Seminars in Cell & Developmental Biology 23 (2012) 458–464

Contents lists available at SciVerse ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

The double-edged sword of Notch signaling in cancer

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ARTICLE INFO

Article history:
Available online 30 January 2012

Keywords:
Notch signaling
Tumor suppressor
Oncogene

ABSTRACT

Recent deep sequencing of cancer genomes has produced an explosion of new data implicating Notch signaling in several human cancers. Unlike most other pathways, these data indicate that Notch signaling can be either oncogenic or tumor suppressive, depending on the cellular context. In some instances, these relationships were predicted from mouse models or presaged by developmental roles for Notch, but in other cases were unanticipated. This review discusses the pathogenic and translational significance of these new findings.

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1. Introduction

Notch receptors control many aspects of development and homeostasis in multicellular animals via a signal transduction pathway that relies on regulated intramembranous proteolysis (for recent review, see [1]). Mammals have four Notch receptors, Notch1–4 (Fig. 1). The extracellular domain of these proteins consists of variable numbers of epidermal growth factor (EGF)-like repeats that participate in ligand-binding, three Lin12/Notch repeats (LNRs), and a juxtamembrane heterodimerization domain. During maturation, Notch receptors are cleaved within the heterodimerization domain by furin-like proteases, producing two subunits that associate non-covalently through contacts in the heterodimerization domain and the LNRs, which together constitute a negative regulatory region (NRR) that is responsible for preventing ligand-independent receptor activation. The intracellular portions of Notch receptors include RAM and ankyrin repeat domains that are involved in protein:protein interactions and a C-terminal PEST degron domain.

Notch signaling is normally initiated by ligands expressed on neighboring cells that belong to the Delta-Serrate-Lag2 (DSL) family, which are also transmembrane proteins (Fig. 1). Ligand binding first triggers cleavage by ADAM-10 or ADAM-17 metalloproteases at a site just external to the transmembrane domain, creating a short-lived membrane-bound intermediate lacking most of the Notch ectodomain that is a substrate for γ-secretase, a multisubunit intramembranous protease. Cleavage by γ-secretase releases the intracellular domain of Notch (ICN), which translocates to the nucleus and forms a short-lived transcription activation

Abbreviations: GSI, γ-secretase inhibitor; NRR, negative regulatory region; EGF, epidermal growth factor; LNR, Lin12/Notch repeat; ADAM, a disintegrin and metalloprotease; DSL, Delta-Serrate-Lag2; ICN, intracellular domain of Notch; MAML, Mastermind-like; RBPJ, recombining signal binding protein for immunoglobulin kappa J region; CLL, chronic lymphocytic leukemia; T-ALL, T-cell acute lymphoblastic leukemia/lymphoma; MCL, mantle cell lymphoma; SCC, squamous cell carcinoma.

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doi:10.1016/j.semcdb.2012.01.017

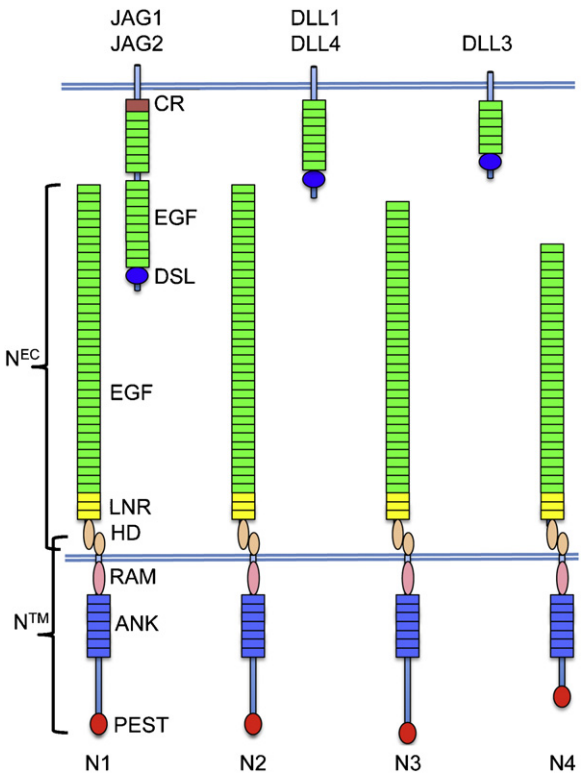

Fig. 1. Structure of mammalian Notch receptors and ligands. Mammals express 5 Notch ligands, four of which activate Notch receptors (JAG1, JAG2, DLL1, and DLL4), and one of which (DLL3) may function as a decoy. Ligands have an N-terminal DSL domain, variable numbers of EGF repeats, and in the case of Serrate-like ligands (JAG1 and JAG2) a juxtamembrane cysteine-rich domain (CR). Mammals have four Notch receptors, Notch1–4, comprised of non-covalently associated extracellular (N^{EC}) and transmembrane (N^{TM}) subunits. N^{EC} is comprised of 29–34 EGF repeats, 3 Lin12/Notch repeats (LNRs), and the N-terminal portion of the juxtamembrane heterodimerization domain (HD), while N^{TM} is comprised of a RAM domain, 7 iterated ankyrin repeats (ANK) repeats, a structurally divergent unfolded region with variable transcriptional activation domain function (greatest in Notch1, least in Notch4), and a C-terminal PEST degron domain.

