Oncogenic and tumor suppressor functions of Notch in cancer: it's NOTCH what you think

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Notch signaling is often considered a model hematopoietic proto-oncogene because of its role as the main trigger of T cell acute lymphoblastic leukemia (T-ALL). Although its role in T-ALL is well characterized and further supported by a high frequency of activating NOTCH1 mutations in T-ALL patients, it still remains an open question whether the effects of Notch signaling are causative in other types of cancer, including solid tumors. Growing evidence supported by recent studies unexpectedly shows that Notch signaling can also have a potent tumor suppressor function in both solid tumors and hematological malignancies. We discuss the intriguing possibility that the pleiotropic functions of Notch can be tumor suppressive or oncogenic depending on the cellular context.

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Notch signaling is a highly evolutionarily conserved pathway implicated in diverse functions during embryogenesis and in self-renewing tissues of the adult organism. These functions include the maintenance of stem cells, cell fate specification, proliferation, and apoptosis (Artavanis-Tsakonas, 1988; Leong and Karsan, 2006). In mammals, there are four Notch receptors (Notch1-4), three Delta-like ligands (Dll1, Dll3, and Dll4), and two ligands of the Jagged family (Jag1 and Jag2). When membrane-bound receptors interact with cognate ligands on an adjacent cell, two consecutive proteolytic cleavages of the receptor are initiated, freeing the intracellular portion of Notch to enter the nucleus and activate the transcription of target genes. The first cleavage (S2) in the heterodimerization domain (HD) by ADAM10 (A disintegrin and metalloprotease 10) generates the substrate for the second cleavage (S3) by the γ-secretase complex. Canonical Notch signaling requires the formation of a complex with a transcription factor of the CSL (CBF-1/Su(H)/Lag-1) family, CBF-1/RBP-Jk/KBF2 in mammals. CBF-1 binds DNA in a sequence-specific manner and acts as a repressor of transcription in the absence of Notch signaling. Displacement of co-repressors bound to CBF-1 by intracellular Notch (ICN) allows the recruitment of co-activators, such as MamL1 (Mastermind Like-1), and histone acetyltransferases, such as p300, to create a short-lived transcriptional activation complex. Recent genome-wide chromatin immunoprecipitation arrays and sequencing have identified a large number of genes that can be regulated directly by Notch (Palomero et al., 2006; Hamidi et al., 2011). Many of these target genes may be cell type specific, but there are a few well characterized transcriptional targets of ICN-CBF1, including the *HES* (*hairy enhancer of split*) family of transcription factors, Notch-related ankryin repeat protein (*NRARP*), *c-MYC*, and *DTX1* (Deltex1; Weng et al., 2006).

Notch as an oncogene

The first evidence for the involvement of Notch signaling in cancer came from T-ALL. T-ALL is a neoplastic disorder accounting for ∼10–20% of all acute lymphoblastic leukemias. In 1991, Ellisen et al. (1991) identified a t(7;9)(q34;q34.4) translocation in T-ALL patients, which resulted in fusion of the 3′ region of *NOTCH1* into the *TCRβ* locus and consequent overexpression of the active form of Notch1 (ICN1). This translocation appeared to be rare, found in <1% of T-ALL cases. However, 13 yr later, Weng et al. (2004) identified activating *NOTCH1* mutations in ∼56% of T-ALL cases examined, introducing *NOTCH1* mutation as the main oncogenic lesion in T-ALL. Two major hotspots of mutations were characterized: mutations in the HD domain that induce ligand-independent activation, and mutations in the PEST (proline-glutamate-serine-threonine-rich) carboxy-terminal domain that increase stability of ICN1 (Thompson et al., 2007). Additionally, inactivating mutations were identified in *FBW7*, an E3 ubiquitin ligase responsible for ICN1 degradation and subsequent termination of Notch signaling (Malyukova et al., 2007; Maser et al., 2007; O'Neil et al., 2007; Thompson et al., 2007). Of note, animal modeling suggested that *NOTCH1* mutations (HD or PEST) are either insufficient to induce disease or are very weak oncogenes in T-ALL, even when they are overexpressed (Chiang et al., 2008). We recently generated knockin mice carrying human *NOTCH1* mutant alleles, and our studies also indicated that none of these mutations are sufficient to induce disease (unpublished data).

