

## Gene Section

### Review

# WNT10B (wingless-type MMTV integration site family)

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## Abstract

WNT10B is a member of the WNT ligand gene family encoding a secreted growth factor that has been reported to have role in a wide range of biological actions. Wnt10b was originally identified from mouse embryos and the virgin mammary gland, the locus was cloned by retroviral insertional activation, similar to the strategy used to identify other mammary oncogenes. During mammary gland development, Wnt10b seems to play a relevant role as it is the earliest expressed Wnt ligand. It has been well established that transgenic expression of Wnt10b in mouse mammary epithelial cells under the control of the MMTV promoter leads to mammary gland hyperplasia, increased proliferation, and branching. Furthermore, WNT10B has epistatic activity on HMGA2, which is necessary and sufficient for proliferation of triple-negative breast cancer. The role of Wnt10b in immune system was first described in helper T cells, and its expression in preB and proB cell lines suggested an involvement in lymphoid development. Furthermore, in CD8 T cells Wnt10b is induced by parathyroid hormone (PTH), suggesting that Wnt10b is playing an important role in T-cell development and function. In a different study increased levels of Wnt10b in the bone marrow were found in a regenerative model, in which both the stromal cells and HSCs had increased Wnt10b expression in response to

injury. Insight into regenerative processes point to WNT10B as a candidate potentially linking tissue regeneration and cancer.

Recently reported evidences support a role of the hematopoietic regeneration-associated WNT10B on AC133+ cells in human Acute Myeloid Leukemia (AML) via a recurrent rearrangement promoted by a mobile human transposable-WNT10B oncogene (ht-WNT10B), as a relevant mechanism for WNT10B involvement in human cancer.

### Keywords

WNT10B, Wnt Signaling Pathway, Leukemia, Breast Cancer

## Identity

**Other names:** SHFM6, STHAg8, WNT12

**HGNC (Hugo):** WNT10B

**Location:** 12q13.2

**Local order:** Minus strand DNA. Start at 48,965,340 and ends at 48,971,858 bp from pter. This gene is clustered with another family member, WNT1, in the chromosome 12q13 region.

## DNA/RNA

### Description

DNA size: 6519 bp, DNA linear. Exon count: 6. This gene has 6 transcripts (splice variants), 56 orthologues, 5 paralogues.

## Transcription

Six transcript variants encoding different isoforms have been found for this gene (font: www.ensembl.org).

WNT10B-001 ENST00000301061.8: mRNA 2274 bp, protein 389 aa).

WNT10B-002 ENST00000203957.5: mRNA 1817 bp, protein 173 aa).

WNT10B-003 ENST00000407467.5: mRNA 1802 bp, protein 191 aa).

WNT10B-004 ENST00000413630.1: mRNA 623 bp, protein 132 aa).

WNT10B-005 ENST00000420388.1: mRNA 559 bp, protein 102 aa).

WNT10B-006 ENST00000475740.1: mRNA 429 bp, no protein encoded.

## Protein

### Description

#### WNT10B

Hardiman et al., in 1997 isolated and characterized for the first time the gene WNT10B that encodes a 389-amino acid protein with 96.6% sequence identity to mouse Wnt10b. They observed the expression pattern of WNT10B in different adult tissues with the highest levels found in heart, skeletal muscle and in several human cancer cell lines with elevated mRNA levels observed in HeLa (cervical cancer) cell (Hardiman et al., 1997).

Dyregulation of WNT10B is implicated in different human pathologies as split hand/foot malformation (SHFM) and obesity (Aziz, 2014; VanCamp 2013).

