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# Wnt Signaling as a Master Regulator of Immune Tolerance in a Tumor Microenvironment

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## Abstract

Aberrant Wnt signaling is a hallmark of many cancer types such as colon cancer. However, the effect of altered Wnt signaling is not only restricted to cancer cells but also dynamically interacts with a tumor microenvironment and has the ability to directly regulate the anti-tumor immune response. It has been reported that tumors induce immune tolerance through the activation of canonical Wnt signaling in dendritic cells promoting T regulatory responses, and also that both canonical and noncanonical Wnt proteins program dendritic cell responses for tolerance. Thus, the Wnt signaling pathway may be a novel and promising therapeutic target for anticancer immunotherapy. In this review, we will discuss the molecular mechanisms involved in immune cell response regulation mediated by canonical and noncanonical Wnt signaling.

**Keywords:** Wnt signaling, tumor microenvironment, immune tolerance, antitumor regulation response, regulatory T cells, dendritic cells

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## 1. Introduction

Tumor-induced immune tolerance is a hallmark of cancer and constitutes a challenge for effective anticancer treatment. Overcoming immune evasion within the tumor microenvironment is crucial to successful immunotherapy to eradicate tumors.

Cancer cells operate in multiple regulatory mechanisms to evade antitumor immunity, but the signaling pathways involved in the regulation of these mechanisms are not well understood. Emerging studies have shown that Wnt signaling is a key pathway regulating tolerance versus

immunity, and that it is a master regulator of T cell immune responses and of dendritic cells. In this respect, the canonical Wnt/ $\beta$ -catenin has been the first oncogene pathway reported that mediates immune exclusion, particularly via dendritic cells and T regulatory cells.

All of these studies suggest, therefore, that the Wnt pathway can be an attractive target to restore immune access to the tumor microenvironment.

## 2. Wnt signaling pathway

The Wnt signaling pathway is involved in the regulation of embryonic development and adult tissue homeostasis. Wnt family of secreted lipid-modified glycoproteins regulates cellular processes including stem cell maintenance, proliferation, differentiation, apoptosis, survival, cell motility, and polarity [1]. Since Wnt signals not only promote proliferation but also can control cell-fate determination and terminal differentiation in a tissue- and temporal-specific manner [2], the deregulation of Wnt signaling causes developmental defects and cancers.

