

## Gene Section

### Review

# NOTCH1 (Notch homolog 1, translocation-associated (Drosophila))

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## Identity

**Hugo:** NOTCH1

**Other names:** TAN1; hN1; notch1; Notch1

**Location:** 9q34.3

## DNA/RNA

**Note:** History and nomenclature: the notch1 gene, previously referred to as TAN1, was first described in 1917 by American giant of genetics and embryology Thomas Hunt Morgan in a strain of the fruit fly *Drosophila melanogaster* with 'notches' apparent in their wings. Molecular study of the notch1 gene product and sequencing was carried out in the 1980s.

The following discussion will refer to the notch1 gene as 'notch1' and the functional gene product (protein) as 'NOTCH1'.

### Description

Notch1 encompasses 51,418 bp of DNA on chromosome 9 (9q34.3) between 138,508,717 and 138,508,135 bp from pter.

### Transcription

The notch1 RNA transcript contains 34 exons and is 9,371 bp in length.

## Protein

### Description

The notch1 gene product NOTCH1 (2,556 amino acids; 272,500 Da) consists of a large extracellular unit which associates in a calcium-dependent, non-covalent interaction with a second unit consisting of the following: a small extracellular region, a single

transmembrane spanning region, and a small intracellular region.

The NOTCH1 extracellular domain is composed primarily of 36 small cysteine knot motifs called EGF-like repeats. Each EGF-like repeat is approximately 40 amino acids, and its structure is defined largely by six conserved cysteine residues that form three conserved disulfide bonds. This feature is critical in ligand binding. The extracellular domain also contains three cysteine-rich Notch/Lin12 (LN) repeats required for the blockage of signaling in the absence of ligand.

The NOTCH1 intracellular domain (NICD) contains a RAM23 domain, six ankyrin/cdc10 repeats involved in protein-protein interactions, two nuclear localization signals (N1 and N2), a transcriptional activation domain (TAD), and a PEST (proline-, glutamic acid-, serine-, and threonine-rich) sequence that negatively regulates protein stability. NOTCH1 undergoes an initial proteolytic cleavage by furin (PACE1) in the Golgi during trafficking to the cell surface.

NOTCH1 is subject to several important post-translational modifications. An O-glucose sugar may be added between the first and second conserved cysteine, and an O-fucose may be added between the second and third conserved cysteine. These sugars are added by an as yet unidentified O-glucosyltransferase, and GDP-fucose protein O-fucosyltransferase 1 (POFUT1) respectively. The addition of O-fucose by POFUT1 is crucial for NOTCH1 function, and without its addition NOTCH1 proteins fail to function properly. As yet, the manner in which the glycosylation of NOTCH1 affects function is not completely understood.

The O-glucose on NOTCH1 can be further elongated to a trisaccharide with the addition of two xylose sugars by xylosyltransferases, and the O-fucose can be elongated to a tetrasaccharide by the ordered addition

of an N-acetylglucosamine (GlcNAc) sugar by an N-Acetylglucosaminyltransferase called Fringe, the addition of a galactose by a galactosyltransferase, and the addition of a sialic acid by a sialyltransferase.

The NOTCH1 ligands are single-pass transmembrane proteins and are members of the DSL (Delta/Serrate/LAG-2) family of proteins. In *Drosophila* there are two involved ligands named Delta and Serrate. In mammals, the corresponding names are Delta-like and Jagged. In mammals there are multiple Delta-like and Jagged ligands, as well as probably a variety of other ligands, such as F3/contactin.

### Localisation

NOTCH1: cell membrane. Single pass type I membrane protein.

NICD: internal surface of cell membrane translocating to the nucleus upon ligand binding.

### Function

The NOTCH1 cell signaling mechanism is conserved in most multicellular organisms including all metazoans (and thus vertebrates). NOTCH1 functions as a receptor for membrane-bound ligands Jagged1, Jagged2, and Delta1 in regulation of cell-fate determination.

Once the NOTCH1 extracellular domain interacts with a ligand, an ADAM-family metalloprotease called TACE (Tumor Necrosis Factor Alpha Converting Enzyme) cleaves the NOTCH1 protein just outside the membrane. Consequently, the extracellular portion of NOTCH1 is released and continues to interact with the ligand. The ligand plus the NOTCH1 extracellular domain is then endocytosed by the ligand-expressing cell. There may be signaling effects in the ligand-expressing cell after endocytosis, however currently these effects are not well understood.

