Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

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

Max Cayo, David Yu Greenblatt, Muthusamy Kunnimalaiyaan, Herbert Chen

Endocrine Cancer Disease Group, University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, H4/750 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792, USA

Published in Atlas Database: August 2007

Online updated version: http://AtlasGeneticsOncology.org/Genes/NOTCH1ID30ch9q34.html
DOI: 10.4267/2042/38494

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 numblike, 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 that 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, hyperplasic 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.

References

Morgan TH. The theory of the gene. The American Naturalist 1917;(609):513-544.

Morgan TH. The theory of the gene, revised. Yale University Press 1938;77-81.

Wharton KA, Johansen KM, Xu T, Artavanis-Tsakonas S. Nucleotide sequence from the neurogenic locus notch implies a gene product that shares homology with proteins containing EGF-like repeats. Cell 1985;43(3 Pt 2):567-581.

Kidd S, Kelley MR, Young MW. Sequence of the notch locus of Drosophila melanogaster: relationship of the encoded protein to mammalian clotting and growth factors. Mol Cell Biol 1986;6(9):3094-3108.

Rechsteiner M. Regulation of enzyme levels by proteolysis: the role of pest regions. Adv Enzyme Regul 1988;27:135-151.

Ellisen LW, Bird J, West DC, Soreng AL, Reynolds TC, Smith SD, Sklar J. TAN-1, the human homolog of the Drosophila notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. Cell 1991;66(4):649-661.

Blank V, Kourilsky P, Israël A. NF-kappa B and related proteins: Rel/dorsal homologies meet ankyrin-like repeats. Trends Biochem Sci 1992;17(4):135-140.

Tamura K, Taniguchi Y, Minoguchi S, Sakai T, Tun T, Furukawa T, Honjo T. Physical interaction between a novel domain of the receptor Notch and the transcription factor RBP-J kappa/Su(H). Curr Biol 1995;5(12):1416-1423.

Zagouras P, Stifani S, Blaumueller CM, Carcangiu ML, Artavanis-Tsakonas S. Alterations in Notch signaling in

neoplastic lesions of the human cervix. Proc Natl Acad Sci USA 1995;92(14):6414-6418.

Chen H, Biel MA, Borges MW, Thiagalingam A, Nelkin BD, Baylin SB, Ball DW. Tissue-specific expression of human achaete-scute homolog-1 in neuroendocrine tumors: transcriptional regulation by dual inhibitory regions. Cell Growth Differ 1997;8(6):677-686.

Chen H, Thiagalingam A, Chopra H, Borges MW, Feder JN, Nelkin BD, Baylin SB, Ball DW. Conservation of the Drosophila lateral inhibition pathway in human lung cancer: a hairy-related protein (HES-1) directly represses achaete-scute homolog-1 expression. Proc Natl Acad Sci USA 1997;94(10):5355-5360.

Ball DW, Azzoli CG, Baylin SB, Chi D, Dou S, Donis-Keller H, Cumaraswamy A, Borges M, Nelkin BD. Identification of a human achaete-scute homolog highly expressed in neuroendocrine tumors. Oncol Rep 1997.

Daniel B, Rangarajan A, Mukherjee G, Vallikad E, Krishna S. The link between integration and expression of human papillomavirus type 16 genomes and cellular changes in the evolution of cervical intraepithelial neoplastic lesions. J Gen Virol 1997;78 (Pt 5):1095-1101.

Li L, Krantz ID, Deng Y, Genin A, Banta AB, Collins CC, Qi M, Trask BJ, Kuo WL, Cochran J, Costa T, Pierpont ME, Rand EB, Piccoli DA, Hood L, Spinner NB. Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. Nat Genet 1997;16(3):243-251.

Oda T, Elkahloun AG, Pike BL, Okajima K, Krantz ID, Genin A, Piccoli DA, Meltzer PS, Spinner NB, Collins FS, Chandrasekharappa SC. Mutations in the human Jagged1 gene are responsible for Alagille syndrome. Nat Genet 1997;16(3):235-242.

