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Review

Regulation of angiogenesis via Notch signaling in breast cancer and cancer stem cells

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ABSTRACT

Breast cancer angiogenesis is elicited and regulated by a number of factors including the Notch signaling. Notch receptors and ligands are expressed in breast cancer cells as well as in the stromal compartment and have been implicated in carcinogenesis. Signals exchanged between neighboring cells through the Notch pathway can amplify and consolidate molecular differences, which eventually dictate cell fates. Notch signaling and its crosstalk with many signaling pathways play an important role in breast cancer cell growth, migration, invasion, metastasis and angiogenesis, as well as cancer stem cell (CSC) self-renewal. Therefore, significant attention has been paid in recent years toward the development of clinically useful antagonists of Notch signaling. Better understanding of the structure, function and regulation of Notch intracellular signaling pathways, as well as its complex crosstalk with other oncogenic signals in breast cancer cells will be essential to ensure rational design and application of new combinatory therapeutic strategies. Novel opportunities have emerged from the discovery of Notch crosstalk with inflammatory and angiogenic cytokines and their links to CSCs. Combinatory treatments with drugs designed to prevent Notch oncogenic signal crosstalk may be advantageous over λ secretase inhibitors (GSIs) alone. In this review, we focus on the more recent advancements in our knowledge of aberrant Notch signaling contributing to breast cancer angiogenesis, as well as its crosstalk with other factors contributing to angiogenesis and CSCs.

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1. Introduction

The formation of new blood vessels from existing ones (angiogenesis) is a crucial requirement for the growth, progression and metastatic spread of a tumor [1]. Low oxygen microenvironment triggers angiogenesis in normal and pathological conditions, i.e., tumor growth [2]. The malignant cells undergo an angiogenic switch leading to secretion of angiogenic factors and proteolytic enzymes in response to hypoxia culminating in the activation of endothelial cell (EC) proliferation, migration and establishment of a robust capillary network. This irregular and ill-organized network is capable of providing the growing tumor mass with all the required metabolites. In addition, the tumor angiogenesis network also provides tumor cells with the opportunity to enter the circulation and the opportunity to form distant metastases [3]. Tumor angiogenesis is elicited and regulated by several factors. Among these factors, Notch signaling plays an important role. Notch is essential for a variety of cell fate decisions and can regulate diverse cellular biological processes especially during embryogenesis. To signal, membrane-bound Notch receptors and ligands need to be co-expressed in adjacent cells. Notch receptors and ligands are expressed in tumor cells as well as in the stromal compartment and have been implicated in tumorigenesis [4,5]. Notch genes encode transmembrane receptors that are highly conserved from invertebrates to mammals. Notch-mediated signals regulate cell-fate decisions in a large number of developmental systems [6,7]. Such signals are mainly transmitted through direct contact between adjacent cells expressing Notch receptors and their ligands. Notch receptors activated in response to ligand expressed by adjacent cells have the potential to regulate cell fate specification, differentiation, proliferation, or survival [8]. Notch signaling pathway is frequently dysregulated in several human malignancies. Over expression of Notch receptors and their ligands has been found in cervical, colon, head and neck, lung, renal carcinoma, pancreatic cancer, acute myeloid, Hodgkin, Large-cell lymphomas, as well as breast cancer [9–11]. Overall, it is well-established that Notch signaling plays an important role in tumor progression [5,12]. Signals exchanged between neighboring cells through the Notch pathway can amplify and consolidate molecular differences, and influence how cells respond to intrinsic or extrinsic developmental cues that are necessary to unfold specific developmental programs [13]. Because the same signaling pathways within different contexts can trigger a variety of cellular activities, cancer progression activities induced by Notch and its crosstalk with other signaling pathways are also context dependent. In light of several valuable reviews published on the role of Notch signaling in several types of cancer [14–17], we wish to focus this review on the more recent advancements in understanding how aberrant Notch signaling and its crosstalk with other factors contribute to breast cancer angiogenesis and CSC.

2. Structure, activation and function of Notch receptors and ligands

The Notch system in vertebrates comprises four receptors (Notch1–Notch4) and at least five ligands from the families Delta and JAG/Serrate (DSL): JAG1, JAG2, Delta-like (Dll)-1, Dll-3, and Dll-4 [10,11,13]. Ligands of Notch receptors can be divided into several groups based on their domain composition. Canonical DSL ligands (JAG1, JAG2 and Dll-1) are type I cell surface proteins, consisting of the Delta/Serrate/LAG-2 (DSL), Delta and OSM-11-like proteins [DOS, which is specialized tandem EGF repeats] and EGF motifs. The other subtypes of DSL canonical ligands include Dll-3 and Dll-4 that lack the DOS motif [18–20]. Both the DSL and DOS domains are crucial for physical binding with Notch receptor [9]. However some membrane-tethered and secreted noncanonical ligands lacking DSL and DOS domains have also been documented to activate Notch signaling both in vitro and in vivo [19,21–26], which may explain the diverse and frequent effects of Notch signaling with the small number of canonical DSL ligands and receptors in vertebrate genomes [19].

Notch receptors belong to a large single-pass type 1 transmembrane protein family; the extracellular domain consists of 29–36 tandem arrays of EGF (epidermal growth factor)-like repeats, followed by a conserved negative regulatory region (NRR or LNR) consisting of three cysteine-rich Notch Lin12 repeats (N/Lin 12) and a heterodimerization (HD) domain [27]. Notch family members differ in the number of EGF-like repeats, however they share many similarities in structure [9,28]. EGF-like repeats mediate ligand binding, whereas NRR functions to prevent both ligand-dependent and -independent signaling [28]. The cytoplasmic portion of Notch is composed of a DNA binding protein (RBP-Jk associated molecule or RAM) domain and six ankyrin (ANK) repeats, which are flanked by two nuclear localization signals (NLS), followed by a transactivation domain (TAD) and a domain rich in proline, glutamine, serine and threonine residues (PESTs) that controls the receptor half life [9,29,30] (Fig. 1).

Membrane localization of Notch requires S1 cleavage of precursor of the Notch receptor. This event occurs in the Golgi network by the action of a furin-like convertase. Then, the two fragments are re-assembled as a non-covalently linked heterodimeric receptor at the cell surface [6]. Mature Notch receptors are heterodimers made up of an extracellular subunit, a transmembrane subunit (N^{TM}) and a cytoplasmic subunit. Activation of Notch consists of two consecutive cleavages of the transmembrane receptor upon the binding of a Notch ligand, which triggers S2 cleavage. This process takes places at the cell surface. N^{TM} subunit is cleaved by ADAM/Tumor necrosis factor-α-converting enzyme (TACE) metalloprotease family at Site 2 (located ~12 amino acids before the transmembrane domain). S2 cleavage releases the Notch extracellular domain (NECD) from the heterodimer and creates a membrane-tethered Notch extracellular truncation (NEXT), which becomes a substrate for γ-secretase. S3 is cleaved by γ-secretase at Sites 3 and 4 [31]. This last cleavage occurs on the plasma membrane and/or in endosome. The new mobile cytoplasmic subunit [Notch intracellular domain (NICD or N^{IC})] is translocated to the nucleus, where it interacts with members of the DNA-binding protein, recombination signal binding protein for immunoglobulin kappa J (RBP-Jk) or CBF1/Su(H)/Lag-1 (CSL) family of transcription factors [8]. Activated NICD–RBP-Jk complex displaces co-repressors and recruits coactivator (co-A) mediating