

## $\beta$ -Catenin Signaling in Fibroproliferative Disease

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**Background.**  $\beta$ -catenin has been historically recognized as both an intermediate in the “canonical Wnt signaling pathway” and as a component of functional adherens junctions.

**Materials and methods.** Cellular accumulation of  $\beta$ -catenin levels can result in transactivation of gene transcription and cellular proliferation during normal cellular and disease development. Recent evidence has identified  $\beta$ -catenin in an additional role as a component of cutaneous wound healing.

**Results.** This finding is in keeping with previous observations that post-translational modifications of  $\beta$ -catenin that are associated with its cytoplasmic accumulation are frequently observed in fibroproliferative diseases with characteristics of dysregulated wound healing. These diseases include hypertrophic scar formation, aggressive fibromatoses, Lederhose disease, and Dupuytren’s contracture (DC).

**Conclusions.** While its precise roles in disease initiation and progression remain to be explored, this review highlights our current knowledge of  $\beta$ -catenin regulation and describes some potential upstream mediators of  $\beta$ -catenin accumulation and signaling in fibroproliferative disease. © 2007 Elsevier Inc. All rights reserved.

**Key Words:** Wnt/beta-catenin signaling; fibroproliferative disorders; Dupuytren’s contracture; wound healing; hypertrophic scarring.

### INTRODUCTION

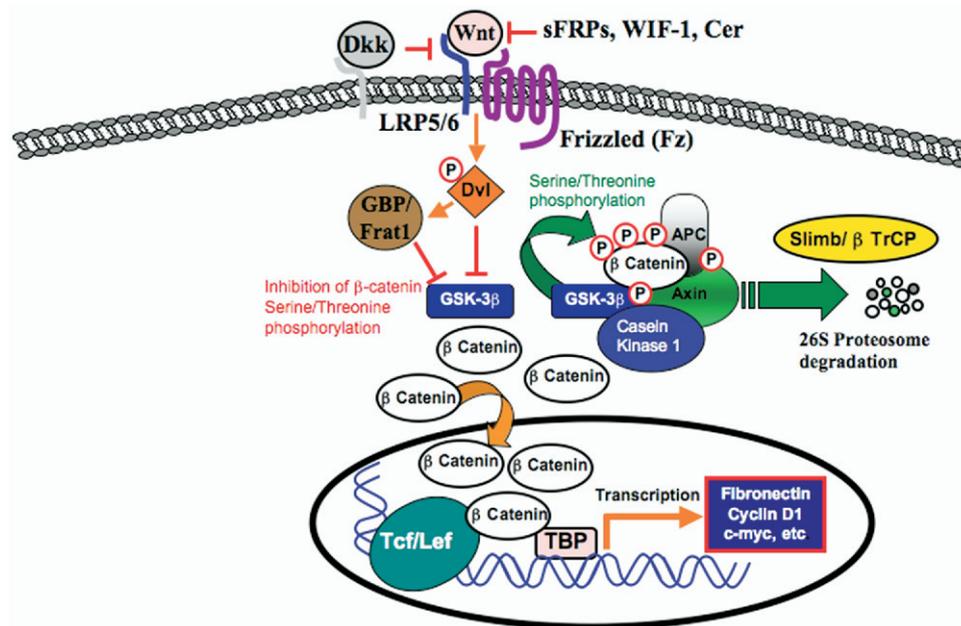
$\beta$ -catenin was once thought to have only two distinct functional roles within the cell. One was as an intermediary in the “canonical Wnt-pathway”, a critical signaling system in embryonic growth and development,

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and the second was as a structural protein that, in conjunction with E-cadherin, served in the functioning of cellular adherens junctions. However, it is now clear that aberrant  $\beta$ -catenin signaling can occur in a number of human diseases, such as certain types of cancer and fibroproliferative disorders, and that a large number of signaling pathways use  $\beta$ -catenin to direct the transcription of genes whose products are characteristic of those conditions. The purpose of this paper is to review the known interactions of  $\beta$ -catenin and place these in the context of newly discovered findings related to a number of fibrotic conditions including hypertrophic scar formation, aggressive fibromatoses (desmoid tumors) and Dupuytren’s contracture (DC). To understand the central importance of this molecule in these areas, we will begin with an overview of the pathways known to regulate  $\beta$ -catenin bioavailability.