Giniger E. A role for Abl in Notch signaling. Neuron 1998;20(4):667-681.

Kao HY, Ordentlich P, Koyano-Nakagawa N, Tang Z, Downes M, Kintner CR, Evans RM, Kadesch T. A histone deacetylase corepressor complex regulates the Notch signal transduction pathway. Genes Dev 1998;12(15):2269-2277.

Gray GE, Mann RS, Mitsiadis E, Henrique D, Carcangiu ML, Banks A, Leiman J, Ward D, Ish-Horowitz D, Artavanis-Tsakonas S. Human ligands of the Notch receptor. Am J Pathol 1999;154(3):785-794.

Ma SK, Wan TS, Chan LC. Cytogenetics and molecular genetics of childhood leukemia. Hematol Oncol 1999;17(3):91-105.

Brou C, Logeat F, Gupta N, Bessia C, LeBail O, Doedens JR, Cumano A, Roux P, Black RA, Israël A. A novel proteolytic cleavage involved in Notch signaling: the role of the disintegrin-metalloprotease TACE. Mol Cell 2000;5(2):207-216.

Bulman MP, Kusumi K, Frayling TM, McKeown C, Garrett C, Lander ES, Krumlauf R, Hattersley AT, Ellard S, Turnpenny PD. Mutations in the human delta homologue, DLL3, cause axial skeletal defects in spondylocostal dysostosis. Nat Genet 2000;24(4):438-441.

Kurooka H, Honjo T. Functional interaction between the mouse notch1 intracellular region and histone acetyltransferases PCAF and GCN5. J Biol Chem 2000;275(22):17211-17220.

Morimura T, Goitsuka R, Zhang Y, Saito I, Reth M, Kitamura D. Cell cycle arrest and apoptosis induced by Notch1 in B cells. J Biol Chem 2000;275(47):36523-36531.

Mumm JS, Kopan R. Notch signaling: from the outside in. Dev Biol 2000;228(2):151-165.

Wu L, Aster JC, Blacklow SC, Lake R, Artavanis-Tsakonas S, Griffin JD. MAML1, a human homologue of Drosophila mastermind, is a transcriptional co-activator for NOTCH receptors. Nat Genet 2000;26(4):484-489.

zur Hausen H. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. J Natl Cancer Inst 2000;92(9):690-698.

Krebs LT, Deftos ML, Bevan MJ, Gridley T. The Nrarp gene encodes an ankyrin-repeat protein that is transcriptionally regulated by the notch signaling pathway. Dev Biol 2001;238(1):110-119.

Morel V, Lecourtois M, Massiani O, Maier D, Preiss A, Schweisguth F. Transcriptional repression by suppressor of hairless involves the binding of a hairless-dCtBP complex in Drosophila. Curr Biol 2001;11(10):789-792.

Sriuranpong V, Borges MW, Ravi RK, Arnold DR, Nelkin BD, Baylin SB, Ball DW. Notch signaling induces cell cycle arrest in small cell lung cancer cells. Cancer Res 2001;61(7):3200-3205.

Cayouette M, Raff M. Asymmetric segregation of Numb: a mechanism for neural specification from Drosophila to mammals. Nat Neurosci 2002;5(12):1265-1269.

Fortini ME. Gamma-secretase-mediated proteolysis in cell-surface-receptor signalling. Nat Rev Mol Cell Biol 2002;3(9):673-684.

Jundt F, Anagnostopoulos I, Forster R, Mathas S, Stein H, Dorken B. Activated Notch1 signaling promotes tumor cell proliferation and survival in Hodgkin and anaplastic large cell lymphoma. Blood 2002;99(9):3398-3403.

Kopan R, Goate A. Aph-2/Nicastrin: an essential component of gamma-secretase and regulator of Notch signaling and Presenilin localization. Neuron 2002;33(3):321-324.