#### Wnt Signaling

Wnt/ $\beta$ -catenin signaling pathway directs cell proliferation and cell fate during embryonic development and adult homeostasis. Moreover, deregulation of Wnt signaling is tightly linked to human disease, such as multiple forms of cancer and bone malformation (Clevers, 2006; Klaus and Birchmeier, 2008). Dysregulation of WNT signalling has been implicated in different types of cancers, (Lu et al, 2004; Simon et al, 2005; Cadigan and Nusse, 1997; Reya and Clevers, 2005), and the first direct connection between the Wnt pathway and human disease came in the early 1990's. Several studies pointed out the important role of the Wnt signaling in regulating mitotic divisions of hematopoietic stem cells (HSCs) (Reya et al., 2003). Wnt proteins were originally identified in *Drosophila* and mice (Nusslein-Volhard and Wieschaus, 1980; Nusse and Varmus, 1982), which were called Wingless (Wg) and Int1. Cadigan and Nusse identified 19 Wnt proteins that are secreted lipid-modified glycosylated signaling molecules, essential in various developmental processes (Cadigan and Nusse, 1997), acting both on the secreting cell and neighbouring cells and 10 frizzled

receptors that can activate the canonical (Wnt/ $\beta$ -catenin), or non-canonical (Wnt/PCP or Wnt/Ca+) Wnt pathways. In the absence of Wnt ligand or presence of Wnt antagonists, the axin/adrenomatous polyposis coli (APC)/casein kinase 1 (CSNK1A1)/glycogen synthase kinase 3 (GSK3) protein complex binds and phosphorylates  $\beta$ -catenin (CTNNB1) resulting in ubiquitination and proteosomal degradation of  $\beta$ -catenin. The pathway is activated when a Wnt ligand binds to the transmembrane domain receptor of the Frizzled family (FZD) and its co-receptor low-density lipoprotein receptor-related protein 5 or 6 (LRP5/(LRP6)). Wnt proteins are characterized by an N-terminal signal sequence and by palmitoylation on a conserved cysteine residue, by the protein Porcupine (PORCN). Wnt proteins are also characterized by cysteine residues and are glycosylated and lipid modified at two conserved residues, defining the hydrophobic profile of proteins. During the ligand receptor interaction, Wnt ligands bind to the extracellular N-terminal cysteine-rich domain of the Frizzled (FZD) receptor, which is related to the low density lipoprotein receptor-related protein 5 or 6 (LRP5/6). Therefore the cytoplasmic protein Dishevelled (DVL1) is recruited to the receptor complex and then CK1 and GSK3 $\beta$  phosphorylates the cytoplasmic tail of LRP5/6. Then AXIN1, is recruited to the receptor complex and assembly of the destruction complex is disrupted. Active dephosphorylated  $\beta$ -catenin will accumulate in the cytoplasm to translocate into the nucleus, where it initiates transcription by activating T cell factor/lymphoid enhancer factor (TCF/LEF1) transcription factors. When  $\beta$ -catenin is bound to the destruction complex is phosphorylated on Serine (Ser) 45 by CSNK1A1 (CK1 $\alpha$ ) which primes  $\beta$ -catenin for the sequential phosphorylation of Threonine (Thr) 42, Ser 39, and Ser 37 by GSK3 $\beta$ . This phosphorylation of  $\beta$ -catenin promotes the recognition by an E3 ubiquitin ligase, which leads to the ubiquitination and proteasomal degradation of  $\beta$ -catenin. In the absence of  $\beta$ -catenin TCF is linked to a transcriptional repressor complex with Groucho, a protein which is physically displaced by  $\beta$ -catenin (Clevers, 2006; Logan and Nusse, 2004; MacDonald et al., 2009; Mosimann et al., 2009; Staal and Clevers, 2005). Under unstimulated conditions,  $\beta$ -catenins are rapidly turned over by ubiquitination and degradation by the proteasome pathway. This requires phosphorylation of  $\beta$ -catenin by a "degradation complex" consisting of APC, Axin, GSK3, and CK1, followed by binding of BTRC ( $\beta$ -Trop) (Rubinfeld et al., 1996; Munemitsu et al.; Willert and Jones, 2006). Signals induced by Wnt proteins interrupt the formation of the degradation complex, there by preventing the phosphorylation and destruction of  $\beta$ -catenin.

