

Neural stem cell signaling dysregulation leading to cancer

Mercedes Tomé

Summary

Notch signaling regulates proliferation, differentiation and survival of neural stem cells (NSCs) in the central nervous system. Transformed NSCs are thought to be the origin of brain cancer stem cells and of the more aggressive tumors such as gliomas. Overactive Notch2 signaling has been also associated with gliomas and poor prognosis. Aberrant Notch2 signaling may therefore contribute to the transformation of NSCs and gliomagenesis. In fact, we have previously shown that constitutive upregulation of the Notch2 intracellular domain (N2ICD) in the NSC lineage enhances proliferation and chemoresistance of NSCs. Here, we investigated the mechanism by which N2ICD promotes chemoresistance in NSCs, an acquired feature that likely contributes to transformation and have potential implication in cancer therapy. We performed ex-vivo studies using NSC cultures from transgenic mice that constitutively express N2ICD. These NSCs exhibit etoposide chemoresistance with inhibited mitochondria-caspase pathway and increased expression of pro-survival proteins. Using a pharmacological approach we interestingly show that N2ICD enhances FGF receptor-1 (FGFR1) activity to specifically target AKT-GSK3 signaling pathway to promote chemoresistance in NSCs. Finally we found that the chemoresistance ability of glioma cell lines is also dependent on Notch2 signaling which supports a role of Notch2 in NSC transformation. We have identified a molecular mechanism through which aberrant Notch2 signaling could contribute to NSC transformation and revealed new aspects of signaling crosstalks that could be of relevance for targeted therapy efficacy.