### THE CANONICAL WNT/ $\beta$ -CATENIN PATHWAY

The canonical Wnt pathway (Fig. 1) is reliant on  $\beta$ -catenin as a central signaling molecule. This pathway is one of the most well-studied regulators of embryonic development [1], exerting remarkable control over cellular proliferation, differentiation, invasion and adhesion [2, 3]. When the canonical Wnt pathway is activated by the appropriate Wnt ligand, the Frizzled (Fz) receptor and co-receptor LRP5/6 (lipoprotein receptor-related proteins 5 or 6) [4–6] form a complex and trigger a cascade of signaling events through the kinase Dishevelled (Dvl), resulting in the phosphorylation, and subsequent inactivation, of glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ). GSK-3 $\beta$  activity is the key component of the so-called “destruction complex” that also includes Axin, the product of the adenomatous polyposis coli gene (APC), and casein kinase-1 (CK-I) [7–9]. When GSK-3 $\beta$  phosphorylates complexed  $\beta$ -catenin on serine and threonine residues, primarily S33, S37, T41, and



**FIG. 1.** The Wnt/ $\beta$ -catenin pathway. The two historically recognized intracellular sources of  $\beta$ -catenin are the canonical Wnt/ $\beta$ -catenin pathway and adherens junctions. Wnt signaling through Frizzled receptor/LRP5/6 results in phosphorylation of Dishevelled (Dvl), which in turn inactivates GSK3 $\beta$ . GSK3 $\beta$  inactivation allows  $\beta$ -catenin to avoid the destruction complex and to accumulate within the cytoplasm, translocate to the nucleus and transactivate the Tcf/Lef transcription complex. (Color version of figure is available online.)

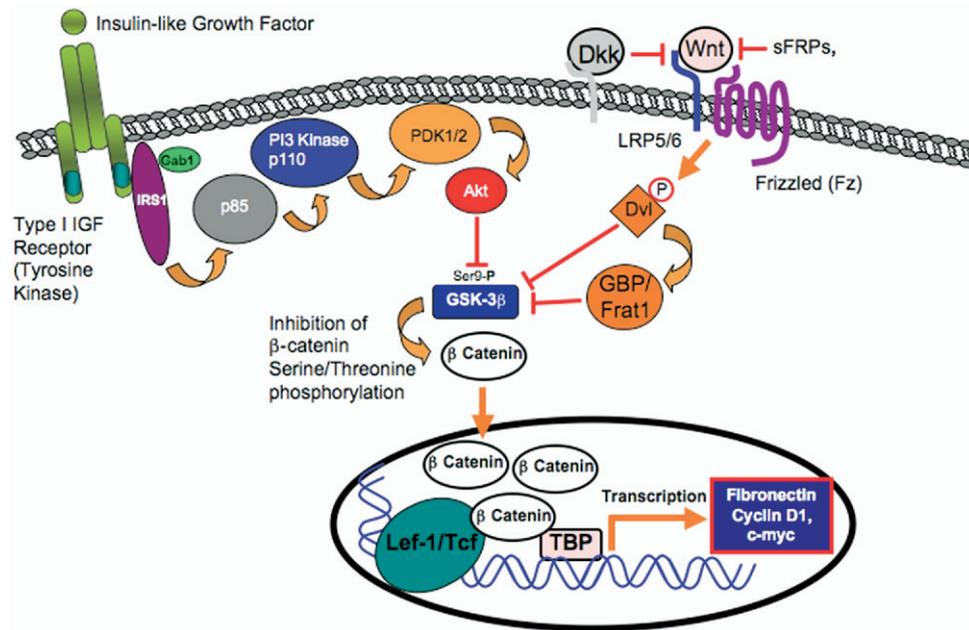
S45, the hyper-phosphorylated  $\beta$ -catenin is recognized by the F-box containing protein slimb/b-TrCP, a component of the E3 ubiquitin (Ub) ligase complex, and  $\beta$ -catenin is targeted for degradation via the 26S proteasome [10–16]. Alternatively, GSK-3 $\beta$  can be inactivated by phosphorylation of Serine 9 resulting in  $\beta$ -catenin release from the destruction complex and its accumulation in the cytoplasm as a stabilized pool. In a poorly understood process, this cytoplasmic pool of  $\beta$ -catenin is then thought to translocate to the nucleus through binding to Tcf4 and BCL9/Pygopus while APC and Axin act to inhibit this process and retain the  $\beta$ -catenin in the cytoplasm [17]. Nuclear  $\beta$ -catenin functions as a transcriptional activator for members of the T-cell factor/lymphoid enhancer factor (Tcf/Lef) family of DNA binding proteins [18, 19] that activate a subset of genes in a cell-context specific manner.

A number of  $\beta$ -catenin-Tcf/Lef target genes have been identified [11] and many of these play an important role in cell cycle control, proliferation and cell fate determination [20, 21]. (A current online list of Wnt/ $\beta$ -catenin target genes with Tcf/Lef binding sites can be found at <http://www.stanford.edu/~rnusse/pathways/targets.html>). Both independently and in conjunction with Tcf/Lef,  $\beta$ -catenin can interact with nuclear receptors resulting in an array of cellular effects including changes in cellular adhesion, tissue morphogenesis, and tumor development. Whereas androgen receptor interactions are perhaps the best characterized, nuclear  $\beta$ -catenin has also been shown to affect the activities of receptors for retinoic acid, vitamin D, glucocor-

ticoid, progesterone, thyroid, estrogen, and peroxisome proliferator-activator and these interactions are reviewed in detail in [22].