## Expression

In human WNT10B is expressed in different tissues and organs, including bone marrow, whole blood, lymph node, thymus, cerebellum, brain, retina, spinal cord, heart, smooth muscle, skeletal muscle, small intestine, colon, adipocyte, kidney, liver, lung, pancreas, thyroid, salivary gland, adrenal gland, skin, ovary, uterus, placenta, cervix and prostate (<http://www.genecards.org/cgi-bin/carddisp.pl?gene=WNT10B>).

Aprelikova et al., showed that MIR148A is downregulated in 94% of cancer-associated fibroblasts (CAFs) compared with matched normal tissue fibroblasts (NFs) established from patients with endometrial cancer. They revealed that WNT10B is a direct target of MIR148A in CAFs from endometrial cancers and demonstrated that its upregulation in these cells increases tumor cell motility (Aprelikova et al., 2013)

## Localisation

WNT10B is a ligand secreted glycoprotein found mainly in the extracellular compartment. WNT10B proteins bind to the extracellular N-terminal cysteine-rich domain of the Frizzled (FZD) receptors, which is in a complex with the low density lipoprotein receptor-related protein 5 or 6 (LRP5/6). FZD receptors are seven-pass transmembrane receptors which have cyteine-rich domains (CRD) in their N-terminus. Through the CRD, FZD receptor binds Wnt ligands.

## Function

It was demonstrated that Wnt10b is expressed in cardiomyocytes and stored in the intercalated discs both in normal human and mouse hearts. Recently, Palk et al., evidenced that after injury, Wnt10b expression is upregulated in cardiomyocytes during the granulation tissue formation phase of cardiac repair, leading an increased angiogenesis by induction of KDR (vascular endothelial growth factor receptor 2, Vegfr-2) expression, formation of coronary-like vessels surrounded by vascular smooth muscle cells (vSMCs) via induction of ANGPT1 (angiopoietin-1) and cardiomyogenesis within scar tissue. The authors, highlightd the role of Wnt10b in a cardiac repair by arteriole formation reducing the fibrosis and stimulating arteriole formation in NF-KB-dependent manner (Paik et al., 2015).

Davis et al., demonstrated that Wnt/beta-catenin signaling is a major regulator of mesenchymal stem cells fate (Davis et al., 2008). Matsushita et al., reported that Wnt10b/beta-catenin signaling is considered to act as a brake for adipogenic differentiation, suggesting an important role of Wnt10b as an endogenous regulator of adipogenesis. In addition, Matsushita et al., in their study demonstrated that AGTR2 (angiotensin II type 2

receptor) inhibits adipocyte differentiation of murine MSCs with Wnt10b/beta-catenin signaling, suggesting a strong interaction between Wnt10b/beta-catenin signaling and the the renin-angiotensin system (RAS), and providing important insights into the pathophysiology of obesity and obesity-related consequences (Matsushita et al., 2016).

Lei et al., evidenced in 2014 that in response to prolonged ectopic Wnt10b-mediated  $\beta$ -catenin activation, regenerating anagen hair follicles grew larger in size. These results were confirmed by Zhang et al., who provided the evidence that Wnt10b can induce hair follicle regeneration, in a time dependent manner, because a prolonged overexpression of Wnt10b induced an abnormal hair follicle regeneration by epidermal keratinocyte transformation, whereas transient overexpression of Wnt10b induces only hair follicle regeneration. They found that Wnt10b promoted the proliferation of hair follicle stem cells from 24 hours after Adenovirus vector AdWnt10b injection, and after seventy-two hours from AdWnt10b injection, cells outside of bulge area began to proliferate, providing the evidence that the overexpression of WNT10B might activate the hair follicle stem cells (HFSCs) inducing hair follicle regeneration (Lei et al., 2014; Zhang et al., 2016).

