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Review Article

Mini-review: Does Notch promote or suppress cancer? New findings and old controversies

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Abstract: Notch signaling in tumorigenesis and cancer progression presents a certain enigma. Numerous experimental studies reported significant effects in cancer, yet of varying magnitude and opposite sign. This mini review is aimed to streamline our understanding of the Notch role in tumor progression, and outline future experiments to clarify the modality of Notch function and perspectives of the Notch-based anticancer treatments.

Keywords: Notch, cancer, PTEN, Wnt

Notch cell fate choice mechanism is the key factor in regulating the balance between the pool of stem and progenitor cells, and differentiating cell lineages in organ development [1]. In vertebrates, Notch signaling is activated by binding of the Notch receptor (Notch1-4) to the extracellular domain of the Notch ligand, represented by Delta-like 1-4 and Jagged 1-2 [2]. Ligand binding initiates the three-step cleavage of the Notch receptor, thereby releasing the Notch Intracellular Domain (NIC) that translocates to the nucleus by a yet unknown transport mechanism, where it interacts with its DNA-binding cofactor RBP-J/CBF1/CSL. In the absence of Notch signaling, RBP-J can still bind to its DNA consensus sequence C/TGTGGGAA, and function as a transcriptional repressor, preventing opportunistic expression of Notch targets [3, 4]. RBP-J/N1IC transcriptional complex activates a set of basic helix-loop-helix transcriptional repressors in a tissue-specific manner: Mash1, Math1, Neurogenin, and other tissue-specific targets. At the early stages of tissue development, these helix-loop-helix factors repress differentiation in cells, positive for Notch signaling (NIC+) [5, 6]. In contrast, neighboring cells, often express high levels of Delta-like 1 (Dll1) or Jagged (Jag) ligands, and are negative for Notch signaling. These cells have de facto escaped maintenance as Notch-dependent progenitors and can choose a differentiation path. At the later stages of tissue maturity, levels and timing of Notch signaling can also regulate selection between terminally differentiated lineages [7-9].

Considering the universality of the Notch mechanism in the maintenance of tissue-specific progenitor cells, investigations of the Notch rolein the incidence and progression of various tumors were pursued from the start of Notch studies. These investigations uncovered many exciting findings. In particular, experiments, using mouse models of human disease, showed that inhibition of Notch receptor can not only slow, but completely reverseprogression of various tumors.For example, pharmacological inhibition of Notch pathway inintestinal adenocarcinomas lead to normal differentiation of goblet cells [10]. This finding was recently extended to include a clinical application for treatment of Barrett's esophagus, a potential predecessor to carcinoma, by inducingnormal intestinal cell differentiation with a site-specificpharmacological inhibition of Notch signaling [11].

On the other hand, multiple studies have consistently showed that cooperative interaction between Notch and Wnt pathways increases the likelihood of cancerous transformation [12,

13]. This effect has been well described for solid tumors [12] as well for cancerous transformation of lymphocytes leading to acute myeloid leukemia [13].

Interestingly, a number of studies reported that at the onset of tumorigenesis, Notch signaling can be adverse to cancer progression. For instance, in adult prostate, Notch signaling activates the helix-loop-helix repressor, Hey1, a co-factor of androgen receptor (AR), which can inhibit AR-dependent targets, including those involved in prostate cancer [14]. In addition, in various organs, including prostate [6, 15] and lymph [16], Notch signaling can play a role of a tumor suppressor by directly regulating transcription of *PTEN* protein phosphatase, a classic negative regulator of the PI3K/PTEN/AKT cell survival and proliferation pathway. Another aspect of Notch/PTEN regulation of tumor microenvironment may be associated with PTEN function in preventing senescence of tumor cells, which can escape immune surveillance and resist hemotherapies [31].

The apparent contradiction in the signof Notch effects in cancer progression may be explained by the importantcaveat thatimpacts of Notch signals are intrinsically linked to the internal clock of tissue differentiation, whether during normal development or in cancer. For instance, we [5, 6] and Wang et al. [17, 18] reported that Notch/RBP-J activity is essential for cell fate specification in the prostate epithelium as well as inthe stromal compartment. Inactivation of *Notch1* or *RBP-J* genes during prostate development results in a confusion in cell fate specification in between basal and luminal epithelium [6, 18], and in degeneration of smooth muscle [6]. In turn, Notch hyperactivation causes overproliferation of prostate epithelium and muscle [6].

In relation to prostate cancer (PCa), interactions between Notch and Wnt pathways is likely to play a pivotal rolein disease progression. Wnt/beta-catenin signaling is a notorious pro-cancer agent in PCa [19, 20], where it leads tooverexpression of genes with proliferative and cell transforming properties, such as cyclins D1/3 and c-myc. Mounting evidence points that Notch signaling is also hyper-activated in advanced and metastatic PCa, where it cooperates with Wnt [21-23]. Few studies to date systematically examined Notch effects at key disease progression steps such as microinvasion of stroma by epithelial cancers, population of blood stream and lymph, and formation of secondary tumors. These reports indicate that in the context of metastatic processes, Notch signals promote disease progression by collaborating with ERK kinases [23] and by inhibiting expression of the tumor suppressor, *PTEN* [16].

Various facets of interaction between Notch and Wnt pathways point to mutual regulation, and reveal organ and cancer-specific features. Intestinal adenomas clearly show simultaneous activation of both pathways [10]. In endothelium, Notch4 activates a negative feedback target, *Nrarp*, which limits forward Notch signaling, but promotes Wnt/beta-catenin action by stabilizing Lef1 protein [24, 25]. During retinal development, Notch and Wnt cooperate in modulating cell fate of retinal stem cells, and this interaction is also exercised through Notch regulation of *Lef1*, and a Frizzled antagonist, *sFRP2* [26]. Wnt regulation of Notch has also been reportedin mouse and human cell line models [27]. In particular, Lef1 can modulate Notch signaling by inducing expression of *Dll1* [28].

Given the individual significance of Notch and Wnt pathways in PCa progression, and mounting evidence of Notch/Wnt interactions [29, 30], further studies should specifically address the effects of Notch/Wnt module in induction and maintenance of cancer cell fate at various stages of tissue, organism and cancer maturity, using genetic mouse model systems to conditionally modulate Notch and Wnt pathways in specific organs in a background of increased cancer risk and progressive disease.

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