The Wnt pathway has now become well recognized as a molecular contributor to the development of many disease states [23–25]. Dysregulation of the canonical Wnt signaling system is involved in greater than 90% of colorectal carcinomas [11] and evidence continues to accumulate supporting the role of this pathway in a multitude of other malignant disorders [2, 26, 27]. Since nuclear translocation of  $\beta$ -catenin and Tcf/Lef interaction can induce transcription of cellular regulators of proliferation and differentiation such as Cyclin D1 and c-myc [11], the Wnt/ $\beta$ -catenin pathway provides a direct connection between extra-cellular signals, gene transcription and cell cycle control. Therefore, aberrant behavior of this pathway as a result of activating mutations of  $\beta$ -catenin have the potential to promote both initiation and the progression of cancer [11, 25]. Not surprisingly, the critical serine/threonine residues required for  $\beta$ -catenin phosphorylation and ubiquitination, normally used as regulators of the canonical Wnt signaling pathway, are ‘hot spots’ in those cancers involving  $\beta$ -catenin mutations. Clinically, strong nuclear or cytoplasmic  $\beta$ -catenin staining in colorectal cancer correlates with more invasive tumor growth, a higher susceptibility of disease recurrence after surgery and a lower survival rate [28].

Similarly, the adenomatous polyposis coli (APC) gene product is a negative regulator of cytoplasmic  $\beta$ -catenin. Part of the Axin/APC/GSK-3 $\beta$  destruction



**FIG. 2.** GSK-3 $\beta$  is a central mediator of Wnt/ $\beta$ -catenin and receptor tyrosine kinase signaling pathways. Receptor tyrosine kinases, such as the type 1 IGF receptor shown here, can signal through a variety of intermediate molecules including PI3 kinase and Akt to inhibit GSK-3 $\beta$  activity. GSK-3 $\beta$  is also a component of the Wnt/ $\beta$ -catenin pathway as shown, and thus acts as a central mediator of  $\beta$ -catenin serine/threonine phosphorylation and subsequent cytoplasmic accumulation. (Color version of figure is available online.)

complex, APC is responsible for sequestering cytoplasmic  $\beta$ -catenin and targeting it for ubiquitination and degradation at the proteasome. Functioning in this regard, APC is an important negative regulator of free cytoplasmic  $\beta$ -catenin, and inactivating mutations of the APC gene play an important role in cancer progression. Monoallelic inactivating mutations in APC occur in patients with familial adenomatous polyposis (FAP), a condition that results in many adenomas in the colorectum [29]. As well, 85% of colorectal cancers demonstrate a mutation in the APC gene and it is implied that the remaining 15% are likely to contain mutations in  $\beta$ -catenin [11, 19, 30, 31]. However, many cases of hepatocellular carcinoma reveal that mutation and nuclear staining of  $\beta$ -catenin correlates with less aggressive tumor growth and increased survival rates [32], while there is no correlation apparent with  $\beta$ -catenin nuclear staining and tumor type in gastric cancer [33]. In summary, while there are obvious correlations between dysregulation of the Wnt/ $\beta$ -catenin pathway and colorectal disease, the relevance of altered  $\beta$ -catenin accumulation in other malignancies is still not clearly defined.

#### WNT-INDEPENDENT $\beta$ -CATENIN SIGNALING

Although the canonical Wnt signaling pathway is a major player in the regulation of stabilized cytoplasmic pools of  $\beta$ -catenin, several Wnt-independent signaling pathways have also been shown to converge at GSK-3 $\beta$

to achieve this result (Fig. 2). These include growth factor signaling pathways such as those used by insulin-like growth factors (IGFs), platelet-derived growth factors (PDGFs), and hepatocyte growth factor (HGF). These molecules induce tyrosine phosphorylation of downstream targets through activation of their respective receptor tyrosine kinases and signal through a variety of intracellular intermediate molecules including phosphatidylinositol 3 (PI3)-kinase [34, 35]. PI3 kinase activity results, via phosphoinositide dependent kinases 1 and 2 (PDK1/2), in the phosphorylation of the serine 473 and threonine 308 residues of Akt. Akt, also known as protein kinase B, is a serine/threonine kinase with an established role in regulating proliferation and apoptosis in cancer [36, 37], wound healing and fibrosis [38]. Among several targets, Akt can phosphorylate GSK-3 $\beta$  at serine 9 resulting in  $\beta$ -catenin accumulation and Tcf/Lef transcription complex activation [34, 39]. From a clinical perspective, androgen-independent prostate cancer is frequently associated with the silencing of PTEN (phosphatase and tensin homologue deleted on chromosome 10), a potent inhibitor of PI3 kinase-mediated activation of Akt. PTEN silencing can indirectly result in inhibition of GSK-3 $\beta$  activity and subsequent nuclear transactivation through interactions of nuclear  $\beta$ -catenin [40].