After the discovery of its involvement in T-ALL, Notch signaling was also implicated in various solid tumors, including breast cancer, medulloblastoma, colorectal cancer, non–small cell lung carcinoma (NSCLC), and melanoma

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(Ranganathan et al., 2011). The oncogenic potential of Notch activation in solid tumors was first observed in mouse mammary tumor virus (MMTV)–driven breast cancer. The integration of MMTV in specific loci of the host genome resulted in dysregulated expression of adjacent genes and subsequent outgrowth of tumorigenic clones. Characterization of one of these loci revealed expression of a truncated constitutively active form of Notch4 (Gallahan et al., 1987). In mouse models, Notch activation can clearly drive mammary tumors, and in human breast cancer, increased expression of Notch or Jag1 correlates with poor prognosis (Reedijk et al., 2005). However, few activating mutations of the Notch pathway have been found in solid tumor patients, with most being observed in NSCLC (Westhoff et al., 2009).

Two recent studies have identified activating *NOTCH1* mutations in chronic lymphocytic leukemia (CLL), a frequent adult leukemia (Fabbri et al., 2011; Puente et al., 2011). CLL is characterized by variable clinical presentation and progression but can be divided into two major subtypes: one with mutated immunoglobulin genes (*IGV*(*H*)), and another more aggressive form with nonmutated *IGV*(*H*) . Both studies identified *NOTCH1*-activating mutations (mainly a frame shift mutation at codon 2515) predicted to impair Fbw7-induced Notch1 degradation. Although the overall frequency was not dramatic (from 8.3 to 12.2%), these *NOTCH1* mutations were primarily found in patients with the more clinically aggressive nonmutated *IGV*(*H*) subtype of CLL (20.4%) in Richter syndrome (31.0%), and in chemorefractory CLL (20.8%). These results suggest that although *NOTCH1* mutations are not pathognomonic or causative of CLL, they are associated with poor prognosis and could define a distinct clinical subtype for therapeutic intervention.

Notch as a tumor suppressor

Although Notch activation (especially at higher levels as conferred by ICN1 expression) can be oncogenic, there is growing evidence that components of the same pathway may have growth-suppressive functions in other hematopoietic cells, skin, and pancreatic epithelium, as well as in hepatocytes.

In the skin, Notch receptor and ligand expression was found largely in the suprabasal cells, and in vitro data suggested that Notch activation induces differentiation and cell cycle arrest (Lowell et al., 2000; Rangarajan et al., 2001; Nguyen et al., 2006). Conditional deletion of *NOTCH1* in the skin resulted in a significant increase of the basal epidermal layer (Rangarajan et al., 2001). Consistent with a tumor-suppressive function for Notch in the skin, *NOTCH1* loss of function resulted in spontaneous basal cell carcinomas that appeared in older mice and sensitization to chemically induced skin carcinogenesis (Nicolas et al., 2003). This work also suggested that Notch acts as a tumor suppressor in the skin through suppression of the Wnt and Sonic–hedgehog pathways. A subsequent study indicated that the tumorigenic effect of Notch1 deletion is the result of a non–cell autonomous defect in the integrity of the skin barrier (Demehri and Kopan, 2009). Thus, mechanistically, tumor inhibition in the skin may involve feedback with the microenvironment in addition to cross talk between Notch and other signaling pathways.

In this issue of the *Journal of Experimental Medicine*, Viatour et al. (2011) propose a novel tumor suppressor role for Notch signaling in hepatocellular carcinoma (HCC). HCC is one of the most devastating cancers, with >600,000 deaths/yr worldwide, and is strongly associated with prior hepatitis virus B or C infection. To gain further insights into the mechanism driving initiation and progression of HCC, the authors generated a mouse model of the disease by deleting the retinoblastoma protein (RB) and its two related family members p107 and p130 in mouse liver. These triple KO (TKO) mice developed liver cancer with histological and molecular features typical of human HCC. In their model, inactivation of the RB pathway led to the expansion of the stem/progenitor compartment in the liver. The authors propose that these adult progenitor cells are the tumor-initiating cells of HCC after RB inactivation. In corroboration with previous findings showing that hyperactivation of E2F and Myc signals are sufficient to induce HCC, both pathways were up-regulated in the TKO mice.

