In: Beta-Catenin ISBN: 978-1-62808-801-4
Editors: A. Braunfeld and G.R. Mirsky

Chapter 7

Clinical Significance of Beta-Catenin in Immunological Disease and Dysfunction: Signaling and Therapy

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Abstract

Beta-catenin is important both as a structural component of cell to cell adhesion and as a key transcriptional transducer of Wnt signaling in a myriad of biological events ranging from development to disease. Historically, research has focused on the role of beta-catenin related signal transduction in development and cancer. More recently, modulations of the Wnt/beta-catenin signaling pathway have been shown to be relevant in the immune suppression characteristic of the cancer microenvironment by altering immune signaling to promote cancer progression. Similarly, beta-catenin can also play a prominent role in the pathogenesis of various inflammatory diseases like colitis associated colon cancer, obesity, rheumatoid arthritis and neuroinflammatory conditions like Alzheimer's disease. This review aims to highlight the role of beta-catenin and Wnt signaling in the pathophysiology of

immunological diseases and dysfunction, as well as address the relevant therapeutic strategies which include small molecule inhibitors and anti-inflammatory compounds that target the Wnt/beta-catenin signaling pathway.

Introduction

Beta-catenin is important both as a structural component of cell to cell adhesion and as a key transcriptional transducer of Wnt signaling in a myriad of biological events ranging from development to disease. Wnt proteins are secreted, palmitoylated glycoproteins found in most tissues. The divergent, yet central role that Wnt signaling can play in development is a key reason why any deregulation of its pathways could lead to disease. Historically, research has focused on the role of beta-catenin related signal transduction in development and cancer. The Wnt signaling pathway was first discovered as a result of discovery of the *Int1* gene that contributed to mammary gland tumor development [1] and the *Drosophila wingless (wg)* gene [2]. Wnt signaling can be classified into two categories, canonical (beta-catenin dependent) and non-canonical (beta-catenin independent) Wnt signaling. Canonical Wnt proteins include Wnt1, Wnt2, Wnt3, Wnt3a, Wnt8a and Wnt10b while the non-canonical Wnts include Wnt4, Wnt5a, Wnt 5b, Wnt6, Wnt7a and Wnt 11.

Beta-catenin is a member of the armadillo family of proteins and it stabilizes cell-cell adhesion as well as transduces canonical Wnt signaling in the nucleus by interacting with (and thus regulating) diverse transcription factors. Given its important role in cell signaling, the levels of beta catenin are tightly controlled by the GSK3-beta/axin destruction complex. In the absence of Wnt signaling, beta-catenin exists as part of a destruction complex where it is subsequently phosphorylated by casein kinase 1 and GSK3-beta for targeted ubiquitin-mediated degradation [3]. Ligation of the Wnt receptor complex requires co receptors of the Low Density Lipoprotein Receptor-Related Protein 5 and 6 (LRP5 and LRP6) family and inhibits the activity of the beta-catenin destruction complex [4]. Subsequently, beta-catenin can translocate to the nucleus where it associates with the DNA binding proteins of the T cell factor (Tcf)/lymphoid enhancer factor (LEF) family to initiate transcription.

Comparatively, the role of beta-catenin and Wnt signaling in the immune system and the related deregulations that lead to disease have been a fairly recent topic of interest. The function of beta-catenin in hematopoietic cells has been controversial – deletion of beta-catenin has been shown to impair T cell

development [5]; however, others have shown that beta-catenin is dispensable for hematopoiesis and lymphopoiesis [6]. Constitutive Wnt/beta-catenin activation in the bone marrow, on the other hand, can result in hematopoietic stem cell and multi-lineage defects [7, 8]. With such significant yet fluid roles in hematopoietic stem cell differentiation and proliferation, it is not surprising that Wnt/beta-catenin signaling would be a central player in immune function.

