigation*, vol. 110, no. 3, pp. 341–350, 2002.
- [42] S. L. Lin, T. Kisseleva, D. A. Brenner, and J. S. Duffield, "Pericytes and perivascular fibroblasts are the primary source of collagen-producing cells in obstructive fibrosis of the kidney," *American Journal of Pathology*, vol. 173, no. 6, pp. 1617–1627, 2008.
- [43] M. p. Rastaldi, F. Ferrario, L. Giardino et al., "Epithelial-mesenchymal transition of tubular epithelial cells in human renal biopsies," *Kidney International*, vol. 62, no. 1, pp. 137–146, 2002.
- [44] H. Robertson, S. Ali, B. J. McDonnell, A. D. Burt, and J. A. Kirby, "Chronic renal allograft dysfunction: the role of T cell-mediated tubular epithelial to mesenchymal cell transition," *Journal of the American Society of Nephrology*, vol. 15, no. 2, pp. 390–397, 2004.
- [45] G. Zheng, J. G. Lyons, K. T. Thian et al., "Disruption of E-cadherin by matrix metalloproteinase directly mediates epithelial-mesenchymal transition downstream of transforming growth factor- β 1 in renal tubular epithelial cells," *American Journal of Pathology*, vol. 175, no. 2, pp. 580–591, 2009.
- [46] S. Bedi, A. Vidyasagar, and A. Djamali, "Epithelial-to-mesenchymal transition and chronic allograft tubulointerstitial fibrosis," *Transplantation Reviews*, vol. 22, no. 1, pp. 1–5, 2008.
- [47] V. J. Thannickal, G. B. Toews, E. S. White, J. p. Lynch, and F. J. Martinez, "Mechanisms of pulmonary fibrosis," *Annual Review of Medicine*, vol. 55, pp. 395–417, 2004.
- [48] B. C. Willis, J. M. Liebler, K. Luby-Phelps et al., "Induction of epithelial-mesenchymal transition in alveolar epithelial cells by transforming growth factor- β 1: potential role in idiopathic pulmonary fibrosis," *American Journal of Pathology*, vol. 166, no. 5, pp. 1321–1332, 2005.
- [49] K. A. Rygiel, H. Robertson, H. L. Marshall et al., "Epithelial-mesenchymal transition contributes to portal tract fibrogenesis during human chronic liver disease," *Laboratory Investigation*, vol. 88, no. 2, pp. 112–123, 2008.
- [50] S. Saika, "TGFbeta pathobiology in the eye," *Laboratory Investigation*, vol. 86, no. 2, pp. 106–115, 2006.
- [51] M. A. Gamulescu, Y. Chen, S. He et al., "Transforming growth factor β 2-induced myofibroblastic differentiation of human retinal pigment epithelial cells: regulation by extracellular matrix proteins and hepatocyte growth factor," *Experimental Eye Research*, vol. 83, no. 1, pp. 212–222, 2006.
- [52] M. Yáñez-Mó, E. Lara-Pezzi, R. Selgas et al., "Peritoneal dialysis and epithelial-to-mesenchymal transition of mesothelial cells," *New England Journal of Medicine*, vol. 348, no. 5, pp. 403–413, 2003.
- [53] T. K. Tan, G. Zheng, T. T. Hsu et al., "Macrophage matrix metalloproteinase-9 mediates epithelial-mesenchymal transition in vitro in murine renal tubular cells," *American Journal of Pathology*, vol. 176, no. 3, pp. 1256–1270, 2010.
- [54] Y. Wu and B. p. Zhou, "New insights of epithelial-mesenchymal transition in cancer metastasis," *Acta Biochimica et Biophysica Sinica*, vol. 40, no. 7, pp. 643–650, 2008.
- [55] R. D. Cardiff, "Epithelial to mesenchymal transition tumors: fallacious or snail's pace?" *Clinical Cancer Research*, vol. 11, no. 24, part 1, pp. 8534–8537, 2005.
- [56] A. S. Yap, "The morphogenetic role of cadherin cell adhesion molecules in human cancer: a thematic review," *Cancer Investigation*, vol. 16, no. 4, pp. 252–261, 1998.
- [57] p. Cowin, T. M. Rowlands, and S. J. Hatsell, "Cadherins and catenins in breast cancer," *Current Opinion in Cell Biology*, vol. 17, no. 5, pp. 499–508, 2005.