Sriuranpong V, Borges MW, Strock CL, Nakakura EK, Watkins DN, Blaumueller CM, Nelkin BD, Ball DW. Notch signaling induces rapid degradation of achaete-scute homolog 1. Mol Cell Biol 2002;22(9):3129-3139.

Talora C, Sgroi DC, Crum CP, Dotto GP. Specific down-modulation of Notch1 signaling in cervical cancer cells is required for sustained HPV-E6/E7 expression and late steps of malignant transformation. Genes Dev 2002;16(17):2252-2263.

Thélu J, Rossio P, Favier B. Notch signalling is linked to epidermal cell differentiation level in basal cell carcinoma, psoriasis and wound healing. BMC Dermatol 2002;2:7.

Thiery JP. Epithelial-mesenchymal transitions in tumour progression. Nat Rev Cancer 2002;2(6):442-454.

Wallberg AE, Pedersen K, Lendahl U, Roeder RG. p300 and PCAF act cooperatively to mediate transcriptional activation from chromatin templates by notch intracellular domains in vitro. Mol Cell Biol 2002;22(22):7812-7819.

Baron M. An overview of the Notch signalling pathway. Semin Cell Dev Biol 2003;14(2):113-119.

Costa RM, Honjo T, Silva AJ. Learning and memory deficits in Notch mutant mice. Curr Biol 2003;13(15):1348-1354.

Iso T, Kedes L, Hamamori Y. HES and HERP families: multiple effectors of the Notch signaling pathway. J Cell Physiol 2003;194(3):237-255.

LaVoie MJ, Selkoe DJ. The Notch ligands, Jagged and Delta, are sequentially processed by alpha-secretase and presenilin/gamma-secretase and release signaling fragments. J Biol Chem 2003;278(36):34427-34437.

Liu ZJ, Shirakawa T, Li Y, Soma A, Oka M, Dotto GP, Fairman RM, Velazquez OC, Herlyn M. Regulation of Notch1 and Dll4 by vascular endothelial growth factor in arterial endothelial cells: implications for modulating arteriogenesis and angiogenesis. Mol Cell Biol 2003;23(1):14-25.

Murtaugh LC, Stanger BZ, Kwan KM, Melton DA. Notch signaling controls multiple steps of pancreatic differentiation. Proc Natl Acad Sci USA 2003;100(25):14920-14925.

Nicolas M, Wolfer A, Raj K, Kummer JA, Mill P, van Noort M, Hui CC, Clevers H, Dotto GP, Radtke F. Notch1 functions as a tumor suppressor in mouse skin. Nat Genet 2003;33(3):416-421.

Romer S, Saunders U, Jäck HM, Jehn BM. Notch1 enhances B-cell receptor-induced apoptosis in mature activated B cells without affecting cell cycle progression and surface IgM expression. Cell Death Differ 2003;10(7):833-844.

Sippel RS, Carpenter JE, Kunnimalaiyaan M, Chen H. The Role of Human Achaete-Scute Homolog-1 in Medullary Thyroid Cancer Cells. Surgery 2003;134(6):866-871; discussion 871-873.

Takeyama K, Aguiar RC, Gu L, He C, Freeman GJ, Kutok JL, Aster JC, Shipp MA. The BAL-binding protein BBAP and related Deltex family members exhibit ubiquitin-protein isopeptide ligase activity. J Biol Chem 2003;278(24):21930-21937.

Dontu G, Jackson KW, McNicholas E, Kawamura MJ, Abdallah WM, Wicha MS. Role of Notch signaling in cell-fate determination of human mammary stem/progenitor cells. Breast Cancer Res 2004;6(6):R605-R615.

Hori K, Fostier M, Ito M, Fuwa TJ, Go MJ, Okano H, Baron M, Matsuno K. Drosophila deltex mediates suppressor of Hairless-independent and late-endosomal activation of Notch signaling. Development 2004;131(22):5527-5537.

Jundt F, Pröbsting KS, Anagnostopoulos I, Muehlinghaus G, Chatterjee M, Mathas S, Bargou RC, Manz R, Stein H, Dörken B. Jagged1-induced Notch signaling drives proliferation of multiple myeloma cells. Blood 2004;103(9):3511-3515.