It is well established that Wnt/beta-catenin signaling plays an important role in T cell development and function [9]. Tcf1, a beta-catenin binding transcription factor in the nucleus, has been shown to be critical for thymocyte maturation, and the N-terminal beta-catenin-binding domain has been identified as being necessary for this process [10, 11]. On the flip side, the stabilization of beta-catenin predisposes immature thymocytes to malignant transformation by interrupting their maturation process [12]. Therefore, it is not unexpected that deregulation of the Wnt/beta-catenin pathway can result in hematopoietic malignancies like leukemia [13, 14]. The role of beta-catenin in the immune system, however, is not merely restricted to its activity as a transcriptional modulator in the nucleus. The carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) was recently shown to inhibit Fas-mediated apoptosis in Jurkat T cells via its interaction with beta-catenin and redistribution of beta-catenin in the actin cytoskeleton, protecting it from degradation [15]. During anti-Fas induced apoptosis in Jurkat T cells, beta-catenin can be distributed to the actin cytoskeleton and degraded by active caspases [14].

With regards to other immune cell types, Wnt3a has been shown to mediate anti-inflammatory signaling in macrophages via up regulation of its receptor, Frizzled1, upon infection with tuberculosis [16, 17]. IL-4-induced beta-catenin regulates the conversion of macrophages to multinucleated giant cells [18], indicating that beta-catenin can be a novel regulator of macrophage responses to IL-4. Therapeutic modulation of the expression or function of beta-catenin may therefore enhance the effectiveness or ameliorate the pathology of IL-4-driven immune responses. Furthermore, Wnt signaling has been shown to regulate the recruitment of neutrophil recruitment after acute colonic injury in mice [19].

In light of these various roles that canonical Wnt signaling can play in the immune system, this review aims to highlight the role of beta-catenin and canonical Wnt signaling in the pathophysiology of immunological diseases and dysfunction. We will also address the relevant therapeutic strategies which include natural compounds and small molecule GSK3-beta inhibitors that target the Wnt/beta-catenin signaling pathway. We will discuss the role of Wnt

signaling in inflammatory diseases and the modulation of anti-tumor immunity.

Wnt Pathway in Inflammatory Diseases

Given the central role that Wnt signaling plays in immune function and development, it is not surprising that deregulation of Wnt signaling can result in pathophysiology of immune function. Inflammatory diseases can have many different manifestations and those that incorporate canonical Wnt/beta-catenin signaling include obesity, colitis associated colon cancer, bronchial asthma, sepsis, and neuroinflammatory conditions like Alzheimer's disease, stroke, traumatic brain injury and Parkinson's disease. In general, the canonical Wnt pathway has been shown to promote anti-inflammatory signaling. For example, modulation of the Wnt/beta-catenin pathway has been shown in asthma patients via microarray analysis of their peripheral blood mononuclear cells [20] and beta-catenin was subsequently shown to be a negative regulator of inflammatory signaling, preventing the over production of inflammatory cytokines like IL-6. Wnt/beta-catenin signaling is significantly reduced in the lungs of *M. tuberculosis*-infected mice, furthering the idea that Wnt/beta-catenin signaling is down regulated in inflamed tissue and activated immune cells [17].

The role of Wnt/beta-catenin signaling in neuroinflammatory diseases has been recently reviewed by Marchetti and Pluchino in [21].The anti-inflammatory effects of canonical Wnt/beta-catenin signaling would suggest a protective role in neuroinflammation. In this regard, it is critical to understand how the effects of anti-inflammatory signaling are initiated during disease in order to promote repair and regeneration. For example, in mice overexpression of GSK3-beta (thus shutting down Wnt/beta-catenin signaling) recapitulated the neuropathology of Alzheimer's disease. On the other hand, transgene shutdown of GSK3-beta in symptomatic mice diminished their neuronal death and cognitive deficit [22]. In traumatic brain injury, macrophages/microglia can produce proinflammatory cytokines and chemokines that stimulate astrocytes to produce Wnt1 type ligands that can promote canonical Wnt/beta-catenin signaling as a survival and repair mechanism [21]. Similarly, it has been shown in an experimental model of Parkinson's disease that stimulation of canonical Wnt/beta-catenin signaling in the neuron can lead to survival and repair [23].