Using whole transcriptome profiling and gene set enrichment analysis, Viatour et al. (2011) showed that the Notch pathway was also up-regulated in TKO mice, suggesting an oncogenic role for Notch signaling in HCC development. Unexpectedly, inhibition of Notch signaling in TKO mice using DAPT, a potent γ-secretase inhibitor, led to accelerated HCC development. And enforced activation of Notch signaling using ICN1 led to cell cycle arrest and apoptosis in primary HCC cells isolated from TKO mice, as well as in human HCC cell lines. To further address the clinical relevance of these observations, the authors looked at Notch activation status in a cohort of patients. They found that patients with better survival showed significantly higher expression of Notch-related genes, including *HES1*. Taken together, these data strongly support a potential tumor suppressor role for Notch signaling in HCC.

Our laboratory has recently found that conditional *Notch* loss-of-function through the deletion of Nicastrin (*NCSTN*), an essential component of the γ-secretase complex, or compound deletion of *NOTCH1* and *NOTCH2*, resulted in a myeloproliferative syndrome with common features of the human disease chronic myelomonocytic leukemia (CMML; Klinakis et al., 2011). Whole transcriptome analysis revealed that Notch signaling inhibited a monocytic/granulocytic differentiation program in an early multipotential progenitor. This was at least partially mediated by direct repression of the *PU.1* and *C/EBPα* promoters by HES1. Sequencing of Notch pathway genes revealed that ∼12% of CMML patients harbored inactivating mutations in *NCSTN*, *MAML1*), *APH1A*, or *NOTCH2*. These mutations were unique to CMML and were not found in other myeloproliferative disorders such as Polycythemia vera and myelofibrosis. Analogous to

Table I. Dual role of Notch signaling in cancer

Tumor type	Role of Notch signaling	Genes mutated	Putative or observed effect	References
T-ALL	Oncogene	*NOTCH1*	Ligand independent activation	Ellisen et al., 1991
		FBXW7	Stabilization of N1-IC	Weng et al., 2004
				Malyukova et al., 2007
				Maser et al., 2007
				O'Neil et al., 2007
				Thompson et al., 2007
CLL	Oncogene	*NOTCH1*	Stabilization of N1-IC	Fabbri et al., 2011
			Correlated with reduced survival	Puente et al., 2011
NSCLC	Oncogene	*NOTCH1*	Stabilization of N1-IC	Westhoff et al., 2009
			Correlated with reduced survival	
PDAC	Oncogene	none	Loss of NOTCH1 decreased tumor latency	Hanlon et al., 2010
	Tumor suppressor		Loss of NOTCH2 increased tumor latency	Mazur et al., 2010
HCC	Tumor suppressor	none	Endogenous activation of Notch induces growth arrest and apoptosis	Viatour et al., 2011
			Activated Notch pathway correlated with better survival	
CMML	Tumor suppressor	*NCSTN*	Loss of function mutations	Klinakis et al., 2011
		MAML1	Activated Notch signaling inhibits myeloid progenitor differentiation.	
		APH1A		
		NOTCH2		
HNSCC	Tumor suppressor	*NOTCH1*	Truncated or ligand-binding inefficient receptors	Stransky et al., 2011
		NOTCH2	Predicted to impair differentiation	Agrawal et al., 2011
		NOTCH3		
B-ALL	Tumor suppressor	none	Endogenous or exogenous activation of Notch induces growth arrest and apoptosis	Zweidler-McKay et al., 2005

PDAC: pancreatic ductal adenocarcinoma; B-ALL: B cell acute lymphoblastic leukemia.

the tumor-suppressive function of Notch in epithelial cells and HCC, these studies suggested that Notch signaling may also act to prevent uncontrolled proliferation and transformation of myeloid cells during hematopoietic development.