Upon ligand activation and cleavage via gamma secretase, the released notch intracellular domain (NICD) forms a transcriptional activator complex via its RAM23 domain with the transcription factor CSL (CBF1 in humans, RBP-JK in mice, Suppressor of Hairless in *Drosophila*, LAG in *Caenorhabditis elegans*). In the absence of NOTCH1, CSL proteins bind to promoters of target genes and recruit histone deacetylases and corepressors (CoR) that inhibit transcription of these genes. Among known corepressor molecules are SMRT/NcoR and SHARP/MINT/SPEN. The NICD/CSL interaction converts CSL from a transcriptional repressor into a transcriptional activator (CBF1 binding complex in humans) by displacing the corepressor complex and recruiting coactivators such as Mastermind-Like 1 (MAM) and histone acetyltransferase.

Several other proteins are known to affect NOTCH1 signaling, including the RING-domain E3 ubiquitin ligase deltex and the phosphotyrosine binding domain (PTB)-containing proteins numb and numlike, which

act as context-dependent negative or positive Notch1 regulators.

In mammals there are three Fringe N-acetylglucosamine (GlcNAc)-transferase enzymes named Lunatic Fringe, Manic Fringe, and Radical Fringe, which are responsible for something called the 'Fringe Effect' on NOTCH1 signaling. If Fringe adds a GlcNAc to the O-fucose sugar, then addition of a galactose and sialic acid will occur. In the presence of this tetrasaccharide, NOTCH1 signals strongly when it interacts with the Delta ligand, but is inhibited when interacting with the Jagged ligand. The means by which this addition of sugar inhibits signaling through one ligand, and potentiates signaling through another is not clearly understood.

Known target genes of NOTCH1 signaling include: members of the basic helix-loop-helix (bHLH) hairy/enhancer of split (Hes) family, the related HRT/Herp (Hes-related repressor protein) transcription factor family, the cell cycle regulator p21, the Notch pathway element Notch-regulated ankyrin repeat protein (Nrarp), deltex1, and the pre-T cell receptor-alpha gene.

The NOTCH1 signaling pathway is important for cell-cell communication, involving gene regulation mechanisms that control multiple cell differentiation processes during embryonic and adult life. NOTCH1 signaling is known to play a role in the following processes:

Neuronal function and development: via lateral inhibition, NOTCH1 in the embryo generates molecular differences between adjacent cells. In the central nervous system, NOTCH1 activity maintains the neural progenitor state and inhibits differentiation. During gliogenesis, NOTCH1 has an instructive role, directly promoting the differentiation of different glial subtypes. More detailed analyses have also revealed that Notch regulates progenitor pool diversification and neuronal maturation. New data suggests that NOTCH1 activity has a role in neuronal function of the adult brain.

Modulating arterial endothelial fate and angiogenesis: expression of NOTCH1 and its ligand in vascular endothelium and defects in vascular phenotypes of targeted mutants in the NOTCH1 pathway suggest a critical role for NOTCH1 signaling in vasculogenesis and angiogenesis. Vascular endothelial growth factor (VEGF) can induce gene expression of NOTCH1 and its ligand, Delta-like 4 (Dll4), in human arterial endothelial cells. The VEGF-induced specific signaling is mediated through VEGF receptors 1 and 2 (FLT1/VEGFR1 and KDR/VEGFR2) and is transmitted via the phosphatidylinositol 3-kinase/Akt pathway. Constitutive activation of NOTCH1 signaling stabilizes network formation of endothelial cells on Matrigel and enhances formation of vessel-like structures in a three-dimensional angiogenesis model.

Blocking Notch signaling can inhibit network formation.

Regulating cell communication events between endocardium and myocardium during ventricular chamber formation: ventricular chamber morphogenesis is critical for proper cardiac function and embryonic viability and depends on cellular interactions between the endocardium and myocardium. Ventricular Notch1 activity is highest at presumptive trabecular endocardium. RBPJk and Notch1 mutants show impaired trabeculation and marker expression, weakened EphrinB2, NRG1, and BMP10 expression and signaling, and decreased myocardial proliferation. Functional and molecular analyses have shown that Notch1 inhibition prevents EphrinB2 expression, and that EphrinB2 is a direct Notch1 target acting upstream of NRG1 in the ventricles.