Obesity is a chronic inflammatory condition associated with insulin resistance, which can in turn lead to type 2 diabetes. Chronic inflammation in obesity is mediated by adipocytokines and inflammatory cytokines released from fat tissue. IL-6 and TNF-α have been implicated as inflammatory cytokines associated with adipose tissue that can activate Wnt/beta-catenin signaling in preadipocytes [24]. Activation of canonical Wnt signaling prevented differentiation of preadipocytes to adipose cells and instead, conferred an inflammatory phenotype on the adipocytes. Furthermore, up regulation of canonical Wnt signaling can reduce stem cell differentiation into adipocytes and reduce subsequent lipid accumulation [25]. Wnt/beta-catenin signaling in adipocytes and preadipocytes through different mechanisms and experimental models has been shown to repress adipogenesis [26, 27]. Collectively, these data suggest that this could be a relevant pathway to target in obesity. Indeed, therapeutic targeting of inflammation-induced obesity by natural compounds like curcumin has been reviewed recently [28]. In addition, an obesity-induced increase in TNF-α has been shown to predispose mice towards colon cancer with subsequent activation of protumorigenic, canonical Wnt signaling in colon cells [29].

Chronic inflammation in the colon during inflammatory bowel disease can also predispose genetically susceptible individuals towards developing colon cancer later on in life. Pathological signaling of the Wnt/beta-catenin pathway is known to promote the development of colon cancer. Therefore, it would be reasonable to assume that the colitis induced inflammation in the colon would have some effect in promoting tumorigenesis. Indeed, indoleamine 2,3 dioxygenase-1 (IDO1) has been shown to activate tumor development via nuclear translocation of beta-catenin in a mouse model of colitis associated colon cancer [30].

Compared to the previously described inflammatory disease, autoimmunity is a different type of unwanted inflammation in the body. A recent genetic analysis has shown that Wnt/beta-catenin signaling is highly enriched in peripheral blood mononuclear cells in autoimmune diseases like rheumatoid arthritis, multiple sclerosis, Crohn's disease, ulcerative colitis, type 1 diabetes and systemic lupus erythematosus [31]. This data is intriguing, given that we have thus far discussed the anti-inflammatory effects of canonical Wnt/beta-catenin signaling in inflammation and cancer. It is possible that Wnt/beta-catenin signaling can act differently in autoimmunity, or that in this case, it is also possible genetic analysis does not necessarily represent the true function of canonical Wnt signaling. In rheumatoid arthritis, nuclear translocation of beta-catenin resulted in increased expression of COX2 in

articular chrondrocytes, suggesting that transcriptionally active beta-catenin may play a role in promoting the inflammatory response of arthritic cartilage [32]. The role of Wnt signaling in rheumatoid arthritis has recently been reviewed by in [33].

Wnt Pathway in Modulating Anti-Tumor Immunity

Inflammation in the context of cancer can be tumor promoting or tumor inhibiting. The desirable outcome of clinical and pre-clinical studies is to generate effective anti-tumor immunity via cancer immune therapy strategies in combination with chemotherapy. Modulations of the Wnt/beta catenin signaling pathway have recently been shown to be relevant in the immune suppression characteristic of the cancer microenvironment by altering immune signaling to promote cancer progression. Activation of Wnt/beta-catenin signaling in human melanoma cells has been shown to contribute to immune suppression and resistance by secretion of immune suppressive IL-10 [34]. In a reciprocal manner, the immune suppressive tumor microenvironment can also activate Wnt signaling to further drive tumor progression. IDO1 metabolites have been shown to activate beta-catenin signaling to promote cancer cell proliferation and colon tumorigenesis in mice [30].

