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Targeting Notch signaling pathway in cancer: Clinical development advances and challenges

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ABSTRACT

Notch signaling plays an important role in development and cell fate determination, and it is deregulated in human hematologic malignancies and solid tumors. This review includes a brief introduction of the relevant pathophysiology of Notch signaling pathway and primarily focuses on the clinical development of promising agents that either obstruct Notch receptor cleavages such as γ-secretase inhibitors (GSIs) or interfere with the Notch ligand–receptor interaction by monoclonal antibodies (mAbs). Antitumor activity by GSIs and mAbs administered as single agent in early phases of clinical trials has been observed in advanced or metastatic thyroid cancer, non-small cell lung cancer, intracranial tumors, sarcoma or desmoid tumors, colorectal cancer with neuroendocrine features, melanoma and ovarian cancer. A number of mechanism-based adverse events particularly gastrointestinal toxicities emerged and mitigation strategies are developed after testing multiple GSIs and Notch targeting mAbs. We also discuss pharmacodynamic biomarkers in conjunction with methods of assessment of the molecular target inhibition validation. Biomarkers of efficacy or benefit may be of importance for a successful development of this class of drugs.

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1. Introduction

The Notch pathway is a highly evolutionally conserved molecular pathway that plays an important role for cell fate determination, proliferation, differentiation and survival in development, neurogenesis and homeostasis (Ranganathan et al., 2011; Takebe et al., 2011). Increasing evidence demonstrates that Notch signaling is deregulated in human hematological malignancies and solid tumors (Nickoloff et al., 2003; Aster & Blacklow, 2012) and implicated in tumor/tissue angiogenesis (Li & Harris, 2005; Dufraine et al., 2008). A role for Notch signaling in

Abbreviations: ADAM, a disintegrin and metalloproteases; CR, complete response; CSCs, cancer stem cells; DLL, Delta-like ligand; DLT, dose limiting toxicity; EDTA, ethylenediaminetetraacetic acid; JAG, Jagged; GBM, glioblastoma multiforme; mAb, monoclonal antibody; GSI, γ-secretase inhibitor; MAML, mastermind-like; MSFE, mammosphere-forming efficiency; MTD, maximum tolerated dose; NICD, Notch intracellular domain; NSCLC, non-small cell lung cancer; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell lymphoblastic lymphoma; TACE, metalloproteinase tumor necrosis factor-α-converting enzyme; TICs, tumor initiating cells.

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the maintenance of cancer stem cells (CSCs), also known as tumor initiating cells (TICs), has been described in preclinical models and recently in clinical studies (Pannuti et al., 2010; Takebe et al., 2011). Based on but not limited to the above-mentioned mechanisms, targeting the Notch pathway either with small molecule inhibitors primarily with γ-secretase inhibitors (GSIs) or large molecule monoclonal antibodies (mAbs) to Notch ligands and Notch receptors are currently in clinical development. However, clinical development has encountered significant challenges with dose limiting intestinal adverse events. In this article, we focus on clinical development advances and limitations as well as strategies of mitigating toxicities associated with Notch inhibitors. We also discuss Notch pathway targets/biomarkers in tissues or plasma that serve as the pharmacodynamics (PD) biomarkers towards validation of Notch signaling inhibition, and/or potentially as markers of efficacy or benefit in the context of development of Notch signaling pathway targeting drugs.

2. Notch signaling pathway

Notch signaling is vital to embryo development through regulation of cell-to-cell communication by controlling cell proliferation, differentiation, and apoptosis. It is also implicated in the postnatal hematopoiesis, breast development, gastrointestinal epithelial maturation, immune regulation, vascular development and neural stem cell survival (Dontu et al., 2004; Androutsellis-Theotokis et al., 2006). Moreover, Notch signaling outcome determines whether promotion or restriction of differentiation occurs, which largely depends on the cell-context, microenvironment and crosstalk with other signaling pathways. Notch regulates normal and cancer stem cell renewal and differentiation, while in cooperation with the Wnt pathway, it provides cues for intestinal epithelial cell fate decisions (Fre et al., 2005; van Es et al., 2005; Ohlstein & Spradling, 2006; Nakamura et al., 2007). In mouse models, pan Notch inhibition by GSIs can turn rapidly proliferative cells in the intestinal crypts into goblet cells, leading to secretory diarrhea (van Es et al., 2005).