Cell lineage specification of both endocrine and exocrine pancreas: multiple cell types of the pancreas appear asynchronously during embryogenesis, which requires that pancreatic progenitor cell potential changes over time. Loss-of-function studies have shown that NOTCH1 signaling modulates the differentiation of these progenitors. It has been demonstrated that misexpression of activated NOTCH1 in Pdx1-expressing progenitor cells prevents differentiation of both exocrine and endocrine lineages. Progenitors remained trapped in an undifferentiated state even if notch1 activation occurred long after the pancreas was specified. Endocrine differentiation is associated with escape from this activity, as Ngn3-expressing endocrine precursors were susceptible to notch1 inhibition, whereas fully differentiated endocrine cells were resistant.

Notch1-dependent bone morphogenic protein (BMP) signaling: NOTCH1 enhances BMP2-induced commitment to the osteoblastic lineage during bone development.

Regulation of cell-fate decision in the mammary gland: it has been suggested that Notch1 signaling plays a critical role in normal human mammary development by acting on both stem cells and progenitor cells, affecting self-renewal and lineage-specific differentiation. Notch signaling can act on mammary stem cells to promote self renewal and on early progenitor cells to promote their proliferation, as demonstrated in one study by a 10-fold increase in secondary mammosphere formation upon addition of a Notch activating DSL peptide. The same study showed that in addition to acting on stem cells, Notch signaling is also able to act on multipotent progenitor cells, facilitating myoepithelial lineage-specific commitment and proliferation. Stimulation of this pathway also promotes branching morphogenesis in three-dimensional Matrigel cultures. Notch1 signaling has no such effect on fully committed, differentiated,

mammary epithelial cells.

Cytoskeletal component formation: it has been suggested that NOTCH1 signaling, via some non-nuclear mechanisms, controls the actin cytoskeleton through the tyrosine kinase Abl.

Normal lymphocyte function: NOTCH1 signaling is involved in the maturation of both CD4+ and CD8+ cells in the thymus. In altered form, NOTCH1 may contribute to transformation or progression in some T-cell neoplasms. NOTCH1 may be important for follicular differentiation and possibly cell fate selection within the follicle.

Regulation of fate choices in the inner ear.

Induction of left-right asymmetry.

Regulation of limb bud development.

Regulation of kidney development.

## Mutations

**Note:** Notch1 mutant mice display defects in somite morphology.

Mutations in the NOTCH1 ligand JAG1 affect the development of many organs, including that of the liver, skeleton, heart and eye.

Mutations in the NOTCH1 ligand DLL3 result in rib fusions and trunk dwarfism.

Notch1 mutations play a dual role in carcinogenesis as either a tumor suppressor or an oncogene. The role of NOTCH1 within and between cells depends on signal strength, timing, cell type, and context.

Notch1 mutant cells infected with a retrovirus transducing the ras oncogene and injected subcutaneously into nude mice form aggressive squamous cell carcinoma (SCC), whereas wild-type cells do not. Loss of notch1 activity may thus cooperate with ras oncogene transformation in keratinocyte tumor development.

In humans, aberrant NOTCH1 expression has been identified as a causative factor in the development of T-cell acute lymphoblastic leukemia and lymphoma (T-ALL). Recurrent t(7;9) translocation that involves the extracellular heterodimerization domain and/or the C-terminal PEST domain of NOTCH1 is associated with T-ALL. The t(7;9) translocation in T-ALL patients is characterized by juxtaposition of the 3' portion of the human notch1 gene with the T cell receptor beta (TCRB) locus. This leads to expression of truncated NOTCH1 transcripts and consequent production of dominant active, ligand-independent forms of the NOTCH1 receptor, causing T-ALL. Less than 1% of human T-ALLs exhibit the t(7;9) translocation, however, activating mutations in notch1 independent of t(7;9) have been identified in more than 50% of human T-ALL.

Cells that are mutant for notch1 form skin and corneal tumors in mice, indicating that Notch1 signaling suppresses tumorigenesis in these instances.

Notch1 mutations cause an early developmental defect in the aortic valve and a later derepression of calcium deposition that causes progressive aortic valve disease. Many other human and murine cancers, including certain neuroblastomas, mammary, skin, cervical and prostate cancers are correlated with alterations in expression of Notch proteins and/or ligands. These cases await better characterization, but these observations suggest broad roles for Notch dysfunction in a wide range of neoplasms.

