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Gene Section
Mini Review

WNT5A (wingless-type MMTV integration site family, member 5A)

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Identity

Other names: WNT-5A

HGNC (Hugo): WNT5A

Location: 3p14.3

Local order: CACNA2D3 - WNT5A - ERC2.

Note: WNT family ligand. WNT family members with conserved 22 or 24 Cys residues are secreted-type glycoproteins, which are implicated in embryogenesis and carcinogenesis. Nineteen WNT family genes exist within the human genome.

DNA/RNA

Note

WNT5A gene at chromosome 3p14.3 and WNT5B gene at chromosome 12p13.33 are paralogs within the human genome.

Description

WNT5A gene consists of 5 exons. First methionine is located in exon 1, while stop codon in exon 5. dbSNP rs655731, located within exon 5 of the human WNT5A gene, is a synonymous SNP corresponding to codon 263.

Transcription

WNT5A is preferentially upregulated in gastric cancer, and melanoma, but downregulated in breast cancer, colorectal cancer, and acute lymphocytic leukemia. Wnt5a is upregulated by IL6 family cytokines through gp130 in cultured cardiomyocytes, by TGFbeta in mammary epithelial cells, and by TNFalpha in gastric cancer cells. WNT5A upregulation in primary tumor is in part due to stromal expression based on tumor-stromal interaction, while WNT5A downregulation in primary tumor is in part due to epigenetic silencing induced by promoter CpG hypermethylation.

Protein

Description

Mature WNT5A protein with conserved Cys residues is a secreted-type glycoprotein.

Expression

WNT5A mRNA is relatively abundantly expressed in salivary gland, bladder, uterus, placenta, and fetal kidney.

Localisation

Naive WNT5A protein is synthesized in the endoplasmic reticulum. Mature WNT5A protein with lipid modifications and glycosylations enters the trans-Golgi network for secretion from the cell surface.

Schematic representation of WNT5A gene.

Function

WNT5A signals are transduced to the canonical and non-canonical WNT signaling cascades. WNT5A signaling through Frizzled-4 (FZD4) or FZD5 receptor and LRP5 or LRP6 co-receptor leads to the stabilization and nuclear accumulation of beta-catenin for the transcriptional activation of target genes, such as MYC, CCND1, and FGF20. On the other hand, WNT5A signaling through Frizzled family receptor or ROR1 or ROR2 co-receptor leads to the activation of the non-canonical WNT signaling cascades, such as DAG - PKC, IP3 - NFAT, or IP3 - NLK signaling cascades. WNT5A-PKC signaling promotes invasion and metastasis of tumors through SNAI1 (Snail)-mediated epithelial-to-mesenchymal transition (EMT), while WNT5A-NLK signaling suppresses carcinogenesis through inhibition of the canonical WNT signaling cascade. Expression of WNT5A is associated with metastatic or aggressive phenotype in gastric cancer, melanoma, and osteosarcoma, but is associated with non-aggressive or better prognostic phenotype in breast cancer, colorectal cancer, and acute lymphocytic leukemia. Together these facts indicate that WNT5A induces oncogenic as well as tumor suppressive functions in a context-dependent manner.

Homology

Human WNT5A shows 98.7% total amino-acid identity with rodent Wnt5a, indicating that mammalian WNT5A orthologs are highly conserved. Among 19 WNT family members, WNT5A is most homologous to WNT5B.

Mutations

Note

WNT5A gene is located at human chromosome 3p14.3 around the susceptible locus of Zimmermann-Laband Syndrome; however, mutation of WNT5A gene has not been detected.

Germinal

Wnt5a knockout mice show smaller somites and shortened presomitic mesoderm, abnormalities in the lungs with the foreshortened trachea, dysplasia of genitals, and ventricular septal defects.

Implicated in

Melanoma

Prognosis

Poor prognosis.

Gastric cancer

Prognosis

Poor prognosis.

Osteosarcoma

Prognosis

Poor prognosis

Breast cancer

Prognosis

Better prognosis.

Colorectal cancer

Prognosis

Better prognosis.

Acute lymphocytic leukemia

Prognosis

Better prognosis.

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