Lai EC. Notch signaling: control of cell communication and cell fate. Development 2004;131(5):965-973.

Nefedova Y, Cheng P, Alsina M, Dalton WS, Gabrilovich DI. Involvement of Notch-1 signaling in bone marrow stroma-mediated de novo drug resistance of myeloma and other malignant lymphoid cell lines. Blood 2004;103(9):3503-3510.

Noseda M, McLean G, Niessen K, Chang L, Pollet I, Montpetit R, Shahidi R, Dorovini-Zis K, Li L, Beckstead B, Durand RE, Hoodless PA, Karsan A. Notch activation results in phenotypic and functional changes consistent with endothelial-to-mesenchymal transformation. Circ Res 2004;94(7):910-917.

Parr C, Watkins G, Jiang WG. The possible correlation of Notch-1 and Notch-2 with clinical outcome and tumour clinicopathological parameters in human breast cancer. Int J Mol Med 2004;14(5):779-786.

Radtke F, Wilson A, Mancini SJ, MacDonald HR. Notch regulation of lymphocyte development and function. Nat Immunol 2004;5(3):247-253.

Weng AP, Ferrando AA, Lee W, Morris JP 4th, Silverman LB, Sanchez-Irizarry C, Blacklow SC, Look AT, Aster JC. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science 2004;306(5694):269-271.

Balint K, Xiao M, Pinnix CC, Soma A, Veres I, Juhasz I, Brown EJ, Capobianco AJ, Herlyn M, Liu ZJ. Activation of Notch1 signaling is required for beta-catenin-mediated human primary melanoma progression. J Clin Invest 2005;115(11):3166-3176.

Devgan V, Mammucari C, Millar SE, Brisken C, Dotto GP. p21WAF1/Cip1 is a negative transcriptional regulator of Wnt4 expression downstream of Notch1 activation. Genes Dev 2005;19(12):1485-1495.

Kunnimalaiyaan M, Traeger K, Chen H. Conservation of the Notch1 Signaling Pathway in Gastrointestinal Carcinoid Cells. Am J Physiol Gastrointest Liver Physiol 2005;289(4):G636-G642.

Kunnimalaiyaan M, Yan S, Wong F, Zhang YW, Chen H. Hairy Enhancer-of-Split (HES-1), a Notch1 Effector, Inhibits the Growth of Carcinoid Tumor Cells. Surgery 2005;138(6):1137-1142; discussion 1142.

Lee SY, Kumano K, Masuda S, Hangaishi A, Takita J, Nakazaki K, Kurokawa M, Hayashi Y, Ogawa S, Chiba S. Mutations of the Notch1 gene in T-cell acute lymphoblastic leukemia: analysis in adults and children. Leukemia 2005;19(10):1841-1843.

Nakakura EK, Sriuranpong VR, Kunnimalaiyaan M, Hsiao EC, Schuebel KE, Borges MW, Jin N, Collins BJ, Nelkin BD, Chen H, Ball DW. Regulation of neuroendocrine differentiation in gastrointestinal carcinoid tumor cells by notch signaling. J Clin Endocrinol Metab 2005;90(7):4350-4356.

Nobta M, Tsukazaki T, Shibata Y, Xin C, Moriishi T, Sakano S, Shindo H, Yamaguchi A. Critical regulation of bone morphogenetic protein-induced osteoblastic differentiation by Delta1/Jagged1-activated Notch1 signaling. J Biol Chem 2005;280(16):15842-15848.

Osada H, Tatematsu Y, Yatabe Y, Horio Y, Takahashi T. ASH1 gene is a specific therapeutic target for lung cancers with neuroendocrine features. Cancer Res 2005;65(23):10680-10685.

Oswald F, Winkler M, Cao Y, Astrahantseff K, Bourteele S, Knochel W, Borggrefe T. RBP-Jkappa/SHARP recruits CtIP/CtBP corepressors to silence Notch target genes. Mol Cell Biol 2005;25(23):10379-10390.