- [58] D. Junghans, I. G. Haas, and R. Kemler, "Mammalian cadherins and protocadherins: about cell death, synapses and processing," *Current Opinion in Cell Biology*, vol. 17, no. 5, pp. 446–452, 2005.
- [59] C. W. Cheng, p. E. Wu, J. C. Yu et al., "Mechanisms of inactivation of E-cadherin in breast carcinoma: modification of the two-hit hypothesis of tumor suppressor gene," *Oncogene*, vol. 20, no. 29, pp. 3814–3823, 2001.
- [60] M. J. Blanco, G. Moreno-Bueno, D. Sarrío et al., "Correlation of Snail expression with histological grade and lymph node status in breast carcinomas," *Oncogene*, vol. 21, no. 20, pp. 3241–3246, 2002.
- [61] p. W. Derksen, X. Liu, F. Saridin et al., "Somatic inactivation of E-cadherin and p53 in mice leads to metastatic lobular mammary carcinoma through induction of anoikis resistance and angiogenesis," *Cancer Cell*, vol. 10, no. 5, pp. 437–449, 2006.
- [62] M. Peifer and p. Polakis, "Wnt signaling in oncogenesis and embryogenesis—a look outside the nucleus," *Science*, vol. 287, no. 5458, pp. 1606–1609, 2000.
- [63] p. Polakis, "Wnt signaling and cancer," *Genes and Development*, vol. 14, no. 15, pp. 1837–1851, 2000.
- [64] T. C. He, A. B. Sparks, C. Rago et al., "Identification of c-MYC as a target of the APC pathway," *Science*, vol. 281, no. 5382, pp. 1509–1512, 1998.
- [65] O. Tetsu and F. McCormick, " β -catenin regulates expression of cyclin D1 in colon carcinoma cells," *Nature*, vol. 398, no. 6726, pp. 422–426, 1999.
- [66] M. Shtutman, J. Zhurinsky, I. Simcha et al., "The cyclin D1 gene is a target of the β -catenin/LEF-1 pathway," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 10, pp. 5522–5527, 1999.
- [67] M. J. Hayes, D. Thomas, A. Emmons, T. J. Giordano, and C. G. Kleer, "Genetic changes of Wnt pathway genes are common events in metaplastic carcinomas of the breast," *Clinical Cancer Research*, vol. 14, no. 13, pp. 4038–4044, 2008.
- [68] A. Ryo, M. Nakamura, G. Wulf, Y. C. Liou, and K. p. Lu, "Pin1 regulates turnover and subcellular localization of β -catenin by

- inhibiting its interaction with APC,” *Nature Cell Biology*, vol. 3, no. 9, pp. 793–801, 2001.
- [69] S. Y. Lin, W. Xia, J. C. Wang et al., “ β -catenin, a novel prognostic marker for breast cancer: its roles in cyclin D1 expression and cancer progression,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 8, pp. 4262–4266, 2000.
- [70] S. Ozaki, S. Ikeda, Y. Ishizaki et al., “Alterations and correlations of the components in the Wnt signaling pathway and its target genes in breast cancer,” *Oncology Reports*, vol. 14, no. 6, pp. 1437–1443, 2005.
- [71] R. T. Sormunen, A. S. Y. Leong, J. p. Vääräniemi, S. S. E. Fernando, and S. M. Eskelinen, “Immunolocalization of the fodrin, E-cadherin, and β -catenin adhesion complex in infiltrating ductal carcinoma of the breast-Comparison with an in vitro model,” *Journal of Pathology*, vol. 187, no. 4, pp. 416–423, 1999.
- [72] A. J. Karayiannakis, L. Nakopoulou, H. Gakiopoulou, A. Keramopoulos, p. S. Davaris, and M. Pignatelli, “Expression patterns of β -catenin in in situ and invasive breast cancer,” *European Journal of Surgical Oncology*, vol. 27, no. 1, pp. 31–36, 2001.
- [73] C. p. Prasad, S. Mirza, G. Sharma et al., “Epigenetic alterations of CDH1 and APC genes: relationship with activation of Wnt/ β -catenin pathway in invasive ductal carcinoma of breast,” *Life Sciences*, vol. 83, no. 9-10, pp. 318–325, 2008.