

Notch signaling: a hero or villain in the war against cancer?

Shireen Chikara, Katie M. Reindl

Department of Biological Sciences, North Dakota State University, Fargo, ND, 58108-6050, USA

Corresponding to: Katie M. Reindl, North Dakota State University, Department of Biological Sciences #2715, Stevens Hall 218, PO Box 6050, Fargo, ND 58108-6050, USA. Email: katie.reindl@ndsu.edu.

Abstract: The Notch signal transduction pathway regulates cell fate decisions throughout embryonic development. The mechanisms through which Notch signaling maintains cellular integrity are well understood. However, Notch signaling is more complex than previously thought as Notch is also involved in cancer where it functions as both an oncogene and tumor suppressor depending on the cellular context. Aberrant activation of oncogenic Notch is found in various cancers prompting the search for therapeutic agents to attenuate constitutively active Notch. However, there is also substantial evidence that Notch signaling suppresses tumor growth and progression, suggesting that Notch activators might be of therapeutic benefit in other cancers. This editorial describes the dual role of Notch signaling observed within and across multiple cancers. We highlight a study in non-small cell lung cancer cells (NSCLC) revealing a tumor suppressive role for endothelial cell Dll4-activated Notch1 and the underlying molecular mechanism involving suppression of PI3K signaling.

Keywords: Notch; Dll4; lung cancer; PI3K



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The Notch pathway is a conserved ligand-receptor mediated signaling mechanism that plays an important role in deciding the fate of a living cell from womb to tomb; including a cell's embryonic development, proliferation, survival, and death (1). The unique ability of the Notch pathway to generate divergent outcomes is dependent upon the interaction between the Notch receptors and ligands and the subsequent signaling events. There are four mammalian Notch receptors (Notch1-4), which interact with their cognate ligands belonging to two subclasses, the delta and the serrate families, designated Delta-like ligand (Dll1, Dll3, and Dll4) or serrate-like ligands (Jagged 1 and Jagged 2). Both the Notch receptors and ligands are transmembrane proteins expressed on various cell types. The interaction between the ligand on one cell can activate the Notch receptor on an adjacent cell.

Notch receptors usually reside in a dormant state but are activated in response to ligand binding which initiates a series of successive proteolytic cleavages. The final intracellular cleavage leads to the release of Notch Intra-Cellular Domain (NICD) which translocates to the nucleus

and binds to the transcription factor CBF1 to regulate the transcription of Notch-regulated genes (2). Notch signaling differs from other signaling pathways in two ways: first, the proteolytic cleavage process is irreversible and, therefore, the intensity and duration of the signal cannot be regulated by removing the activated receptor from the plasma membrane. Second, the signal is direct and does not use a secondary messenger; hence, signal amplification is limited (3).

Given the importance of Notch signaling in development and maintenance of normal tissues, it is not surprising that dysregulated Notch signaling contributes to tumorigenesis. The tumor-promoting effects of oncogenic Notch signaling are associated with (I) aberrant expression of the Notch ligands and receptors and (II) cross-talk of Notch signaling with other oncogenic signaling pathways. Several studies have shown that constitutive Notch signaling promotes tumor growth in a variety of cancer types (4). For example, enhanced expression of Notch ligands and receptors has been reported in brain, breast, prostate, and pancreatic cancers where they enhance cellular proliferation and inhibit apoptosis (5-9). Further, cross-talk between Notch

signaling with other tumor-promoting pathways such as EGFR and NF- κ B has been noted in breast and pancreatic cancer, respectively (10,11).

Conversely, evidence suggests that Notch signaling may also inhibit proliferation and/or induce apoptosis in cancer cells. For example, high expression levels of Notch 2 in well-differentiated breast tumors were associated with increased patient survival and a tumor-suppressive effect (12). Further, activation of Notch signaling suppressed the growth of human hepatocarcinoma cells through induction of cell cycle arrest and apoptosis (13). Together, the literature suggests that the numerous cellular responses directed by Notch signaling depend upon the cell-specific expression patterns of its ligands and receptors and the potential cross-talk between Notch and alternative signaling pathways.

A recent study by Ding *et al.* (14) demonstrated the tumor-suppressive potential of Notch signaling in non-small cell lung cancer cells (NSCLC). The authors investigated the underlying mechanisms regulating the suppressive nature of endothelial cell Delta like-ligand 4 (EC-DII4), a vascular-specific ligand of Notch, in the proliferation of NSCLC lung cancer cells. The highlight of this study is the articulate cross-talk between DII4 on endothelial cells and Notch receptors on lung cancer cells. The DII4 ligand positively regulated Notch1, but not Notch2 and Notch3, signaling in NSCLC cell lines A549 and H460, and also in xenografts induced using a mixture of NSCLC cells and EC-DII4 cells. Increased Notch signaling was accompanied by increased expression of downstream transcriptional targets such as HES1 and HEY1. The authors concluded that increased activation of Notch signaling via EC-DII4 negatively regulates the proliferation of NSCLC cells.

DII4 is the vascular-specific ligand of Notch, uniquely expressed in endothelial cells. DII4 expression is associated with enhanced tumor vasculature. However, the observed increase in blood vessels density may actually hinder the growth of tumors due to formation of nonfunctional vessels that are unable to efficiently deliver blood to the tumor (15,16). While many studies have focused on the effect of DII4 on Notch signaling in autonomous endothelial cells, the study by Ding *et al.* is one that focused on the effect of endothelial cell DII4 on Notch signaling in tumor epithelial cells (14).

The diverse outcomes of Notch signaling in various cells likely result from its interaction with other intracellular signaling pathways. Activation of Notch signaling is known to up-regulate phosphatidylinositol 3-kinase (PI3K/AKT), c-Myc, EGFR, and NF- κ B signaling in various cancers

(11,17); and activation of these pathways contributes towards uncontrolled cell growth, tumor cell survival, as well as resistance to cytotoxic agents. In contrast, the study by Ding *et al.* (14) highlighted a growth-suppressive effect of Notch on PI3K that resulted in reduced proliferation of NSCLC cells. DII4 on the surface of endothelial cells activated Notch1 signaling in lung cancer cells which led to enhanced expression of phosphatase and tensin homolog (PTEN). PTEN negatively regulated the PI3K pathway and resulted in reduced lung tumor cell growth. The work by Ding *et al.* highlights the importance of studying Notch signaling in the context of the tumor microenvironment where Notch ligand-receptor interactions on non-equivalent cells can activate alternative signaling pathways.

Conclusions

Notch signaling plays a critical role in normal tissue development, including the lung (18). Additionally, alterations in the expression and activity of the Notch pathway proteins are frequently observed in cancers where Notch plays either an oncogenic or tumor suppressive role. The duplicitous nature of Notch signaling, which is activated in response to ligand-receptor interactions, largely depends upon the location of the expressed ligand and its corresponding receptor. Different interactions between Notch ligands and receptors on various cell types activate additional signal transduction pathways resulting in divergent cellular responses. Therefore, Notch signaling is highly context-dependent and a more thorough understanding of cell type-specific interactions is needed in order to understand the potential for therapeutic targeting of the Notch pathway in cancer treatment.

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