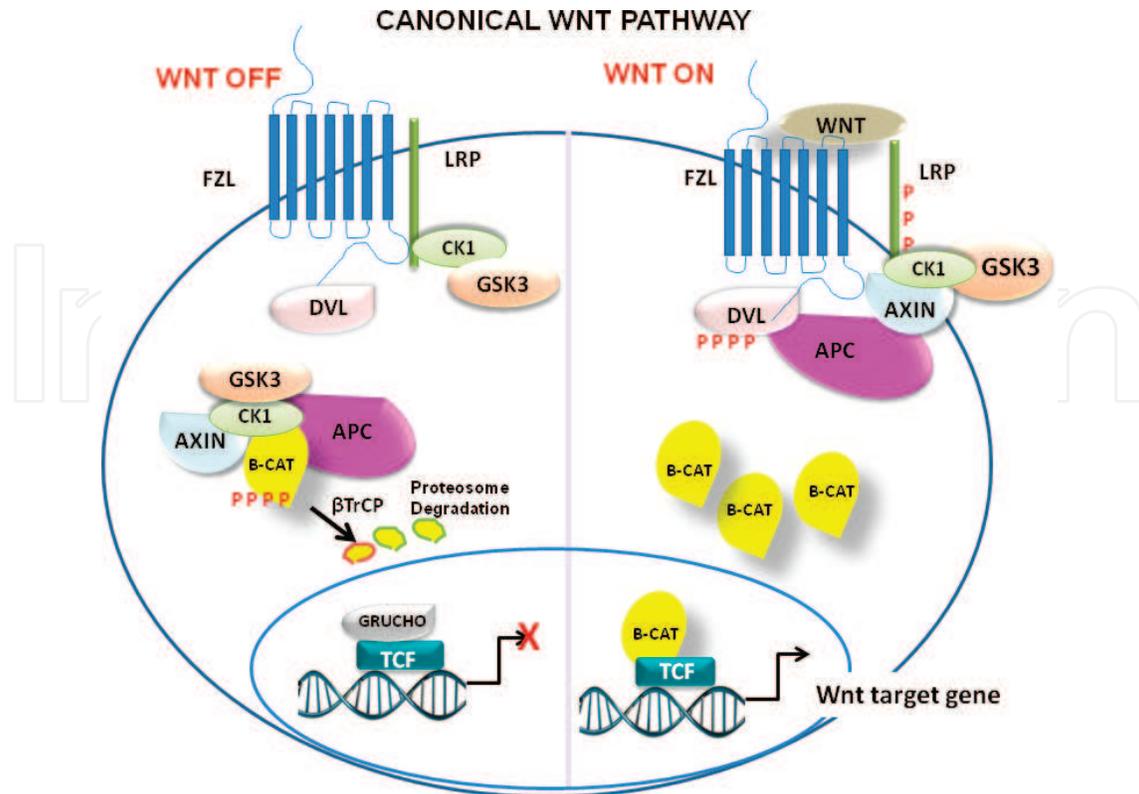
In humans, 19 Wnt ligands have been identified. They bind to several receptors including Frizzled (FZD) family receptors, receptor tyrosine kinase-like orphan receptor family (ROR), low-density lipoprotein receptor-related protein co-receptors (LRP), and the related to receptor tyrosine kinase (RYK) receptor [1–3]. Wnt activates the canonical pathway that regulates transcription of target genes through the  $\beta$ -catenin/TCF pathway (**Figure 1**) and the noncanonical pathways that are independent of  $\beta$ -catenin. Disheveled (Dvl) protein is an essential element in the transduction of both canonical and noncanonical Wnt signals (**Figure 2**).

### 2.1. Canonical Wnt signaling

Canonical Wnt signals operate through regulating the phosphorylation, degradation, and localization of the transcription co-activator  $\beta$ -catenin (**Figure 1**). Without stimulation by Wnt,  $\beta$ -catenin is assembled into a destruction complex, in which APC protein plays a central role, and includes Axin, GSK-3 $\beta$ , and Casein kinase 1 (CK1). This complex directs a series of phosphorylation events in  $\beta$ -catenin mediated by CK1 and GSK-3 $\beta$  that targets it for ubiquitination and subsequent proteolysis via the proteasome [2, 3].

Upon binding of Wnt to FZD and LRP co-receptors, the LRP receptors are phosphorylated by CK1- $\alpha$  and GSK-3 $\beta$ , which recruit disheveled (DVL) and axin proteins to the plasma membrane where Dvl becomes polymerized [1–3]. The DVL polymers inactivate the destruction complex allowing  $\beta$ -catenin to accumulate and enter the nucleus, where it interacts with T cell factor/lymphoid enhancer factor (TCF/LEF) family members and activate a Wnt target gene program [2–4].

The tumor microenvironment (TME) contains high levels of Wnts, and aberrant  $\beta$ -catenin signaling occurs in many tumors. However, the effect of aberrant canonical Wnt signaling is not only restricted to cancer cells but also dynamically interacts with the microenvironment and immune system [5]. Over the last few years, it has been reported by several laboratories that Wnt signaling may also regulate T cell-mediated immune responses, and the Wnt/ $\beta$ -catenin/TCF pathway in dendritic cells (DCs) plays a critical role in balancing immunity and tolerance [5].



