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Targeting Notch degradation system provides promise for breast cancer therapeutics

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ABSTRACT

Notch receptor signaling pathways play an important role, not only in normal breast development but also in breast cancer development and progression. As a group of ligand-induced proteins, different subtypes of mammalian Notch (Notch1-4) are sensitive to subtle changes in protein levels. Thus, a clear understanding of mechanisms of Notch protein turnover is essential for understanding normal and pathological mechanisms of Notch functions. It has been suggested that there is a close relationship between the carcinogenesis and the dysregulation of Notch degradation. However, this relationship remains mostly undefined in the context of breast cancer, as protein degradation is mediated by numerous signaling pathways as well as certain molecule modulators (activators/inhibitors). In this review, we summarize the published data regarding the regulation of Notch family member degradation in breast cancer, while emphasizing areas that are likely to provide new therapeutic modalities for mechanism-based anti-cancer drugs.

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1. Introduction

Breast cancer is the most common cancer diagnosed among women worldwide. According to recent global cancer statistics released by the IARC (International Agency for Research on Cancer), breast cancer accounts for 25% of all types of cancer cases and 15% of all cancer deaths among females (Torre et al., 2015). Current standardized therapy for breast cancer, used often in combination, includes surgery, radiation, hormone therapy, and chemotherapeutic agents such as anthracyclines, cyclophosphamide, taxanes and platinum compounds (Ono et al., 2015). However, recurrence still occurs in a substantial proportion of breast cancer patients after comprehensive treatment. Besides the HER2 signaling pathway when over-expressed, Notch signaling has also been described as a major player in breast cancer cells, in particular in cancer stem cells (McCubrey et al., 2014; Ischenko et al., 2008). Aberrant activation and dysregulation of Notch pathways have been detected in breast cancer (Stylianou et al., 2006). This is corroborated by Notch involvement in a number of oncogenic signaling pathways and drug resistance incidents (Guo et al., 2011). However, the intricacies of Notch signaling mechanisms in breast cancer progression remain elusive and controversial. In this review, we describe some central mechanistic aspects of Notch degradation in breast cancer. In addition, we discuss anti-cancer therapeutic agents that selectively target Notch. Finally, we evaluate how Notch down-regulation is likely to participate given current knowledge in breast cancer research and highlight potential clinical implications for Notch down-regulation in this malignant disease.

2. Overview of the Notch signaling pathway

The Notch (neurogenic locus notch homologue protein) pathway is an evolutionarily conserved signaling pathway that regulates stem cell maintenance, cell fate specification, differentiation, proliferation, motility, and survival. Throughout the past several decades, the function of Notch proteins have been studied in many diverse organisms, from worms to humans, beginning in 1919 with its discovery and naming based on its effect on the partial loss of wings phenotype in Drosophila (Artavanis-Tsakonas, 1988). Since then, numerous researchers have contributed to the discovery of the components and various regulators to the Notch signaling pathway involved in the loss of wings phenotype. Different organisms possess different, yet homologous, Notch receptors. For example, Drosophila have only one receptor (Notch) and two ligands (Delta and Serrate) while mammals possess more complicated components of the Notch signaling pathway, which is consistent with the more diverse array of Notch function in humans (Andersson et al., 2011). Although homologous Notch receptors differ in their extracellular and cytoplasmic domains, they exhibit remarkable similarity in function.