Based on analysis of neuroendocrine tumors and cell lines, NOTCH1 appears to be absent in this type of cancer. Expression of ectopic NOTCH1 in human medullary thyroid carcinoma and carcinoid tumor cell lines resulted in suppression of cancer cell growth. These data suggest that in neuroendocrine malignancies notch1 may act as a tumor suppressor.

## Implicated in

### **Medullary thyroid cancer (MTC)**

#### **Disease**

A neuroendocrine tumor (NET) derived from parafollicular C cells of the thyroid, MTC is the third most common form of thyroid cancer accounting for 3-5% of all thyroid cancers. Symptoms include airway obstruction and diarrhea. MTC typically secretes the bioactive hormone calcitonin. Currently, surgery is the only curative therapy for these patients, consisting of total thyroidectomy with lymph node dissection. 50% of these patients suffer persistent disease.

#### **Oncogenesis**

20% of patients with MTC have an autosomal dominant inherited form of the disease, which has been shown to be the result of well-characterized point mutations in the RET protooncogene. The results of human MTC tissue sample analysis revealed an absence of active NOTCH1 protein in all tumors tested whereas NET markers such as chromogranin A (CgA) and ASCL1 were highly expressed. Activation of doxycycline-inducible notch1 in MTC cells by varying concentrations of doxycycline led to a dose-dependent increase in NOTCH1 protein and HES-1 protein expression. The level of ASCL1 was reduced with increase in NOTCH1. Further, it was observed that activation of notch1 significantly reduced the growth of MTC cells and the reduction in growth was dependent on the level of active NOTCH1 protein. NOTCH1 also down-regulates aberrant calcitonin secretion in a dose-dependent manner.

### **Gastrointestinal (GI) carcinoid tumors**

#### **Disease**

GI carcinoids are rare tumors that arise from the diffuse neuroendocrine tissue of the gut with a reported incidence of 1-8 per 100,000. They frequently metastasize to the liver and are the second most

common source of isolated liver metastases. GI carcinoids secrete various bioactive hormones such as 5-HT (serotonin) and CgA. Patients with hepatic metastases suffer debilitating symptoms such as abdominal pain, flushing, bronchoconstriction, and diarrhea. Standard palliative treatment for these hormone-induced symptoms includes somatostatin analogs (such as octeotride).

#### **Oncogenesis**

RT-PCR reactions for various Notch receptors and ligands showed the presence of transcripts for notch1, notch2, notch3 and DLL1 in all carcinoid tumors tested. The human pancreatic carcinoid BON cell line also showed detectable amounts all three NOTCH receptors (1-3). An absence of active NOTCH1 intracellular domain (NICD) protein in BON cells was noted, suggesting that the NOTCH1 signaling pathway is inactive in carcinoids. Transient expression of active NOTCH1 via adenoviral vector in BON cells resulted in growth suppression and significant reduction in NET markers such as 5-HT, CgA, synaptophysin, neuron specific enolase (NSE), and ASCL1, confirming the tumor suppressor role of Notch1 signaling in carcinoid tumors. Further, it was shown that the reduction in serotonin is at the level of transcription of tryptophan hydroxylase 1 mRNA suggesting that NOTCH1 signaling regulates tryptophan hydroxylase 1, a rate-limiting enzyme in 5-HT biosynthesis. In addition, stable expression of a NOTCH1 fusion protein in BON cells also resulted in high levels of functional NOTCH1 that led to an increase in the level of HES-1, an immediate downstream NOTCH1 effector. Increases in the level of HES-1 significantly reduced the level of ASCL1 protein. Similar to transient adenoviral NOTCH1 activation, the stable expression of NOTCH1 in BON cells also caused reductions in the levels of serotonin, CgA, NSE, and synaptophysin.

Treatment of human carcinoid cancer cells with histone deacetylase (HDAC) inhibitors resulted in activation of NOTCH1 signaling and inhibition of carcinoid cell growth in vitro and in vivo. These findings suggest that NOTCH1 activation with HDAC inhibitors may be an attractive approach for the treatment of these tumors.

### **Small-cell lung cancer (SCLC)**

#### **Disease**

SCLC tends to present with metastatic and regional spread. SCLC is extremely aggressive and is characterized by rapid growth and early metastases. SCLC arises from major bronchi, and expresses NSE, CgA, and synaptophysin.