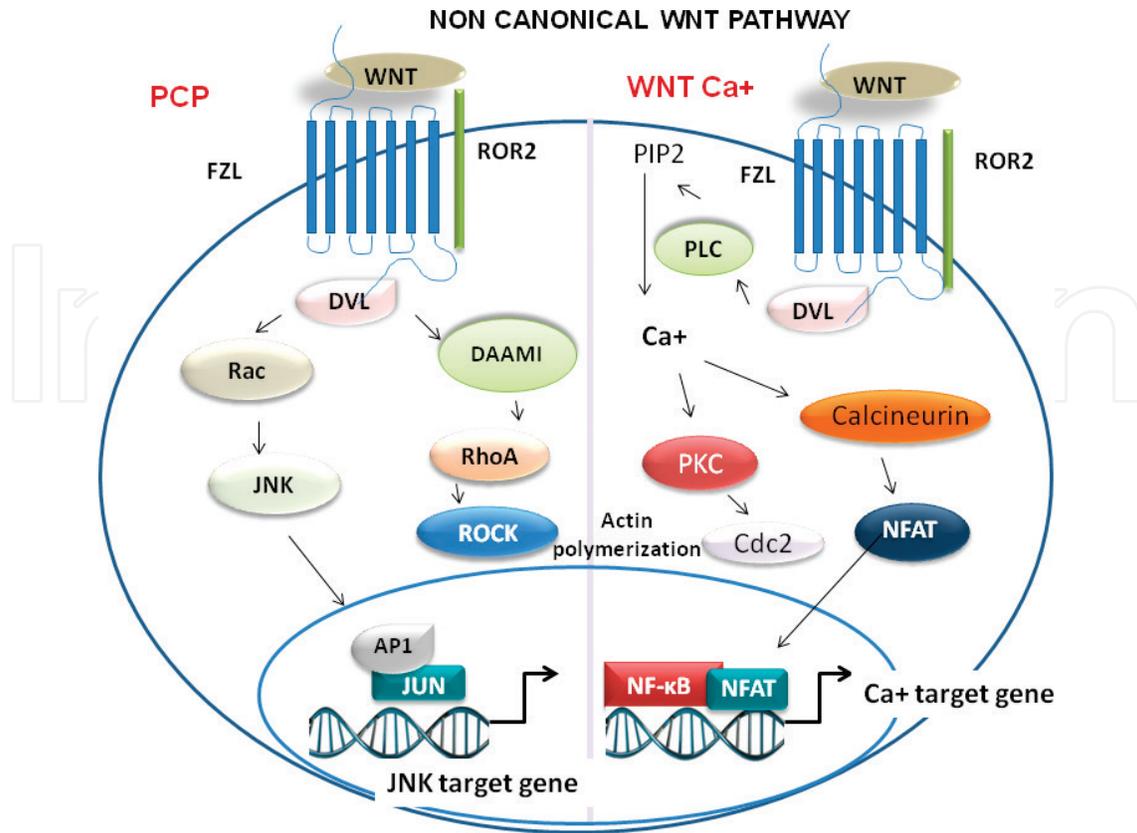
**Figure 1.** Canonical Wnt signaling. In the absence of Wnt ligand,  $\beta$ -catenin is degraded by a complex composed of Axin, APC, CK1, and GSK3. Once Wnt ligand such as archetypal Wnt3a is bound with Frizzled and LRP5/6 co-receptor, Dvl scaffolds  $\beta$ -catenin degradation complex resulting in accumulation of  $\beta$ -catenin in cytosol and nucleus.  $\beta$ -Catenin forms a complex with TCF to transcribe target genes.

## 2.2. Noncanonical Wnt signaling

Wnt signaling that is independent of  $\beta$ -catenin is referred to as the noncanonical pathway where a transcriptional response is elicited via an alternative mode of downstream signaling not involving  $\beta$ -catenin-TCF or  $\beta$ -catenin-LEF [6]. There are several noncanonical Wnt pathways, depending on the configuration of FZDs and co-receptors involved, but they can be broadly categorized into two pathways: the planar cell polarity (PCP) pathway and the Wnt/Calcium (Wnt/ $\text{Ca}^{2+}$ ) pathway, as it can be observed in **Figure 2**.

