

Capstone Presentation:

Abstract:

The effects of ephrinB2 signaling on proliferation and invasion in glioblastoma multiforme

The aggressive nature of glioblastoma multiforme (GBM) may be attributed to the dysregulation of pathways driving both proliferation and invasion. EphrinB2, a membrane-bound ligand for some of the Eph receptors, has emerged as a critical target regulating these pathways. In this study, we investigated the role of ephrinB2 in regulating proliferation and invasion in GBM using intracranial and subcutaneous xenograft models. The Cancer Genome Atlas analysis suggested high transcript and low methylation levels of ephrinB2 as poor prognostic indicators in GBM, consistent with its role as an oncogene. EphrinB2 knockdown, however, increased tumor growth, an effect that was reversed by ephrinB2 Fc protein. This was associated with EphB4 receptor activation, consistent with the data showing a significant decrease in tumor growth with ephrinB2 overexpression. Mechanistic analyses showed that ephrinB2 knockdown has anti-invasive but pro-proliferative effects in GBM. EphB4 stimulation following ephrinB2 Fc treatment in ephrinB2 knockdown tumors was shown to impart strong anti-proliferative and anti-invasive effects, which correlated with decrease in PCNA, p-ERK, vimentin, Snail, Fak, and increase in the E-cadherin levels. Overall, our study suggests that ephrinB2 cannot be used as a sole therapeutic target. Concomitant inhibition of ephrinB2 signaling with EphB4 activation is required to achieve maximal therapeutic benefit in GBM.