While the role of Wnt/beta-catenin signaling in T cell development is very well established, its role in the function and biology of mature T cells is still relatively new. In this regard, the function of CD8 T cells and development of CD8 T cell memory with regards to anti-tumor immunity is probably one of the more central issues surrounding cancer immunotherapy. The Wnt pathway effector Tcf-1 has subsequently been shown to play an essential role in the establishment of functional CD8 T cell memory [35] (recently been reviewed by Gattinoni et al. [36]). In this regard, constitutive activation of Wnt signaling in T cells favors the generation of memory CD8 T cells [37]. Induction of canonical Wnt–beta-catenin signaling by inhibiting GSK3-beta or the using Wnt3a as a ligand arrested $CD8^+$ T cell development into effector cells. By blocking T cell differentiation, Wnt signaling promoted the generation of $CD44^{low}CD62L^{high}Sca\text{-}1^{high}CD122^{high}Bcl\text{-}2^{high}$ self-renewing multipotent $CD8^+$ memory stem cells with proliferative and antitumor capacities exceeding those of central and effector memory T cell subsets. These findings reveal a key role for Wnt signaling in the maintenance of 'stemness' in mature memory $CD8^+$ T

cells and have major implications for the design of new vaccination strategies and adoptive immunotherapies [38].

Mechanistically, canonical Wnt/beta-catenin as well as non-canonical Wnt signaling have been shown to program dendritic cells to a tolerogenic state, limiting the inflammatory response and subsequent anti-tumor immunity in cancer [39, 40]. The Wnt/beta-catenin signaling pathway has been implicated as a major player in the myelopoiesis of dendritic cells [41]. It is therefore not surprising that defective signaling in the Wnt pathway during myelopoiesis can result in the accumulation of $CD11b^{+}Gr1^{+}$ myeloid derived suppressor cells (MDSCs), a heterogeneous population of immature myeloid cells that contribute towards the immune suppressive tumor microenvironment [42, 43]. Down regulation of beta-catenin during inflammation (unpublished data, Poh and Gendler, 2013) or tumorigenesis [42] is associated with increased levels of MDSCs in experimental murine models. Inhibition of beta -catenin degradation with GSK3-beta inhibitors prevented the increase in MDSCs *in vitro* [42]. In a recently published murine model of skin cancer, $CD11b^{+}Gr1^{+}$ myeloid cells have been shown to secrete Wnt ligands to promote Wnt/beta-catenin signaling in the neighboring epithelium, thus enhancing tumor growth [44]. In addition to MDSCs, T regulatory (Treg) cells are also major players in establishing and maintaining the immune suppressive tumor microenvironment by suppressing T cell function. It has been shown that stabilized beta-catenin enhances the survival of regulatory $CD4^{+}CD25^{+}$ T cells *in vitro* and confers anergy on naïve $CD4^{+}CD25^{-}$ T cells, resulting in anti-inflammatory effects in inflammatory bowel disease (IBD) [45].

Targeting Beta-Catenin in Therapy

Overall, these studies suggest that Wnt signaling can be targeted in the immune system to modulate tumor suppression for more effective immune therapy in cancer. Over the years, a variety of natural and synthetic compounds have been shown to target the Wnt/beta-catenin signaling pathways, thus ameliorating disease pathology in which these pathways are activated. However, many of these compounds have nonspecific effects, either as a result of the pleiotropic roles of Wnt/beta-catenin signaling in cell physiology, or due to the effects of these compounds on other important signaling biological pathways. In addition, many of these compounds have been shown to have therapeutic efficacy by targeting Wnt signaling in non-hematopoietic cells like epithelial cells, cancer cells and adipocytes. At the

same time, many of these compounds have been extensively studied therapeutically in cancer cells and in *in vivo* models in the context of cancer signaling. Although it is known that canonical Wnt/beta-catenin signaling can modulate immune function, the effects of many of these compounds on the immune system have not been studied extensively. For example, NSAIDs are known for their anti-inflammatory effect in cancer, acting primarily by inhibition of COX2, but they have also been shown to reduce beta-catenin/TCF mediated signaling [46]. However, most of this work has been studied in cancer but with little regard to effects of modulating Wnt/beta-catenin signaling in the immune cell. In light of this, we will discuss some of the known effects that these canonical Wnt/beta-catenin targeting compounds can have on immune function.