Furthermore, two recent studies of head and neck squamous cell carcinoma (HNSCC), the sixth most common cancer worldwide, identified mutations affecting Notch receptors. Agrawal et al. (2011) identified 28 different *NOTCH1* mutations in 21/120 patients (17.5%). 11 of these mutations were nonsense or insertion/deletions predicted to result in loss of function, supporting a tumor-suppressive function for Notch in HNSCC. The remaining 17 were missense mutations, mostly within the extracellular EGF-like repeats that are required for receptor–ligand interaction. A study by Stransky et al. (2011) identified *NOTCH1* mutations in 11% of patients analyzed and *NOTCH2* or *NOTCH3* mutations in an additional 11% of patients. Mutations identified in this study were nonsense, missense, or insertion/deletions targeting the extracellular domain of the Notch receptors and therefore predicted to be loss-of-function mutations. The significance of these mutations in HNSCC requires further validation; nevertheless, they implicate *NOTCH1* as a tumor suppressor in HNSCC.

Finally, in B cell malignancies, Notch was also reported to suppress growth and induce apoptosis, providing additional evidence that Notch could act as a tumor suppressor in hematopoietic cells (Zweidler-McKay et al., 2005). Another recent study suggested a similar tumor suppressor role for Notch signaling in neuroblastoma (Zage et al., 2011). However these data were mostly generated from in vitro studies using enforced overexpression of ICN1 or stimulation with recombinant Notch ligand and will require further in vivo validation. It will thus be important to test the role of Notch in these disease models using in vivo genetic approaches.

Conclusion/future directions

Given that Notch is involved in an array of fundamental processes both during embryonic development and in adult tissues, it is perhaps not surprising that aberrant Notch signaling can result in a wide range of pathological consequences. The oncogenic function of Notch in lymphocytes and mammary tissue, versus the growth-suppressive role in HCC, CMML, HNSCC, and skin, highlights the intriguing dual role of a single signaling pathway (see Table I for a listing of Notch function in selected cancer types). Indeed, depending on the cellular context, Notch may promote stem cell maintenance or induce terminal differentiation.

The detailed mechanistic explanation of this duality of action remains under investigation. We propose that in both cases (oncogenic and tumor suppressive function), Notch signaling mainly targets programs of stem and progenitor cell differentiation, acting as a cell fate determinant. By affecting normal differentiation, Notch could set the stage for additional mutations and eventual cell transformation. For example, in myeloid leukemia, defective Notch signaling (caused either by mutations or by

gene silencing) commits stem cells and multipotential progenitors to the granulocytic/monocytic progenitor (GMP) fate, expanding the pool of putative leukemia-initiating cells (LICs). Additional oncogenic lesions, such as TET2 mutations (Moran-Crusio et al., 2011), could transform these cells and lead to the initiation of monocytic/granulocytic leukemia. On the flip side, Notch1-activating mutations direct progenitors toward the T cell lineage but are not sufficient for the induction of T-ALL in the absence of additional oncogenic lesions. Another possibility could be that Notch signaling is involved in terminal differentiation of multipotential progenitors, suppressing the accumulation of a potential cancer-initiating population. This latter mechanism could be involved in the induction of HCC, as Notch signaling seems to be activated in committed progenitors, defined by Viatour et al. (2011) as an HCC-initiating population, and not before their commitment.

Further detailed studies are required to integrate such hypotheses, including a detailed analysis of Notch receptor interactions with ligands in specialized tissue microenvironments. Moreover, with growing interest in clinical applications of γ-secretase inhibitors (GSIs) and blocking antibodies to Notch ligands, it is vital to understand all possible systemic consequences of Notch/RBP-J inhibition (Real et al., 2009). Whereas inhibition of Notch may have clinical efficacy where Notch has an oncogenic role, activation of Notch using peptides or antibodies should be evaluated as a therapeutic target in malignancies where NOTCH plays a tumor-suppressive role.

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