Reedijk M, Odorcic S, Chang L, Zhang H, Miller N, McCready DR, Lockwood G, Egan SE. High-level coexpression of JAG1 and NOTCH1 is observed in human breast cancer and is associated with poor overall survival. Cancer Res 2005;65(18):8530-8537.

Talora C, Cialfi S, Segatto O, Morrone S, Kim Choi J, Frati L, Paolo Dotto G, Gulino A, Screpanti I. Constitutively active Notch1 induces growth arrest of HPV-positive cervical cancer cells via separate signaling pathways. Exp Cell Res 2005;305(2):343-354.

Zweidler-McKay PA, He Y, Xu L, Rodriguez CG, Karnell FG, Carpenter AC, Aster JC, Allman D, Pear WS. Notch signaling is a potent inducer of growth arrest and apoptosis in a wide range of B-cell malignancies. Blood 2005;106(12):3898-3906.

Bray SJ. Notch signalling: a simple pathway becomes complex. Nat Rev Mol Cell Biol 2006;7(9):678-689.

Kunnimalaiyaan M, Vaccaro AM, Ndiaye MA, Chen H. Overexpression of the NOTCH1 intracellular domain inhibits cell proliferation and alters the neuroendocrine phenotype of medullary thyroid cancer cells. J Biol Chem 2006;281(52):39819-3930.

Liu ZJ, Xiao M, Balint K, Smalley KS, Brafford P, Qiu R, Pinnix CC, Li X, Herlyn M. Notch1 signaling promotes primary melanoma progression by activating mitogen-activated protein kinase/phosphatidylinositol 3-kinase-Akt pathways and up-

regulating N-cadherin expression. Cancer Res 2006;66(8):4182-4190.

Lu L, Stanley P. Roles of O-fucose glycans in notch signaling revealed by mutant mice. Methods Enzymol 2006;417:127-136.

Thiery JP, Sleeman JP. Complex networks orchestrate epithelial-mesenchymal transitions. Nat Rev Mol Cell Biol 2006;7(2):131-142.

Bolós V, Grego-Bessa J, de la Pompa JL. Notch signaling in development and cancer. Endocr Rev 2007;28(3):339-363.

Greenblatt DY, Cayo MA, Ning L, Jaskula-Sztul R, Haymart M, Kunnimalaiyaan M, Chen H. Suberoyl bis hydroxamic acid (SBHA) inhibits cellular proliferation by inducing cell cycle arrest in carcinoid cancer cells. Journal of gastrointestinal surgery 2007;11(11):1515-1520.

Greenblatt DY, Vaccaro A, Jaskula-Sztul R, Ning L, Haymart M, Kunnimalaiyaan M, Chen H. Valproic acid activates Notch1 signaling and regulates the neuroendocrine phenotype in carcinoid cancer cells. Oncologist 2007 Aug;12(8):942-51.

Grego-Bessa J, Luna-Zurita L, del Monte G, Bolós V, Melgar P, Arandilla A, Garratt AN, Zang H, Mukouyama YS, Chen H, Shou W, Ballestar E, Esteller M, Rojas A, Pérez-Pomares JM, de la Pompa JL. Notch signaling is essential for ventricular chamber development. Dev Cell 2007;12(3):415-429.

Kunnimalaiyaan M, Chen H. Tumor suppressor role of Notch-1 signaling in neuroendocrine tumors. Oncologist 2007;12(5):535-542.

Platta CS, Greenblatt DY, Kunnimalaiyaan M, Chen H. The HDAC Inhibitor Trichostatin A Inhibits Growth of Small Cell Lung Cancer Cells. The Journal of surgical research 2007;142(2):219-226.

This article should be referenced as such:

Cayo M, Greenblatt DY, Kunnimalaiyaan M, Chen H. NOTCH1 (Notch homolog 1, translocation-associated (Drosophila)). Atlas Genet Cytogenet Oncol Haematol.2008;12(2):111-119.