Notch receptors are synthesized in the endoplasmic reticulum as an inactive single peptide precursor, which is proteolytically cleaved by a furin-like convertase in the trans-Golgi network before it reaches the plasma membrane (Fig. 1). The first cleavage (S1) produces non-covalently bound heterodimers comprising a N-terminal ligand-accessible Notch extracellular subunit (NEC), and a C-terminal Notch transmembrane fragment (NTM) that includes an extracellular stub, transmembrane domain and Notch intracellular domain (NICD). There are four Notch receptors (Notch1, 2, 3 and 4) and five ligands including delta-like ligand (DLL) 1, 3, and 4, and Jagged (JAG) 1 and 2 in mammals. All Notch receptors and their ligands are single-pass transmembrane proteins featuring multiple epidermal growth factor (EGF)-like repeats in the extracellular region. The extent of EGF-like repeat fucosylation by the glycosyltransferases (Lunatic Fringe, Radical Fringe and Manic Fringe) determines the affinity strength between the receptors and their ligands (Rampal et al., 2005).

The characteristic of Notch signaling is juxtacrine signaling between neighboring cells. That is, the signaling is initiated by binding of a Notch ligand expressed on one cell to a Notch receptor on an adjacent cell (Fig. 1). Upon ligand binding to the receptors, they undertake conformational change followed by the second cleavage (S2) catalyzed

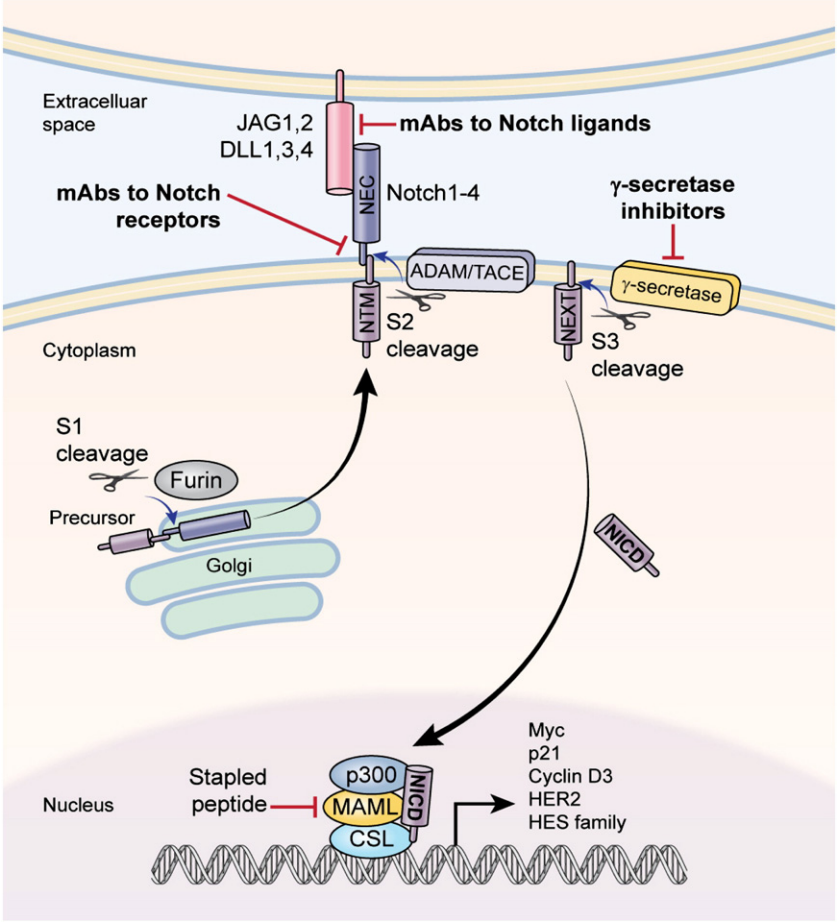

Fig. 1. Notch signaling pathway and agents in clinical development. Two major classes of Notch inhibitors are currently in early clinical development: γ-secretase inhibitors (GSIs) and monoclonal antibodies (mAbs) against Notch receptors or ligands.