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 tumorogenesis.

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

Notch pathway and breast cancer

The connection between breast cancer and the Notch pathway was first analyzed in 1992 by Jhappan et al., 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 Acidid Protein (WAP) promoter. Both studies resulted in abnormal mammary gland development and formation of mammary carcinomas with subsequent lung metastasis. Moreover, in 2004 both Notch 1 and 4 genes were studied as targets for insertion and rearrangement by the MMTV that promoted epithelial mammary tumorogenesis. There are evidence that breast tumor xenografts over express the Dll4. Jubb et al., 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 and 38 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.

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.

Acknowledgements

None.
Conflict of interest

The author declares no conflict of interest.

References