Natural Compounds

Curcumin, a yellow pigment present in turmeric, has pleiotropic biological effects, which include modulation of the Wnt/beta-catenin pathway [28]. Curcumin has been shown to promote beta-catenin accumulation through inhibition of GSK3-beta both *in vitro* and *in vivo* [47]. Furthermore, the inflammatory effects associated with obesity can be modulated by the ability of curcumin to activate Wnt/beta-catenin signaling, thus suppressing adipogenic differentiation [48]. Similar inhibition of adipogenesis via sustained Wnt signaling has been shown with active extracts of Lindera obtusiloba [49] and soy protein isolates [26]. In the study with Lindera obtusiloba, anti-inflammatory effects were demonstrated in the 3T3-L1 preadipocytes and in the study with soy protein isolates, fat accumulation was alleviated in the livers of obese mice through activation of Wnt/beta-catenin signaling.

The majority of the effects of most natural compounds that affect Wnt signaling, however, have been described in epithelial and other non-immune cells. While we could assume that Wnt/beta-catenin signaling may be similarly modulated in the immune cell, there has not been any comprehensive study that shows specific activity of natural compounds on Wnt/beta-catenin signaling in the immune system.

However, modulation of the effects of the immune system on Wnt signaling can occur in indirect ways as well. Vitamin D3, the most active metabolite of vitamin D, is a chemo preventative agent that can antagonize canonical Wnt signaling in colorectal carcinoma cells, thus reducing

tumorigenicity [50]. Interestingly, vitamin D3 is also able to inhibit the ability of tumor-associated macrophages (TAMs) to stimulate pro tumorigenic canonical Wnt signaling in colon carcinoma cells. It acts by blocking the constitutive activation of STAT1 and the release of IL-1beta by TAMs, thus negating cross talk between TAMs and the tumor microenvironment [51].

GSK3-Beta Inhibitors

The levels of beta-catenin in the cell are dependent on its phosphorylation by GSK3-beta within the axin destruction complex which targets it for ubiquitin-dependent degradation. Therefore, canonical Wnt/beta-catenin signaling can be modulated by a variety of GSK3-beta inhibitors (both nonspecific, e.g. lithium, and specific, recently reviewed in [52]), of which many are in clinical and pre-clinical use. Unlike curcumin and other previously discussed natural compounds that have been studied for their effects on Wnt/beta-catenin signaling in cancer and other non-hematopoietic cell types, GSK3-beta inhibitors have been shown to be able to modulate innate and adaptive immune responses [53].

We and others have shown that activation of canonical Wnt/beta-catenin signaling with GSK3-beta inhibitors can promote the differentiation of dendritic cells and inhibit the development of immature myeloid cells and/or tumor promoting MDSCs [42, 43].

As mentioned earlier in this review, the GSK3-beta inhibitor, 4,6-disubstituted pyrrolopyrimidine (TWS119), can augment T cell memory formation [38]. Systemic administration of the GSK3-beta inhibitor, SB216763, enhanced suppressive Treg activity and resulted in prolonged islet survival in an allotransplant mouse model [54]. These data suggest that targeting of beta-catenin signaling in Treg cells could be useful in increasing the stability and function of Treg cells for inducing allotransplant tolerance or treating autoimmune conditions.

Conclusion

The field of Wnt/beta-catenin signaling has progressed a long way since the initial discovery of the *Int1* gene.

The central role of Wnt/beta-catenin signaling in development, cancer and immune function makes it challenging to design specific beta-catenin targeted therapy for clinical use across a wide range of pathological conditions. There is increasing interest in role of canonical Wnt signaling in immune function and it would be reasonable to assume that most of the compounds that modulate Wnt signaling in cancer and other non-hematopoietic cell types would also have immune modulatory functions.

Ultimately, the ideal goal would be to fully understand the effects of these Wnt/beta-catenin modulating compounds across all cell types to orchestrate an effective therapeutic response in disease.

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