### 2.2.1. Noncanonical PCP pathway

The PCP pathway genes code for proteins that regulate cellular polarization and directional cell movement, as initially observed during embryogenesis. The loss of normal cell polarity and adhesion, along with the acquisition of motility and invasiveness, are also fundamental steps during tumor progression and metastasis. This pathway is activated when ligands such as the noncanonical prototype ligand Wnt5a bind to FZD receptors or to FZD alternative receptors ROR1, ROR2, or RYK or through FZD with ROR or RYK as co-receptors [6, 7]. WNT/PCP signals are converted to actin cytoskeletal dynamic reorganization via the activation of small G-proteins Rac and Rho (**Figure 2**), and then, Rac and Rho activate Rho-associated kinase (Rho-kinase) and Jun N-terminal kinase (JNK)-dependent transcription [8].



**Figure 2.** Noncanonical Wnt signaling. The activation of Frizzled by Wnt ligand such as Wnt5a is mediated by Dvl or heterotrimeric G-proteins. The two better characterized noncanonical branches are shown: planar cell polarity (at the left of the figure) in which Dvl mediates the activation of small GTPase (Rho and Rac) and JNK to promote polarized cell migration. In the other branch, the Wnt/Ca<sup>2+</sup> pathway shown at the right of the figure, archetypal noncanonical Wnt5a activates phospholipase C (PLC) to produce diacylglycerol and Ca<sup>2+</sup> mobilization that activates PKC isoforms, other Ca<sup>2+</sup>-modulated kinases and calcineurin phosphatase, which in turn promotes NFAT translocation to the nucleus.

### 2.2.2. Noncanonical Wnt/Ca<sup>2+</sup> pathway

The Wnt/Ca<sup>2+</sup> pathway is initiated by the interaction of the Wnt5a/FZD receptor complex along with the participating co-receptor ROR1/2 which leads to the activation of a phospholipase C (PLC) via G protein, resulting in the production of inositol 1,4,5-triphosphate (IP3) and 1,2-diacylglycerol (DAG). IP3 induces cytosolic Ca<sup>2+</sup> elevation through Ca<sup>2+</sup> release from the endoplasmic reticulum, and both Ca<sup>2+</sup> and DAG activate conventional and novel PKC isoforms. Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CAMK2) and calcineurin are also representative downstream effectors of the WNT/Ca<sup>2+</sup> signaling cascade. In addition, WNT/Ca<sup>2+</sup> signaling-dependent calcineurin activation leads to dephosphorylation and subsequent nuclear translocation of NFAT for the transcriptional activation of NFAT-target genes [8].

It is well established that noncanonical Wnt ligands can antagonize the functions of canonical ligands inhibiting canonical signaling, and that there is considerable overlap between the Wnt pathway [9]. For example, CAMK2 activation leads to phosphorylation and activation of Nemo-like kinase (NLK), which can inhibit canonical Wnt/ $\beta$ -catenin signaling in some cells [8, 10]. However, in other contexts, Wnt5a is able to activate  $\beta$ -catenin-dependent transcription in

the presence of Fzd4 [11]. In addition, Wnt5a can work in cooperation with the Ror2 receptor to promote  $\beta$ -catenin degradation independently of GSK3 and therefore inhibits Wnt3a-mediated canonical Wnt signaling [9, 12].

### 3. Wnt signaling in dendritic cell regulation

Dendritic cells (DCs) are professional antigen presenting cells acting as central players in control of innate and adaptive immunities. Emerging evidence indicates that DCs also play a pivotal role in mediating immune tolerance. Indeed, DCs are critical in maintaining tissue homeostasis by acquiring, processing, and presenting antigens to naive and resting memory T cells leading to their activation, clonal expansion, and differentiation. Paradoxically, some DCs suppress T cell responses by promoting T cell apoptosis and enhancing the development of T cells with regulatory function including CD4<sup>+</sup> Foxp3-lineage T cells (Tregs) [13].