#### **Oncogenesis**

Similar to the observations in other neuroendocrine tumors such as carcinoids and MTC, neither the Notch1 nor the raf-1 pathway is active in SCLC cells. In addition, these tumors express high levels of ASCL1. Inhibition of ASCL1 expression by anti sense or RNA

interference has been shown to suppress the growth of SCLC cells and reduce expression of NET markers, furthering the idea that ASCL1 plays a critical role in SCLC development.

RNA interference against ASCL1 significantly inhibited growth both in vitro and in vivo xenograft model. It was also demonstrated that the growth inhibition by suppression of ASCL1 is mediated by cell cycle arrest and apoptotic cell death. It is also known that NOTCH1 is a negative regulator of ASCL1 and it is inactive in various SCLC cell lines tested. Adenoviral mediated expression of active NOTCH1 in these cell lines resulted in both NET marker reduction and growth suppression. Furthermore, the reduction in ASCL1 by Notch1 is achieved both at the level of transcription and post-translational degradation of the ASCL1 protein. These results further confirm that the Notch1 pathway is not active in SCLC at baseline. Activation of NOTCH1 signaling in SCLC led to growth inhibition and NET marker reduction, suggesting a tumor suppressor role for notch1 in SCLC.

### **T cell malignancies.**

#### **Disease**

Human acute T cell acute lymphoblastic leukemia/lymphoma (T-ALL) is the prototypical notch1-associated cancer. The disease constitutes approximately 15 or 20% of ALL in children and adults.

#### **Oncogenesis**

Oncogenesis is attributed to constitutively active notch1 due to t(7;9) (q34;q34.3) activating mutations. This leads to expression of NICD in a T cell receptor-beta-regulated manner. Although the t(7; 9) mutation is rare (less than 1% of T-ALL), the majority of human T-ALL have gain-of-function mutations in notch1, leading to aberrant increases in downstream signaling.

### **B-cell malignancies**

#### **Disease**

Several mature B-cell and therapy-resistant B-cell malignancies have been shown to be susceptible to NOTCH1-mediated growth inhibition/apoptosis including Hodgkin, myeloma, and mixed-lineage leukemia (MLL)-translocated cell lines. These results suggest that therapies capable of activating Notch/Hes1 signaling may have therapeutic potential in a wide range of human B-cell malignancies.

In direct contrast to the previously mentioned studies, several groups have reported NOTCH1-mediated growth proliferation in such B cell malignancies as multiple myeloma and Hodgkin and anaplastic large cell lymphoma.

#### **Oncogenesis**

Several studies support the existence of a dual-role for NOTCH1 signaling as either a tumor suppressor or oncogene in malignant B cells. These studies conflict,

indicating that more definitive research is needed. A reasonably comprehensive study targeted the effect of Notch activation in multiple murine and human B-cell tumors, representing both immature and mature subtypes. They found that expression of constitutively active, truncated forms of several mammalian Notch receptors (including NOTCH1) inhibited growth and induced apoptosis in both murine and human B-cell lines. Similar results were obtained in human precursor B-cell acute lymphoblastic leukemia lines when Notch activation was achieved by coculture with fibroblasts expressing the Notch ligands Jagged1 or Jagged2. Truncated NOTCH1 receptors, as well as the Jagged ligands, induced HES-1 transcription. Retroviral expression of Hairy/Enhancer of Split-1 (HES-1) recapitulated the NOTCH1 effects, suggesting that HES-1 is an important mediator of NOTCH1-induced growth arrest and apoptosis in B cells.

### **Breast cancer**

#### **Disease**

Breast cancer is the most commonly diagnosed malignancy in women after skin cancer, and is a leading cause of cancer death in women from western countries.

#### **Oncogenesis**

NOTCH1 is over-expressed in solid tumors of the breast in the human model. Moreover, NOTCH1 expression is increased in poorly differentiated tumors. A separate study found that elevated coexpression of the NOTCH1 ligand Jagged1 and NOTCH1 is characteristic of a subclass of breast cancer with a very poor outcome. Patients with tumors expressing high levels of JAG1 or NOTCH1 had a significantly poorer overall survival compared with patients expressing low levels of these genes (5-year survival rate of 42% versus 65% and median survival of 50 versus 83 months, respectively, for JAG1 (High vs. Low) ( $P = 0.01$ ); 49% versus 64% and 53 versus 91 months, respectively, for NOTCH1 (High vs. Low) ( $P = 0.02$ )). Moreover, a synergistic effect of high-level JAG1 and high-level NOTCH1 coexpression on overall survival was observed (5-year survival rate of 32% and median survival of 40 months;  $P = 0.003$ ).