The role of Wnt10b in immune cells was first described in helper T cells (Hardiman et al., 1996), Wnt10b mRNA has been found during thymic development at embryonic day 13 (E13), and it is also found in the adult thymus (Balciunaite et al. 2002), suggesting that it should play a critical role, in an intrathymic T-cell development. Furthermore, it was demonstrated that in CD8<sup>+</sup> T cells Wnt10b is induced by parathyroid hormone (PTH) in an osteoporosis model (Terauchi et al. 2009).

Wolf et al, in 2016 examined the interaction between PTH (parathyroid hormone) and WNT10B in periodontal regeneration, evidencing the interplay of T cells and human periodontal ligament (hPDL) cells via the WNT10B pathway as a modulating factor for the anabolic properties of the hormone in periodontal regeneration.

During last years, the research group of Miranda-Carboni showed that Wnt10b has an important role during the mammary gland development, because is expressed at the earliest time during differentiation of the mammary placode (Veltmaat et al. 2004;), suggesting that Wnt10b could be the placode specifier.

Its specific role remains to be investigated. Moreover, Hamamoto et al highlighted that SMYD3upregulates WNT10B as a direct downstream gene and could promote breast carcinogenesis by directly regulating expression of the proto-oncogene WNT10B (Hamamoto et al., 2006).

Recently, Yu et al, in 2016 revealed a heterozygous missense mutation (c.632G>A [p.Arg211Gln]) in WNT10B in all family members affected by oligodontia, a severe form of tooth agenesis, is genetically and phenotypically a heterogeneous condition (Yu et al., 2016).

Finally, Beghini et al, in 2012 examining the role of Wnt signaling in acute myeloid leukemia, provided direct evidence of a ligand-dependent activation of the regeneration-associated Wnt pathway (Congdon et al, 2008), defining the term "regeneration" as the physiological phenomena of reconstitution from injury requiring rapid expansions of HSCs by reactivation of developmental pathways (Angers and Moon, 2009; Bowman, et al., 2012). They revealed that the ligand-dependent Wnt signaling is induced in AML through a diffuse expression and release of WNT10B, a hematopoietic stem cells regenerative-associated molecule (Beghini et al., 2012).

### Homology

The WNT10B gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, zebrafish, fruit fly, mosquito, and frog.

## Implicated in

### Acute Myeloid Leukemia

Recently, Beghini et al., evidenced that the regenerative function of WNT signaling pathway is defined by the up-regulation of WNT10B, WNT10A, WNT2B and WNT6 loci, revealing that the ligand-dependent Wnt signaling is induced in Acute Myeloid Leukemia patients, through a diffuse expression and release of WNT10B, a hematopoietic stem cells regenerative-associated molecule. WNT10B was identified as a major locus associated with the regenerative function and over-expressed in bone marrow sections of all AML patients. The Wnt signaling activation signature represented by accumulation of the active form of dephosphorylated beta-catenin (ABC), is shared by only the subpopulation of AC133<sup>bright</sup> AML cells (8-10 µm diameter of the nuclei), likely induced through an autocrine/paracrine mechanism. Using the mRNA in situ detection, a new molecular tool for the mRNA molecules detection directly in situ, they evidenced the constitutive activation of WNT10B transcription in the Bone Marrow (BM) sections derived from AML patients, suggesting that the regenerative WNT signaling is a stem cell-associated function altered in AML stem cell fraction (Beghini et al., 2012).

By the molecular evaluation of the WNT10B locus, it was identified the presence of a recurrent rearrangement that generate the WNT10B<sup>R</sup> allele, within intron 1 (IVS<sup>1</sup>) and flanked at the 5' by an unknown non-human sequences (Lazzaroni et al., 2016). The expression of the transcript variant

(WNT10B<sup>IVS1</sup>) was restricted in a cohort of patients with intermediate/unfavorable risk AML. It has also been identified at genomic level an intronless WNT10B oncogene short form named ht-WNT10B, and characterized by the 77 IVS1 nucleotides in the 5'-flanking region, the absence of exons 1 and 4, and the presence of a G/A single nucleotide variation at the exon junction 2-3. The ht-WNT10B suggests its involvement in a non-random microhomology-mediated recombination generating the rearranged WNT10B<sup>R</sup> (Lazzaroni et al., 2016).