In mammalian signal-sending cells, the Notch pathway consists of ligands (Delta-like proteins 1/3/4, Jagged1/2) and receptors (Notch1/2/3/4) (Ilagan and Kopan, 2007). Notch ligands contain an amino-terminal Notch ligand motif (in all ligands except for the Notch inhibitory ligand DLL3), followed by an N-terminal DSL (Delta-Serrate-LAG-2) domain, specialized tandem EGF repeats (called a DOS domain, Delta and OSM-11) and EGF-like repeats. The binding to Notch receptor is dependent on DSL and the DOS domains. Mammals have four Notch receptors, which all exhibit the same overall structure: EGF-like repeats and an LNR domain in the extracellular domain (NECD), several ankyrin-like repeats, a PEST domain, multiple nuclear localization sequences and a CSL-binding site called RAM in the intracellular domain (NICD); as well as a transmembrane domain (TM) (Bray, 2006; Bianchi et al., 2006). In contrast to other DSL ligands, the inhibitory DLL3 did not activate Notch signaling pathway in multiple assays. Moreover, DLL3 did not bind to cells expressing any of the four Notch receptors, and Notch1 did not bind DLL3-expressing cells (Ladi et al., 2005). Although new insights into the Notch-ligand recognition event have been gained from the application of structural biology, it is required to identify the affinity of different Notch ligand complexes, including the design of fragments for co-crystallization and ELISA based assays of fragments of Notch and Delta (Chillakuri et al., 2012). The ligand selectivity of Notch signaling and Notch-ligand therapeutics need more investigation.

Once bound to its ligand on a neighboring cell, the Notch receptor is activated, undergoing at least three critical proteolytic steps (Kopan and Ilagan, 2009). In this vital process, ligand-receptor binding triggers a metalloprotease cleavage of the Notch receptor followed by proteolysis of the NICD by the γ-secretase complex. Then, the NICD is free to attach itself to specific DNA-binding proteins located in the nucleus, where it associates with the CSL (CBF1/Su(H)/Lag-1) transcription factor complex, resulting in subsequent activation of the canonical Notch target genes: myc, p21, and the HES-family members (Efstratiadis et al., 2014).

3. The controversial roles of Notch signaling pathway in breast cancer

The role of the Notch signaling pathway was recognized decades ago when changes of Notch pathway members were found responsible for various human diseases. Identification of a recurrent t(7;9)(q34;q34.3) chromosomal translocation was discovered to be related with the Notch1 gene, found in a small subset of human pre-T-cell acute lymphoblastic leukemias (T-ALL) (Ellisen et al., 1991). Since then, a list of aberrant Notch signaling has grown to include cancer, immune disorders and developmental syndromes. Alagille syndrome (an autosomal dominant genetic disorder) and the late-onset syndrome CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) are two classic epitomes of developmental diseases caused by mutations of Notch2 and Notch3, respectively (Ortica et al., 2014; Joutel et al., 1996). With similar but independent characters, Notch receptors (Notch1, 3, 4) and ligands (JAG1 and DLL4) were all found to be highly and widely expressed in human breast cancers, compared with normal breast tissues from the margin of tumor section, leading to abnormal growth of breast cancer cells (Zang et al., 2007).

The mechanism of cancer initiation and development is not yet fully understood. One theory about the initiation and metastasis of solid tumors, including breast cancer, is the involvement of stem-like cells/cancer-initiating cells (CSC/CIC), whose partial characteristics are known of increased CD44 and decreased CD24 ($CD44^+/CD24^-$) (McCubrey et al., 2014; Al-Hajj et al., 2003). Abundant studies on mutations in Notch signaling pathway have presented its significant roles in breast malignancies. For instance, Notch1 influences breast CSC/CIC self-renewal by increasing HER2 transcription (Ju et al., 2013; Suman et al., 2013). Erythropoietin (Epo) on the surface of breast CSC/CIC could increase the CSC/CICs' self-renewing capacity in a Notch-dependent manner (Phillips et al., 2007). Harrison et al. (2010) evaluated the activation status of all Notch receptors in breast CSC/CIC as compared to luminally differentiated $CD24^+$ cells and found that the activation of Notch4 is much higher in BCSC-enriched cells while Notch4 knock-down could suppress tumor initiation completely. More precisely, Nagamatsu et al. (2014) pointed out that Notch4 over-expression increased the proliferation and invasiveness of triple-negative breast cancer (TNBC) cells and Notch4 inhibition reduced proliferation and invasiveness of TNBC cells as well as tumor volume and tumorigenicity.