The types of cytokines secreted by DCs dictate the outcome and type of immune response, but the receptors and signaling networks that program DCs into a tolerogenic or inflammatory state are poorly understood [14].

Tumors evade anti-tumor immunity and dendritic cells also play a key role in this. However, signaling networks for driving DC tolerogenesis in the setting of cancer remain poorly characterized. However, emerging studies has highlighted that the Wnt signaling pathway, particularly in DCs, plays a major role in regulating tolerance versus immunity. In this respect, it has been reported that Wnts in the tumor microenvironment condition dendritic cells to a regulatory state and suppress host antitumor immunity. Supporting this, Hong et al. [15] and Suryawanshi et al. [16] have shown that DCspecific deletion of Wnt coreceptors LRP5/6 in mice markedly delayed tumor growth and enhanced host antitumor immunity. These authors also found that tumors activate  $\beta$ catenin/TCF4 in DCs programming them to a regulatory state, which promotes T regulatory responses while suppresses effector T cell responses [15] indicating that  $\beta$ -catenin activation in DCs induces regulatory T cell response and limits effector T cell response to tumors.

Spranger et al. [17] showed that a Wnt signature in cutaneous melanoma samples correlates with T cell exclusion. These authors showed that T cell priming against tumor antigens fails due to defective recruitment of CD103<sup>+</sup> dendritic cells. In addition,  $\beta$ -catenin signaling down-regulates the chemokine CCL4, which negatively affects the recruitment of dendritic cells to the tumor. Moreover, upregulation of IL-12 production in melanoma by increased  $\beta$ -catenin signaling can also lead to impaired dendritic cell maturation and induction of regulatory dendritic cells [18].

Importantly, both canonical and noncanonical ( $\beta$ -catenin-independent) Wnt signals have been reported to shift DCs from promoting immune responses into a tolerogenic state. In this regard, Oderup et al. [19] have found that Wnt3a activates canonical  $\beta$ -catenin signaling in DC, while Wnt5a triggers noncanonical signaling cascades. They found that although both canonical Wnt3a and noncanonical Wnt-5a support a tolerogenic DC phenotype, they induce

distinct patterns of tolerogenic cytokine production and differential DC responses to toll-like receptors (TLRs). In addition, they showed that Wnt3a preferentially induced TGF $\beta$ , while Wnt5a was a potent stimulus for IL-10 production, and that Wnt3a but not Wnt5a, strongly stimulated DC production of VEGF-A, as well [19].

Acquired immune privilege is mediated, in part, by DCs expressing the enzyme indoleamine 2,3 dioxygenase (IDO), since IDO-expressing DCs possess potent T cell regulatory functions [13]. IDO is a heme-containing enzyme known to catalyze the rate limiting step in the degradation of the essential amino acid tryptophan to its metabolic byproducts known collectively as the kynurenines. In DCs, IDO activity has profound effects on the ability of T cells to respond to antigenic stimulation. IDO may attenuate the ability of DCs to stimulate effective T cell responses in a number of ways: T cells activated by DCs expressing IDO recognized antigen and entered the cell cycle, but IDO activity blocked subsequent cell cycle progression and enhanced T cell apoptosis [13].

Loss of TGF- $\beta$  receptor III (T $\beta$ RIII) expression has been shown to occur during the progression of several cancers [20]. It has been demonstrated that loss of T $\beta$ RIII and the upregulation of Wnt5a by developing cancers play a role in the extrinsic control of IDO activity by local dendritic cell populations residing within tumor. These genetic changes are capable of modulating paracrine signaling pathways in the early stages of carcinogenesis to establish a site of immune privilege by promoting the differentiation and activation of local regulatory T cells [20].

It has also been reported that tumors program DCs to produce retinoic acid (RA), which promotes immune suppression by inducing T regulatory responses [21]. This is mediated through the induction of vitamin A-metabolizing enzymes via the activation of the  $\beta$ -catenin/TCF pathway in DCs, which in turn drives T regulatory responses and suppresses T cell effector response limiting antitumor immunity [21].