### Endometrial Cancer

Chen et al., recently demonstrated that the positive expression of WNT10B molecule in cancerous endometrial tissues, was higher than hyperplastic or normal endometrium. They identified that difference in Wnt10b levels was significant among cancer subgroups for histological type, grade of differentiation, and lymphovascular metastasis. During the follow-up, it was demonstrated that WNT10B gene expression was frequently upregulated in Endometrial Cancer (EC) and associated with better prognosis in EC patients, suggesting that WNT10B expression is stage-dependent.

Collectively, the authors suggested that the up-regulation of WNT10B may contribute to Endometrial Cancer with favorable prognosis, characterized by high-grade, advanced-stage and no lymph node metastasis (Chen et al., 2012).

### Prostate Cancer

Recently it was revealed that WNT10B molecule is upregulated in prostate cancer reactive stroma and it is expressed in the prostate stromal cell lines, by decreasing apoptosis in LNCaP cancer cells and increasing angiogenesis. The authors identified an autocrine stimulation of expression of stem cell associated genes as BDNF that enhances VEGFA expression in an autocrine manner. These findings suggested the WNT10B role in regulating expression of genes associated with mesenchymal stem cell biology in prostate stroma as it does in bone and adipose tissue (Dakhova et al., 2014).

### Breast cancer

Bui et al., in 1997 have isolated as the first time, a WNT gene which has not previously been described in human, a human homologue of mouse Wnt10b (Bui et al., 1997). According to their research, the high WNT10B mRNA expression in different breast cell lines, was strictly related to mammary gland development and disease. Following this point of view, Lane et al., provided the evidence that overexpression of WNT10B leads the branching of mammary ducts and the alveolar development. Indeed, Veltmaat et al., in 2004 evidenced that Wnt10b expression is the earliest fundamental ectodermal event (E11.25) defining the mammary

gland ridge and mammary lineage (Veltmaat et al, 2004).

Recently, Wend et al., highlighted that the elevated expression of Wnt10b results in mouse mammary tumorigenesis, and it has been also revealed in human breast carcinoma cell lines (Wend et al, 2011). They have also demonstrated that human triple-negative breast cancers (TNBC) express WNT10B, that activates canonical  $\beta$ -catenin signalling leading to proliferation and up-regulation of HMGA2, the high-mobility group A protein highly expressed in breast cancer (Peluso and Chiappetta, 2010) that is significantly correlated with the capacity to predict metastasis in their TNBC cohort of patients.

By culturing MCF-7 cell line in conditions that form spheres they exhibit more cancer stem cell like features, (e.g. expressing AC133+), it has been detected the WNT10B-FZDs interacting complexes using the in situ Proximity Ligation Assay molecular tool, providing evidences for an autocrine activation primed by the formation of WNT10B-FZD4/5 complexes (Lazzaroni et al., 2016).

### Osteosarcoma

According to Chen et al., Human Osteosarcoma (OS) tumor samples that express WNT10B have reduced likelihood of survival compared to OS that lack WNT10B expression, suggesting that Wnt signaling may play an important role in OS tumorigenesis and metastasis (Kevin Chen BS et al., 2008).

Recently, Modder et al., demonstrated that WNT10B, stimulates the NF $\kappa$ B and Notch pathways in the U2OS osteosarcoma cancer cell model, suggesting that WNT10B can activate the Notch pathway as a mechanism to inhibit differentiation in osteosarcoma, perhaps leading to a more aggressive tumor (Modder et al., 2011).

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