In another Wnt-independent  $\beta$ -catenin regulatory pathway, integrin receptors connect the extra-cellular

matrix (ECM) to the actin cytoskeleton [41] at the cell membrane. Stimulation by the appropriate ligand then leads to integrin receptor clustering and recruitment of actin filaments and signaling proteins [42] to the complex. In this way, ECM molecules can regulate cellular survival by signaling through integrin receptors and integrin-linked kinase (ILK) to activate, among others, the PI3 kinase and Akt pathways [43] inducing  $\beta$ -catenin/Tcf/Lef-mediated transcription of cell cycle genes such as cyclin D1 [44, 45].

### $\beta$ -CATENIN AND ADHERENS JUNCTIONS

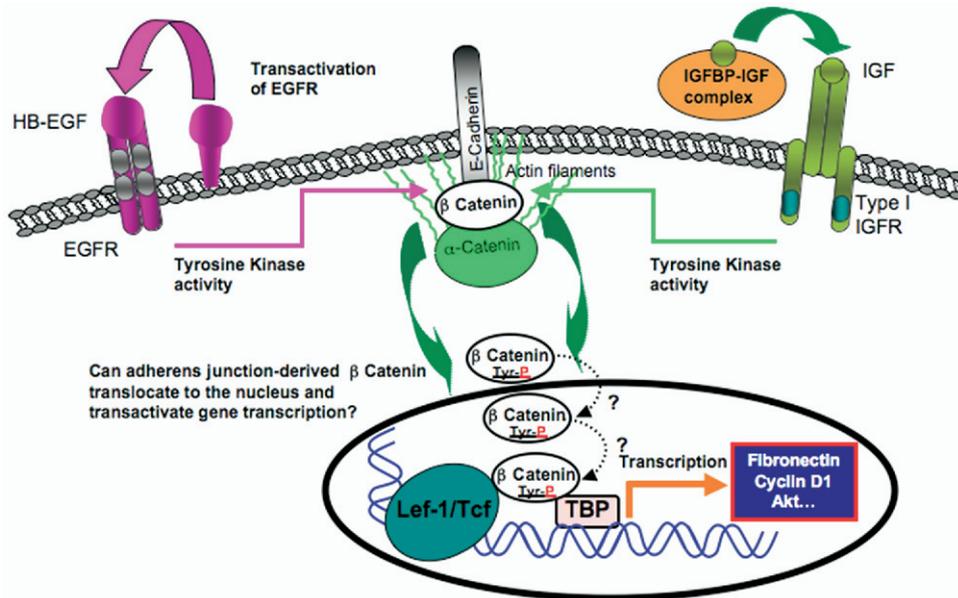
Other than as a component of the Wnt-dependent and independent  $\beta$ -catenin pathways,  $\beta$ -catenin has long been established as a component of adherens junctions in association with cadherins. Cadherins are a large family of calcium-dependent cell adhesion proteins that include epithelial cadherin (E-cadherin), neural cadherin (N-cadherin), placental cadherin (P-cadherin), muscle cadherin (M-cadherin), and vascular endothelial cadherin (VE-cadherin, or CDH5). While N-cadherin and P-cadherin have also been shown to associate with  $\beta$ -catenin and  $\alpha$ -catenin, E-cadherin is the best characterized cadherin component of adherens junctions [46].  $\beta$ -catenin is an essential component of this molecular complex, linking transmembrane E-cadherin to the actin cytoskeleton through  $\alpha$ -catenin as well as other catenin molecules such as plakoglobin (or  $\gamma$ -catenin) [47, 48]. Adherens junctions allow for cell-cell adhesion, and when required, can disassemble to allow cell migration [3], a process important in embryological development [21], the wound healing response [49] and epithelial-mesenchymal transition [50, 51]. Association of the transmembrane cadherins with the intracellular cytoskeleton is essential for the regulation of cell-cell adhesion, stability and contact [52]. Clinically, a loss of the E-cadherin/ $\beta$ -catenin adhesion complex correlates with poor prognosis in some malignancies [53], and therefore could potentially act as a modulator of disease progression.