#### 4. Wnt signaling in CD4 regulatory T cells

It is well known that anti-tumor T cell responses arise in cancer patients but are disabled upon tumor progression by suppressive mechanisms triggered by the interplay between malignant cells, infiltrated immune cells, and the tumor microenvironment [22].

T cells with regulatory functions (Tregs) are CD4<sup>+</sup> CD25<sup>+</sup> and express transcription factor Foxp3. They are physiologically engaged in the maintenance of immunological self-tolerance and immune homeostasis. Tumor-infiltrating Tregs can suppress effector T cells specific for tumor antigens [5].

Over the last years, it has been reported that the Wnt signal transduction pathway plays an important role both in the regulation of hematopoietic stem cell (HSC) function and in the development in the thymus, where it provides proliferation signals to immature thymocytes [22].

Accumulating experimental evidence has led to the understanding that pro-inflammatory Th17 cells are favored in their function by Wnt signaling, whereas Tregs are inhibited by canonical Wnt signaling [5]. In this respect, it has been reported that some Th17 cells are

long-lived, express high levels of TCF1, and  $\beta$ -catenin for their self-renewal-like proliferation. Consistent with this, Gounari et al. [23] showed that Wnt- $\beta$ -catenin signaling induced the expression of ROR $\gamma$ T resulting in high amounts of IL-17 and predisposition to inflammation, colitis, and intestinal tumors. Coffey et al. [24], in contrast, showed that Wnt signaling directly modulates Foxp3 activity and thereby Treg function. TCF1 directly binds to FoxP3 and  $\beta$ -catenin-TCF inhibits Foxp3 transcriptional activity, thus reducing Treg-mediated suppression *in vitro* and *in vivo*. All these data therefore indicate that canonical Wnt signaling is likely a master regulatory pathway in governing the balance between Th17/Treg and thereby influences the outcome of immune responses [5].

## 5. Wnt signaling in CD8 cytotoxic T cells

The CD8<sup>+</sup> lymphocytes act against intracellular pathogens, including viruses and bacteria or malignant cells. Upon activation, CD8<sup>+</sup> T cells produce cytokines such as IFN- $\alpha$  and TNF- $\gamma$ , with antitumoral or antimicrobial effects, and also produce cytotoxic perforins and granzymes, similar to Natural Killer (NK) cells. Activated CD8<sup>+</sup> T cells also express FasL on the cell surface, which binds to its receptor, Fas, on the surface of the target cell, inducing the activation of the caspase cascade resulting in apoptosis.

A characteristic of the CD8<sup>+</sup> T cell is the development of immunological memory, which confers protection against a secondary presentation with the same pathogen [25].

As mentioned before, Wnt signaling controls proliferation, maturation, and differentiation of T cells and dendritic cells. Staal et al. [5] have demonstrated that the Wnt-responsive transcription factors, TCF1 and LEF1, are highly expressed by naive mouse and human CD8<sup>+</sup> T cells. The Wnt responsive transcription factor T cell factor 1 (TCF1) is well known to be critical for normal thymic T cell development. Recent studies have also revealed critical requirements for TCF1 in generation and persistence of functional memory CD8(+) T cells. Canonical Wnt signaling induced by activated  $\beta$ -catenin, Wnt3a canonical ligand, or GSK3 $\beta$  inhibitors, arrested CD8<sup>+</sup> T cell differentiation and favored CD8<sup>+</sup> T cell memory formation by suppressing their maturation into terminally differentiated effector T cells [26]. Importantly, constitutive activation of the canonical Wnt pathway not only favors memory CD8<sup>+</sup> T cell formation during initial immunization but also enhanced immunity upon second encounter with the same antigen. Consistent with this, TCF1 deficiency was shown to limit the proliferation of CD8<sup>+</sup> effector T cells and impair differentiation toward a central memory phenotype [24, 26].

