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The dual nature of Notch in tissue homeostasis and carcinogenesis

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The Notch pathway is an evolutionarily conserved signaling system that plays a critical pleiotropic role in regulating stem cell self-renewal and differentiation. The functional outcome of Notch signaling is highly dependent on cellular context and signal dosage. For example, distinct levels of Notch activity can either promote or suppress proliferation of mammary gland epithelial cells. In addition, Notch activation increases the self-renewal capacity of hematopoietic, neural and muscle stem cells but induces differentiation of stem cells in skin, breast, lung and thymic epithelia. Our recent study showed that Notch activation in different cell lineages within the same tissue system can result in completely opposite biological consequences.[1] In prostate basal cells, Notch activation suppresses proliferation and induces differentiation, while in prostate luminal cells, the same signaling instead enhances proliferation.

The mechanisms through which Notch directs distinct biological outcomes have not been definitively determined. One prevailing hypothesis is that crosstalk between Notch and other signaling transduction pathways affects where Notch binds, hence influencing transcriptional output. A plethora of studies have shown that transcription factors such as β-catenin, Smad3 and NFκB can directly interact with Notch intracellular domain (NICD) to modulate its transcriptional activity.[2] In addition, an interesting observation is that Notch usually suppresses the proliferation of epithelial stem cells that express P63, a transcription factor belonging to the P53 superfamily. Crosstalk between P63 and Notch at various regulatory levels may also influence the functional outcome of Notch signaling.[3] Genome-wide chromosomal immunoprecipitations of either NICD or RBP-J have been performed in conjunction with tiling arrays or deep sequencing techniques to globally identify direct Notch targets. Recent studies have demonstrated that binding sites for certain transcription factors are in proximity with those of Notch so that they bind DNA concomitantly or competitively and influence Notch signaling.[4] This provides a sound mechanism underpinning differential gene regulation by Notch in different cellular contexts. Of course, it is possible that the dual role of Notch in tissue homeostasis can be mediated by common Notch downstream targets such as Hes1.

Not surprisingly, the roles of Notch in carcinogenesis also vary depending on the tissue and cellular context.[5] Despite the consensus that Notch signaling is deregulated in a wide spectrum of malignancies, whether Notch serves as an oncogene or tumor suppressor still remains inconclusive in many tumor models, including prostate cancer. While Notch serves as an oncogene in T-cell acute lymphoblastic leukemia and breast cancer, it acts as a tumor suppressor in skin and liver cancer. It has been previously shown that Notch can play both tumor-promoting and -suppressive roles in the hematopoietic system, which is analogous to our finding that Notch mediates distinct biologies in different cell lineages within the prostate.[6] The dual role of Notch may be due to its synergy with or antagonism of other oncogenic signals, given that Notch may regulate different sets of genes in distinct cell contexts. However, an alternate mechanism is that Notch affects cell differentiation and alters the availability of certain cellular populations that are susceptible to oncogenic transformation, hence affecting disease progression.[7] Finally, Notch can affect disease progression in a cell non-autonomous manner, which serves as another explanation for its multifaceted roles.[8]

The γ-secretase inhibitors that block Notch receptor activation are the major agents that target Notch signaling in the clinic. However, due to widely distributed Notch signaling in various organs, systemic and long-term Notch inhibition causes adverse side effects such as dose-limiting intestinal toxicity and vascular neoplasms. Therefore, dissecting the molecular mechanisms underlying the tissue/lineage-specific responses to Notch activation will inspire novel therapeutic avenues to target Notch with less systemic toxicity.

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