A variety of growth factors and ECM molecules have been demonstrated to exert effects on cytoplasmic  $\beta$ -catenin accumulation by disrupting the E-cadherin/ $\beta$ -catenin/ $\alpha$ -catenin complex. Pleiotrophin has an effect on cell adhesion in part by signaling through receptor protein tyrosine phosphatases  $\beta/\zeta$  to promote the disruption of adherens junctions [54]. HGF not only promotes adherens junction disruption but is involved in E-cadherin endocytosis [55, 56] and  $\beta$ -catenin release [57]. Epidermal growth factors (EGFs) signaling through the EGF receptor (EGFR), initiate changes in cell morphology [58] that are associated with EGFR co-localization with cadherin molecules at the cell membrane [58, 59]. This co-localization induces tyrosine phosphor-

ylation of  $\beta$ -catenin and destabilization of E-cadherin/ $\beta$ -catenin complexes in adherens junctions [59, 60], in turn resulting in cytoplasmic accumulation of tyrosine phosphorylated  $\beta$ -catenin. Glycosylation has a role in this process, as the addition of bisecting N-acetylglucosamine residues to E-cadherin combined with epidermal growth factor stimulation alters tyrosine phosphorylation of  $\beta$ -catenin [61]. Similarly, IGF-I and -II acting through the type 1 IGF receptor (IGFR1), can also induce dismantling of the E-cadherin/ $\beta$ -catenin cellular scaffold (Fig. 3).

Phosphorylation events are clearly paramount in the structural integrity of the cadherin-catenin complex. In general, when  $\beta$ -catenin or E-cadherin are serine/threonine phosphorylated the complex is stabilized [62, 63]. However, when  $\beta$ -catenin is tyrosine phosphorylated by an intracellular signaling event, the E-cadherin- $\beta$ -catenin complex is generally disrupted and cell adhesion is lost [60, 64, 65]. It has also been demonstrated that the interaction between  $\beta$ -catenin and  $\alpha$ -catenin is regulated by the tyrosine kinases Fer/Fyn, which are in turn activated by the tyrosine kinase, Yes [66]. At least two critical tyrosine residues on  $\beta$ -catenin are targeted by these kinases: tyrosine 142 by cMet (the HGF receptor), Fyn and Fer, and tyrosine 654 by Src and the EGF receptor [67]. Tyrosine phosphorylation can result in release of  $\beta$ -catenin from E-cadherin, decreased cell-cell adhesion and increased cell migration and invasiveness [64, 68].

The role of adherens junction-derived  $\beta$ -catenin in promoting Tcf/Lef mediated gene transcription is still an area of some debate [69]. The literature suggests that there are at least two molecular pools of  $\beta$ -catenin and that  $\beta$ -catenin associated with E-cadherin at adherens junctions is preferentially bound to  $\alpha$ -catenin and functionally distinct from the  $\beta$ -catenin that promotes Tcf/Lef transcription [70]. Other studies have found evidence that suggests tyrosine-phosphorylated  $\beta$ -catenin is capable of transactivating signal transduction. For instance, the tyrosine phosphatase SHP-1 has been shown to decrease  $\beta$ -catenin signaling [71] implying that tyrosine phosphorylation of  $\beta$ -catenin enhances its transactivation of the Tcf/Lef transcription complex. In some systems, transcriptional activity associated with tyrosine phosphorylated  $\beta$ -catenin appears dependent on the presence of growth factors including IGF and HGF [72, 73]. For example, IGF signaling has been reported to promote disruption of adherens junctions with associated nuclear translocation of  $\beta$ -catenin and subsequent expression of  $\beta$ -catenin-Tcf/Lef target genes *in vitro* [72, 74]. It is still unclear, however, whether the adherens junctions-derived  $\beta$ -catenin itself promotes cell proliferation and, if it does, this process may be cell-type specific.



**FIG. 3.** Does adherens junction-derived  $\beta$ -catenin contribute to gene transcription? Activation of tyrosine kinase receptors, such as the EGFR by EGF or type 1 IGF receptor by IGFs, can result in adherens junction disruption and increased levels of cytoplasmic tyrosine phosphorylated  $\beta$ -catenin. It is unclear, however, whether  $\beta$ -catenin derived from adherens junctions contributes to transactivation of gene transcription. (Color version of figure is available online.)

### $\beta$ -CATENIN SIGNALING IN THE REGULATION OF FIBROSIS

$\beta$ -catenin clearly demonstrates strong oncogenic properties in colorectal disease and the evidence described above implicates  $\beta$ -catenin in the progression of malignancy, albeit in a tumor-type specific manner. More recently, however, research in  $\beta$ -catenin signaling has shed new light on the molecular pathogenesis of a number of fibroproliferative disease states to suggest that  $\beta$ -catenin-Tcf/Lef-mediated signaling dysfunction may also play a role in wound healing disorders, aggressive fibromatosis and DC.

