NOTCH INHIBITION AS A PROMISING NEW APPROACH TO CANCER THERAPY

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Abstract: The Notch pathway powerfully influences stem cell maintenance, development and cell fate and is increasingly recognized for the key roles it plays in cancer. Notch promotes cell survival, angiogenesis and treatment resistance in numerous cancers, making it a promising target for cancer therapy. It also crosstalks with other critical oncogenes, providing a means to affect numerous signaling pathways with one intervention. While the gamma-secretase inhibitors are the only form of Notch inhibitors in clinical trials, other forms of Notch inhibition have been developed or are theoretically feasible. In this chapter we review the rationales for Notch inhibition in cancer and then discuss in detail the various modalities for Notch inhibition, both current and speculative.

INTRODUCTION: BACKGROUND OF THE NOTCH PATHWAY IN CANCER

In the current era in oncology, much of the hope for powerful new therapies lies with targeted inhibition of pathways dysregulated in cancer. An initial wave of targeted pathway inhibitors has yielded some successes but more disappointments and major efforts are underway to refine our application of some of these approaches. However, there is no slowdown in attempting to find newer and perhaps more effective targets in cancer cells and the Notch pathway is generating growing enthusiasm in this regard. As is described in detail elsewhere in this volume, Notch is a key player in development, stem cell maintenance and cell survival and its specific roles in individual cancers are covered in other chapters here. In this chapter, the rationale for Notch inhibition as a
cancer therapy and its potential drawbacks will be discussed, with extended description of established and experimental methods for Notch inhibition.

**RATIONAL FOR NOTCH INHIBITION**

Numerous functions have been ascribed to Notch, with some of these helping to explain its cancer-promoting effects in many tissues. Notch helps maintain certain stem cell populations,\(^1\text{-}^5\) but interestingly it is also a master regulator of cell fate at critical differentiation branch points in various organ systems.\(^5\text{-}^8\) Notch seems more likely to play an oncogenic role in cell types that it favors in development and differentiation, such as glial cells or T-cells.\(^9\text{-}^{12}\) Notch activity promotes cell survival and has anti-apoptotic function\(^13\text{-}^{15}\) and numerous mechanisms have been proposed for this. It can also drive cell division in some settings and in some settings may be required for the cell cycle.\(^16\text{-}^{17}\)

Notch is one of the most powerful of the stem cell-promoting pathways, in conjunction with the Hedgehog and Wnt pathways, making it highly relevant for cancer given the undifferentiated/de-differentiated state of most cancer cells. Stem cell pathways such as Notch may be especially attractive targets given the growing evidence for the cancer stem cell hypothesis. This hypothesis states that cancers contain a usually small subpopulation that retains stem cell character and gives rise to the other cells making up tumors (reviewed in refs. 18,19). Various terms exist for this subpopulation, including “cancer-initiating cells,” “cancer stem cells,” or, given the uncertainty about their nature, “cancer stem-like cells.” Despite variability in nomenclature, there is general agreement on the criteria that define these cells in the laboratory. Their isolation and culture has allowed detailed study of cancer stem cells and a number of features have emerged. They are capable of unlimited self-renewal, generation of more differentiated progeny and formation of cancers in animal models.\(^20\text{-}^{21}\) These cells are more resistant than bulk cancer cells or established older cancer cell lines to standard treatments such as chemotherapy and radiation.\(^22\text{-}^{23}\) However, cancer stem cells seem equally sensitive—or even more so—to potential therapies blocking prominent stem cell pathways like Notch.\(^24\text{-}^{26}\) Inhibition of these pathways may cause differentiating effects in cancer stem cells, as well as more commonly seen cytotoxic effects. In keeping with this, a few reports have shown differentiating effects in cancer stem cells secondary to Notch inhibition.\(^24\text{-}^{26}\)

Some of the impact of Notch inhibition in cancer cells results from its extensive crosstalk with critical cancer proteins and pathways. Numerous studies have shown that Notch activity sustains the PI3kinase/Akt pathway\(^27\text{-}^{30}\) and Notch has also been demonstrated to operate in an interdependent fashion with the Ras pathway.\(^31\text{-}^{32}\) Notch regulates expression of important receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor receptor-1 (VEGFR-1)\(^33\text{-}^{35}\) and also interacts with fibroblast growth factor receptor (FGFR) signaling.\(^36\) Notch and the NF-kB pathway are intimately intertwined, with multiple points of interaction described\(^37\text{-}^{41}\) The myc oncogene is a direct target of Notch, mediating much of the oncogenic effects of Notch in T-cell malignancies.\(^42\) In some instances, other oncogenic pathways have been shown to boost Notch or its downstream activity, as is the case for the hypoxia/HIF-1 alpha pathway.\(^43\) Most of the best-known oncogenic pathways have been shown to cross-talk with the Notch pathway at some level; however, it is important to note that some of these interactions are context-dependent and do not occur in all cellular backgrounds.