### **Skin cancer**

#### **Disease**

In basal cell carcinoma (BCC), the most common non-melanocytic human skin cancer, hyperplastic cell division may lead to invasion of the dermis by epidermal tissues. NOTCH1 signaling has been linked to BCC. NOTCH1 signaling has also been linked to primary melanoma. Melanomas originate from pigment-producing melanocytes. In human skin, melanocytes are positioned at the epidermal-dermal junction and are interspersed every 5 to 10 basal keratinocytes.

### Oncogenesis

Notch1 is implicated differentially as an oncogene in melanocyte-derived carcinoma and as a tumor suppressor gene in keratinocyte-derived carcinoma.

Notch1 may act as a tumor suppressor gene in basal cell carcinoma (BCC). This conclusion was drawn from the observation that when keratinocytes were hyperproliferating, as in BCC, notch1 expression was essentially absent.

A study showed that blocking NOTCH1 signaling suppressed, whereas constitutive activation of the NOTCH1 pathway enhanced, primary melanoma cell growth both in vitro and in vivo yet had little effect on metastatic melanoma cells. Activation of NOTCH1 signaling enabled primary melanoma cells to gain metastatic capability. Furthermore, the oncogenic effect of notch1 on primary melanoma cells was mediated by beta-catenin, which was upregulated following notch1 activation. Inhibiting beta-catenin expression reversed notch1-enhanced tumor growth and metastasis. Another study continued, finding that NOTCH1 signaling drives the vertical growth phase (VGP) of primary melanoma toward a more aggressive phenotype. Constitutive activation of NOTCH1 by ectopic expression of the NICD enables VGP primary melanoma cell lines to proliferate in a serum-independent and growth factor-independent manner in vitro and to grow more aggressively with metastatic activity in vivo. They show that notch1 activation also enhances tumor cell survival when cultured as three-dimensional spheroids. Such effects of NOTCH1 signaling are mediated by activation of the mitogen-activated protein kinase (MAPK) and Akt pathways. Both pathways are activated in melanoma cells following Notch1 pathway activation. Inhibition of either the MAPK or the phosphatidylinositol 3-kinase (PI3K)-Akt pathway reverses the NOTCH1 signaling-induced tumor cell growth.

### Cervical cancer

#### Disease

Cervical carcinomas are a major type of epithelial keratinocyte-derived tumors. Infection with human papillomaviruses (HPVs), more specifically the high-risk HPV16 and HPV18, is associated with most cervical cancer and is thought to have a causal link with the disease.

#### Oncogenesis

NOTCH1 signaling is believed to play an oncogenic role in early disease stages and a tumor suppressive role in late disease stages.

Immunohistochemical data have indicated that notch1 expression is elevated in squamous metaplasia of the columnar epithelium, and in early HPV-induced lesions (CINI-III) and well-differentiated superficial carcinomas of the cervix. A study shows that in invasive cervical cancers, notch1 expression is

substantially reduced. This dual-role pattern of notch1 expression suggests that the protein may play an oncogenic function in the early stages of cervical carcinogenesis, and a tumor suppressive function in the later stages.

### Epithelial-mesenchymal transition (EMT)

#### Disease

EMT occurs during tumor progression when cells from a primary epithelial tumor change phenotype, become mesenchymal, and disseminate as single carcinoma cells, invading other organs as metastases. EMT may also be involved in the dedifferentiation program that leads to malignant carcinoma.

#### Oncogenesis

Jagged1 activation of endogenous Notch receptors in human endothelial cells promotes EMT in endothelial cells. NICD induction in the human adenocarcinoma cell line MCF7 promotes migratory behavior associated with E-CADHERIN loss.

TGFb is another well-known inducer of EMT during embryonic development and the later stages of tumor progression. One possible mechanism of Notch-induced tumor development and progression may involve modulation of the TGFb signaling pathway, as it has been suggested that TGFb may be Notch-dependent.

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