### $\beta$ -CATENIN AND WOUND HEALING

The wound healing response has long been recognized as a complex process requiring the dynamic interaction of cellular and blood-borne elements. Many cellular, extracellular, vascular, and cytokine-related components interact with one another during the three major phases of wound healing; the inflammatory response, proliferative phase and remodeling phase. Reconstruction of the skin during the proliferative phase depends on granulation tissue to produce the provisional extracellular matrix required for re-epithelialization [49]. A number of growth factors, such as transforming growth factors  $\alpha$  and  $\beta$  (TGF $\alpha$  and TGF $\beta$ ), epidermal growth factor (EGF) and IGFs are released by macrophages at the site of injury and stimulate fibroblast migration and proliferation [75]. During dynamic healing of the injured area, fibroblasts assume a myofibroblast phe-

notype, depositing bundles of actin microfilaments and collagen that act to compact or contract the wound. The final stage of wound healing is marked by the transition of wound granulation tissue, rich in fibroblasts, into a largely acellular scar. In this process, matrix metalloproteinases secreted by a number of cell types, including fibroblasts, gradually degrade the collagen laid down during healing [75].

At a molecular level,  $\beta$ -catenin has been identified as playing a cell-type specific role in normal wound healing.  $\beta$ -catenin levels are elevated in mesenchymal cells during the proliferative phase [49] and are believed to regulate dermal fibroblast proliferation rate, motility and invasiveness [76]. EGF and TGF $\beta$ 1 stimulated murine dermal fibroblast cultures have been shown to express increased  $\beta$ -catenin protein levels and Tcf/Lef mediated transcriptional activity as a result of GSK-3 $\beta$  inactivity [77]. Additionally, recent data has shed further light on the interactions between TGF- $\beta$  and  $\beta$ -catenin in cutaneous wound healing. TGF- $\beta$  is one of the first cytokines expressed after wounding [78] and exerts its biological effects through TGF $\beta$ I and TGF $\beta$ II receptors, which form a heteromeric complex to facilitate signaling [79]. The activated type 1 TGF- $\beta$  receptor phosphorylates Smads 2 and 3, which in turn interact with Smad4, resulting in nuclear translocation and activation of target gene transcription. Interestingly, full-thickness incisional wounding of Smad3 null mice results in an enhanced rate of re-epithelialization associated with a reduction in the number of fibroblasts, leading to an overall decrease in wound size

[80–82]. Cheon *et al.* have recently demonstrated that this phenotype is dependent on  $\beta$ -catenin expression, because stabilized  $\beta$ -catenin expression reverses the Smad3 null effect on wound size. TGF  $\beta$ -mediated fibroblast proliferation and hyperplastic wound formation was also shown to be dependent on  $\beta$ -catenin expression, demonstrating the central role of this molecule in the healing process [83] and highlighting the negative effects of  $\beta$ -catenin dysregulation. HGF signaling, which can induce tyrosine phosphorylated  $\beta$ -catenin release from adherens junctions, has also been shown to promote wound healing [84, 85], although a role of  $\beta$ -catenin signaling in this context has not been reported. In contrast to the fibroblast response,  $\beta$ -catenin inhibits migration of human epithelial cells in culture [86] and, as normal epithelial cell differentiation and proliferation in wounded  $\beta$ -catenin null mice demonstrates, it is not an essential component of the epithelium for wound healing [87].

When the wound healing response is dysregulated, a variety of epithelial and mesenchymal disorders can occur. Fibroproliferative disorders, characterized by excessive proliferation of mesenchymal cells, range in severity from hypertrophic scars to neoplasms such as aggressive fibromatosis (desmoid tumors). These conditions display cellular and biochemical features that are remarkably similar to those involved in wound healing [49]. This similarity has given rise to the widely accepted hypothesis that fibroproliferative disorders may be the result of an unchecked or exaggerated wound healing response.

#### HYPERPLASTIC SCARRING AND $\beta$ -CATENIN

Hyperplastic scars are composed of fibrous bundles in both the deeper and upper dermis. Although the molecular cause of hyperplastic scarring is still unknown, cytological and gene expression studies comparing this disorder to wound healing suggest that it is an exaggerated, prolonged healing response. Wounding of  $\beta$ -catenin overexpressing mice results in hyperplastic scar formation [76] giving rise to the speculation that  $\beta$ -catenin plays a significant role in the pathomechanism driving hyperplastic scarring. In wound healing, the elevated  $\beta$ -catenin levels normally found in granulation tissue (fibroblasts) only during the proliferative phase are detectable in hyperplastic scar tissue for more than 2 years after initial injury [49]. Although  $\beta$ -catenin protein levels in hyperplastic scars do not correlate with mRNA levels, they do correlate with levels of inactive (phospho-serine 9) GSK-3 $\beta$ . This suggests that the increased  $\beta$ -catenin levels present during normal wound healing and in hyperplastic scars are a result of a post-transcriptional mechanism involving signaling systems that inhibit GSK-3 $\beta$  activity. Additionally, cell cultures derived from normal wound and hyperplastic scar patient excisions show  $\beta$ -catenin-Tcf/Lef transcriptional activation [49]. Increased levels of