complex with the DNA-binding factor RBPJ (also known as CSL) and coactivators of the MAML family. Rapid turnover of this complex is normally ensured in part by the C-terminal PEST degron in ICN.

Although some studies point to transcription-independent crosstalk between Notch and other signaling pathways such as Wnt and PI3K/Akt, genetic studies suggest that most Notch effects are mediated through transactivation of target genes by the RBPJ/ICN/MAML transcription complex. The outcome of signaling through this "canonical" pathway is strongly influenced by dose and cellular context; indeed, the lack of enzymatic amplification and putative transcription coupled degradation of ICN means that one activated Notch receptor probably transactivates at most one target gene prior to degradation, allowing for precise regulation of signal strength and duration.

Depending on the cellular context, Notch signaling can be an arbiter of survival versus death; proliferation versus growth arrest; or differentiation versus "stemness". Given these varied effects, it is not surprising that widely divergent context-dependent roles for Notch have emerged in cancer. It is well established that Notch1 acts as an oncoprotein in T-cell acute lymphoblastic leukemia/lymphoma (T-ALL), an aggressive tumor that occurs mainly in children and adolescents. Recent application of deep sequencing approaches to hundreds of human cancer genomes and transcriptomes has detected somatic mutations in Notch receptor genes in an increasingly wide spectrum of tumors, expanding the breadth of Notch's roles in cancer. Mouse modeling foretold some of these discoveries, but others were unexpected. This review mainly focuses on these new findings, which clearly document Notch's ability to function as either an oncoprotein or a tumor suppressor depending on cellular context.

2. Notch as an oncoprotein: Notch1 in T-ALL as a paradigm

Before delving into recent discoveries (summarized in Tables 1 and 2), brief review of oncogenic Notch mutations in T-ALL is in order as a point of reference (for detailed review, see [2]). To date somatic gain-of-function mutations in human T-ALL are confined to *NOTCH1* and fall into two general classes. The most common class consists of point substitutions or small in-frame deletions, insertions or duplications involving the Notch1 NRR or transmembrane domain that allow ligand-independent proteolysis and activation. The second class consists of nonsense or frameshift mutations that result in the deletion of the C-terminal PEST degron domain. Some T-ALLs possess mutations of both classes in *cis*, an alignment that produces synergistic increases in signaling. Rarely in human T-ALL the *NOTCH1* locus is broken by (7;9) translocations that fuse the 3′ end of *NOTCH1* to *TCRB* promoter/enhancer elements. These rearranged *NOTCH1* alleles express truncated transcripts encoding polypeptides that lack the NRR entirely. Similarly, in murine T-ALLs *notch1* is commonly disrupted by RAG-mediated deletions that remove the 5′ end of the gene and activate a cryptic internal promoter that drives the expression of mRNAs encoding truncated polypeptides lacking the NRR. Thus, in T-ALL there is strong selection for somatic mutations that disrupt the Notch1 NRR and permit ligand-independent receptor activation. In the case of T-ALL, ligand-independent signaling may promote the spread of the tumor beyond the confines of the ligand-rich thymic microenvironment.

Another theme emerging from T-ALL is that the oncogenic role of Notch1 appears to be an exaggeration of its normal functions.

Table 1
Activating Notch mutations in human cancers.

	NOTCH1	Other Notch genes	Somatic aberration	Comments
T-ALL	~60% in human T-ALL	?NOTCH3 (rare)	In-frame NRR mutations and C-terminal PEST degron deletions	Mutations cause ligand-independent activation (NRR) or enhance protein half-life (PEST)
CLL	5–12%	Unknown	PEST degron deletions (>90% codon 2514(del(CT)))	Associated with transformed and refractory CLL, absence of somatic hypermutation, trisomy 12
MCL	~10%	Confined to *NOTCH1*	PEST degron deletions (>50% codon 2514(del(CT)))	*NOTCH1* locus also hypomethylated in MCL
Breast adenocarcinoma	<5%	*NOTCH2* fusion genes also detected	Activating gene fusions	All rearrangements in ER-cancers, functionally validated