Dickkopf-related protein 2 (DKK2) acts as a natural antagonist of the canonical Wnt signaling by binding to LRP5/6 co-receptor and inducing its cellular internalization. Xiao et al. [27] recently reported that the loss of adenomatous polyposis coli (APC) in intestinal tumor cells or of the tumor suppressor PTEN in melanoma cells, upregulates the expression of DKK2, which with its receptor LRP5, provides an unusual mechanism for tumor immune evasion. DKK2 secreted by tumor cells acts on CD8<sup>+</sup> cytotoxic lymphocytes independently of the Wnt/ $\beta$ -catenin pathway inhibiting STAT5 signaling by blocking STAT5 nuclear localization via LRP5. Genetic or antibody mediated inhibition of DKK2 activates natural killer (NK) cells and CD8<sup>+</sup> T cells in tumors, inhibiting tumor progression [27].

## 6. Wnt signaling in natural killer cells

Natural killer (NK) cells are innate immune effector cells. The NK cells are derived from the hematopoietic progenitor cells (HPC) CD34<sup>+</sup> and have been characterized by the expression of surface markers CD56<sup>+</sup> CD3<sup>-</sup>, which have been isolated mainly from lymphoid nodules and secondary lymphoid tissues. However, a lower amount of NK cells are found in bone marrow, blood, and spleen [28] and have also been found in the skin, intestine, liver, lungs, and uterus, among other tissues [29].

It has been demonstrated the existence of a population of cells expressing NK and T cell markers, which were referred as natural killer T (NKT) cells. These cells are a relevant population of hepatic lymphocytes in both humans and mice and play important roles not only in innate defense against viral and bacterial infections but also in immune responses during carcinogenesis, autoimmunity, injury, and fibrosis [30]. Unlike T cells, NKT cells respond to lipid-based antigens: they respond to self and foreign glycolipid and phospholipid antigens presented by the MHC-I-like molecule CD1D in antigen-presenting cells (APCs), rapidly secreting the cytokines interferon gamma (IFN- $\gamma$ ) and IL-4 [30].

The Wnt/ $\beta$ -catenin signaling pathway has been implicated also in the generation of NK cells and in directing NKT cell development and functions [31]. Conditional knockout of  $\beta$ -catenin in mice decreases thymic NKT cell numbers, in contrast to increases in NKT cell numbers upon transgenic  $\beta$ -catenin overexpression [32, 33]. Consistent with this, it has been reported that the canonical Wnt inhibitor, Dickkop-1, decreased the number of NK cells in a dose-dependent manner [31].

As mentioned before, TCF/LEF mediates a nuclear response to extrinsic Wnt proteins via their binding to the co-activator  $\beta$ -catenin. The experimental evidence has shown that, similar to T cell maturation, TCF-1 and LEF-1 function redundantly during NK cell development: a role of LEF-1 emerges when TCF-1 levels are reduced as compared with the wild type [34]. In addition, human CD1D gene expression, which is essential for the function of NKT cells in immune regulation and surveillance of tumor cells, is regulated by LEF-1 through distal promoter regulatory elements [35].

## 7. Concluding remarks

Wnt signaling is not only restricted to cancer cells but also dynamically interacts with the microenvironment and the immune system. Dysregulation of the Wnt pathway has been implicated in many tumors, and many tumors express high levels of Wnts.

Here, we have showed that Wnt signaling is a master regulatory pathway that regulates T cell-mediated immune responses, governing the balance between activation/suppression of immune responses. As shown here, accumulating experimental evidence has demonstrated that the Wnt pathway modulates dendritic cells, CD4 T regulatory cells, cytotoxic CD8<sup>+</sup> T cells, and NK cell functions. Thus, the Wnt signaling pathway, both canonical and noncanonical,

plays pivotal roles in mediating tolerance versus immunity. Hence, blocking the Wnt pathway represents an attractive therapeutic target to overcome tumor-mediated immune suppression and to improve immunotherapy.

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## Conflict of interest

Authors declare there are no conflicts of interest.

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