$\beta$ -catenin and activation of  $\beta$ -catenin-Tcf/Lef mediated gene transcription in both the proliferative phase of wound healing and hyperplastic wounds suggests  $\beta$ -catenin may play an important role in hyperplastic scar formation, as well as other fibrotic disorders.

#### $\beta$ -CATENIN AND AGGRESSIVE FIBROMATOSIS

Aggressive fibromatoses or desmoid tumors are clonal lesions characterized by locally invasive and proliferative fibroblast-like spindle cells [88]. Evidence suggests that desmoid tumors are neoplastic in nature, deriving from a single progenitor cell with a growth advantage [89]. Desmoid tumors can occur as a sporadic lesion or as part of familial adenomatous polyposis (FAP) caused by a germline mutation of the APC gene [90]. Recent studies focused on the molecular cause of desmoid tumors suggest that this disorder may be a result of abnormal  $\beta$ -catenin signaling. Desmoid tumors show  $\beta$ -catenin stabilizing mutations in both the APC and  $\beta$ -catenin genes [91, 92] and demonstrate cytoplasmic and nuclear accumulation of  $\beta$ -catenin as shown by immunohistochemical (IH) analysis [91]. Additionally,  $\beta$ -catenin stabilization in desmoid tumors activates Tcf/Lef transcriptional gene expression [93] and similar results are found in IH analysis of solitary fibrous tumors, another type of spindle cell neoplasm [94].

Transgenic mouse models expressing a stabilized form of  $\beta$ -catenin in mesenchymal cells develop symptoms of aggressive fibromatosis as well as hyperplastic cutaneous wounds [76]. Fibroblasts derived from these mice display increased proliferation, motility and invasiveness when grafted into nude mice and primary cell cultures demonstrate Tcf-dependent transcriptional activation [76], consistent with the hypothesis that nuclear  $\beta$ -catenin transactivation of target genes is a primary component of this fibrosis.

Oligonucleotide array analysis of global gene expression in desmoid tumors has identified insulin-growth factor binding protein-6 (IGFBP6), an established inhibitor of IGF-II signaling [95], as one of these target genes of  $\beta$ -catenin transactivation of the Tcf/Lef transcription complex. Unusually, IGFBP6 mRNA expression is down-regulated by  $\beta$ -catenin-Tcf/Lef mediated transcription [96], implying that expression of the IGFBP6 gene might be inhibitory to the development of this disease. In association, the gene encoding A Disintegrin And Metalloprotease 12, ADAM12, has been shown to be up regulated in aggressive fibromatoses [97]. ADAM12 is a protease of IGFBPs including IGFBP-3 and -5. A combination of up-regulated ADAM12 and down-regulated IGFBP-6 levels is predicted to result in increased IGF signaling, a situation previously shown to promote adherens junction disruption, nuclear localization of  $\beta$ -catenin [72, 74] and fibroblast proliferation [98]. Overall, these data suggest that dysregulation of the  $\beta$ -catenin signaling mechanisms and  $\beta$ -catenin-Tcf/

Lef mediated transcription are key factors in the pathogenesis of aggressive fibromatoses and imply that targeting  $\beta$ -catenin may have therapeutic utility for treatment of this disease.

#### $\beta$ -CATENIN AND BENIGN SUPERFICIAL FIBROMATOSIS

Histologically and biochemically, benign fibroproliferative disorders including DC, Peyronie's disease (fibromatosis of the penis), Lederhose disease (plantar fibromatosis), and frozen shoulder syndrome (FSS) share many similarities with wound granulation tissue, leading to the view that these conditions represent a dysregulated, fibrotic wound healing responses in different physiological contexts.

DC is a superficial fibromatosis that affects the palmar fascia and displays an invasive phenotype. The earliest stage of the disease is characterized by the appearance of a hyperproliferative nodule composed of both fibroblasts and activated myofibroblasts which deposit type 3 collagen in thick bundles throughout the affected area [99, 100]. Eventually, this process gives rise to a scar-like contractile collagen rich cord, resulting in permanent digit contracture [101]. Histological analysis has shown that DC and wound granulation tissue share many biochemical characteristics including the appearance of collagen type 3 and TGF $\beta$  [102, 103]. TGF $\beta$ 1 stimulation of DC derived fibroblast cultures *in vitro* results in an increased myofibroblast phenotype as determined by the presence of a smooth muscle actin [102]. Additionally, TGF $\beta$  stimulates collagen production in cultured fibroblasts from DC and patient matched control tissue [104]. Type 3 collagen is usually absent in normal adult palmar fascia but is commonly found in DC tissue extracted from patients [103]. This biochemical change in palmar fascia composition is similar to the changes that occur during the proliferative phase of wound healing suggesting that DC may be a type of dysregulated wound healing process.

