

Anti-Dll4: a unique therapeutic approach for breast cancer

Abstract

In 1917 the alleles of the Notch gene were identified by Thomas Hunt Morgan but it wasn't until 1980s that gene sequencing and experimentation were analyzed. The Notch signaling pathway mediates cell fate destinations and it is a vital parameter for every local cell-to-cell communication system. Through gene regulation mechanisms it is involved in various processes of angiogenesis, vasculogenesis and vascular maintenance, that play an integral role in tumor growth and metastasis. Evidence from recent studies promote the dominant oncogenic role of Delta like ligand 4, a particular ligand of the Notch pathway, in breast cancer and tumorigenesis.

Keywords: notch pathway, breast cancer, delta like ligand 4, anti-Dll4

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Abbreviations: Dll4, delta like ligand 4; MMTV, mammary tumor virus; WAP, whey acid protein

Introduction

Tumors require additional vasculature to sustain continuous growth. Different mechanisms participate in this procedure. Tumor cells excrete proteins that bind to endothelial cells and stimulate blood vessel growth, a process called angiogenesis. One of the major pathways involved in the procedure of angiogenesis involves activation of the Notch signaling pathway.

The notch signalling pathway

The cascade of events that leads to angiogenesis starts when one of the Notch agonists (Jag1-Jag2, DLL1, DLL3, and DLL4) activates the pathway. The Notch cellular receptors are single pass trans-membrane receptor proteins that consist of an extracellular, a trans-membrane and an intracellular domain. There are four receptors identified in mammals (NOTCH 1, NOTCH 2, NOTCH 3, NOTCH 4). The receptors are processed in the endoplasmic reticulum and Golgi within the signal-receiving cell. They are triggered only via direct cell-to-cell contact. When activated, different cleavages take place that result in separation of the intracellular domain which enters nucleus and with the activation of CSL transcription factor it allows nuclear translocation and activation of the canonical notch target genes.^{1,2}

Delta like ligand - 4

Delta-like proteins are Drosophila protein Delta mammalian homologs that participate as ligands for the Notch 1, 3 and 4 pathway receptors. In humans, Delta like ligand 4 (Dll4) is encoded by Dll4 gene and although most ligands are expressed in many tissues, Dll4 reveals a highly selective expression pattern within the vascular endothelium and especially in mature arteries and in actively growing vessels. Thus, it is considered to have a crucial role on promoting angiogenesis via activation of the Notch system.³

Notch pathway and breast cancer

The connection between breast cancer and the Notch pathway was first analyzed in 1992 by Jhappan et al.,⁴ where the mouse mammary tumor virus (MMTV) was first inserted in the Int3 (Notch 4) genes. In addition, in 1996 truncated Int3 (Notch4) was expressed under the control of Whey Acid Protein (WAP) promoter. Both studies resulted in abnormal mammary gland development and formation of mammary carcinomas with subsequent lung metastasis.^{4,5} Moreover, in 2004 both Notch 1 and 4 genes were studied as targets for insertion and rearrangement by the MMTV that promoted epithelial mammary tumorigenesis.^{6,7} There are evidence that breast tumor xenografts over express the Dll4.⁸ Jubb et al.,⁸ presented in 2010 a study where 296 breast adenocarcinomas and 38 ductal carcinoma in situ tissues were examined. The authors resulted in a Dll4 expression associated with breast cancer cells (Dll4 was expressed by intratumoral endothelial cells in 73% to 100% of breast adenocarcinomas and 18% of in situ ductal carcinomas). Also, some studies report that inhibition of Dll4 has antitumor efficacy with delay in tumor regrowth in a wide range of human tumor xenografts (including breast cancer), while other support that blocking Dll4 increases the chemotherapeutic antitumor effectiveness.^{9,10}

Conclusion

It is commonly accepted that the Notch Signaling Pathway plays a major role in tumor angiogenesis and as mentioned, Delta like ligand 4 reveals a highly selective expression within the vascular endothelium. Recent evidence support that targeting Dll4 not only enhance adjuvant chemotherapy but also reduce tumor size. Even though no firm conclusions can yet be gathered and more studies are required to reach safe conclusions, these findings suggest that anti-Dll4 antibodies might be a novel therapy that could be used even as an initial treatment for breast cancer.

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Conflict of interest

The author declares no conflict of interest.

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