Although the molecular cause of DC still remains to be elucidated, similarities in the clinical progression of DC with the wound healing response and additional accumulating molecular evidence suggests that  $\beta$ -catenin may be a component of the initiation and progression of DC. IH and Western blot analysis of DC patient tissue reveals increased cytoplasmic and nuclear staining of tyrosine phosphorylated  $\beta$ -catenin compared to control tissue [105]. Unlike aggressive fibromatoses, however, there is no evidence of  $\beta$ -catenin mutations in disease or control samples [105]. Furthermore, *in vitro* analysis of DC primary cells cultured in a fibroblast populated collagen lattice (FPCL), a three dimensional collagen environment designed to mimic *in vivo* disease conditions, demonstrates increased levels of  $\beta$ -catenin compared to levels in control lattices [106]. Interestingly, cellular levels of  $\beta$ -catenin are rap-

idly and differentially regulated by tension in FPCL culture compared to two-dimensional tissue culture, implying that both extra-cellular matrix (ECM) interactions and mechano-tension are essential components of this disease [106]. These results suggest that  $\beta$ -catenin may be a key player in the development of this and related superficial fibromatoses and that alterations in  $\beta$ -catenin accumulation in DC are potentially regulated by the ECM.

Cytoplasmic and nuclear accumulation of  $\beta$ -catenin accumulation has been reported in Lederhose disease and, in common with other superficial fibromatoses, no mutations in either exon 3 of  $\beta$ -catenin or in APC were detected. Whether the presence or absence of these mutations directly affects the clinical characteristics of this and other superficial fibromatoses, which are typically less invasive and proliferative than deep fibromatoses, such as desmoid tumors that frequently contain such mutations, remains unclear at present [107].

Adhesive capsulitis of the joint capsule, or FSS, is characterized by painful and restricted shoulder motion and affects an estimated 2% of adults. Based on immunohistochemical studies and clinical correlation, it has been suggested that FSS may share a similar patho-mechanism with that of DC [108, 109]. Histologically, both conditions are characterized by the presence of collagen-rich (types 1 and 3) nodules and bands that are populated by contractile fibroblasts and myofibroblasts. Furthermore, clinical studies suggest that these two connective tissue disorders are strongly associated with one another. A recent study of patients with FSS showed a marked increase in the incidence of DD compared to the general population [110]. Preliminary observations from our laboratory indicate that  $\beta$ -catenin expression is up-regulated in FSS compared to arthroscopy samples derived from subacromial decompression for rotator cuff syndrome (unpublished data). As with DC and Lederhose disease, the role of cytoplasmic  $\beta$ -catenin in this fibrotic disorder is presently unknown.

Peyronie's disease is a localized fibrotic lesion within the tunica albuginea of the penis [111, 112] that is very poorly understood at a molecular level. While there are no reports of  $\beta$ -catenin accumulation in this fibrosis, recent microarray analysis of gene expression in Peyronie's disease plaques compared normal tunica albuginea identified the mRNA for pleiotrophin as markedly up-regulated in the disease plaques [113]. As described previously, pleiotrophin regulates cell adhesion by signaling through receptor protein tyrosine phosphatases  $\beta/\zeta$  [54], which can promote the disruption of adherens junctions and release of cytoplasmic  $\beta$ -catenin. Whether this process is involved in the pathophysiology of this disease is at present not clear.

In conclusion, dysregulation of  $\beta$ -catenin processing and cellular accumulation are likely to be important

components of the pathogenesis of a number of fibrotic disorders. Mutational analysis of the  $\beta$ -catenin and APC genes in aggressive fibromatosis indicate that, as in cancers associated with familial adenomatous polyposis, somatic and germline mutations are very likely contributing to disease progression. However, mutations in  $\beta$ -catenin and related biomolecular partners are not evident in hypertrophic scarring and benign fibrotic conditions such as DC, Lederhose disease and FSS, disorders which display characteristics of an exaggerated wound healing response. Evidence suggests that  $\beta$ -catenin is dysregulated in these disorders through protein signaling pathways yet to be fully elucidated. Accumulating evidence supporting the importance of  $\beta$ -catenin in a variety of signaling pathways suggests that this molecule plays a much larger role in cellular processes than is currently appreciated.

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