EGFR Targeted Inhibition Resistance: Compensatory Activation of ERBB Family Members in Glioblastoma Cancer Stem-Like Cells Promotes Proliferation

Receptor tyrosine kinase (RTK) signaling is found to be aberrant in approximately 88 percent of glioblastoma multiforme (GBMs). Most notably, the epidermal growth factor receptor (EGFR) is amplified or mutated in approximately half of all these cases, with a majority of these cases harboring the EGFRvIII mutation, an in-frame deletion of exons 2 to 7. Consequently, this deletion gives rise to a truncated receptor that retains its signal peptide, transmembrane and intracellular kinase and autophosphorylation domains, making it constitutively active and ligand independent. Furthermore, the constitutively active mutant has been shown to confer GBMs hallmark with increased and aggressive proliferation, survival and invasive phenotype, thus is associated with tumorigenesis.

The putative cancer stem cell (CSC), a small subset of the tumor bulk, with the capacity to self-renew has been postulated by the CSC hypothesis to be the driver behind tumor propagation and recurrence. Isolation and characterization of this population through the marker CD133 (Prominin-1) has shown that they are highly effective in creating neoplasms in immunodeficient mice, with as little as $10^2$ to $10^3$ cells necessary for successful xenographs, while those injections absent of CSCs rarely develop a neoplasm. Moreover, CSCs have shown the ability to be resistant to common anticancer treatments such as radiation therapy and chemotherapy. With various EGFR targeted agents (e.g., erlotinib, lapatinib, and cetuximab) currently in clinical trial only producing modest improvements in a small portion of the patient population, Clark et al. then went on to analyze the downstream signaling of these cells with and without exogenous mitogenic factors and determined, unsurprisingly, that AKT and ERK1/2 (MAPK) activation remained relatively constant with and without exogenous EGF. However, they also observed upregulation and activation of ERBB2/3 after removal of exogenous EGF. Importantly, Clark and colleagues went on to observe that treating CSCs with lapatinib, which block activation of both EGFR and ERBB2, was significantly more effective at...
inhibiting proliferation compared to cetuximab (blocks EGFR alone) and other monospecific EGFR inhibitors (antibodies and TKIs.) Based on these results, Clark et al, concluded that GBM therapeutic resistance to anti-EGFR targeted therapies may in part be responsible for the compensatory activation of EGFR-related family members (ERBB2/3) by enabling CSC proliferation.

In glioma the mechanisms that drive therapeutic resistance and progression are largely a mystery and are the factors that make this disease so deadly and aggressive, however Clark et al offer some possible explanations for this. Firstly, autocrine or paracrine stimulation of EGFR through ligands such as EGF and amphiregulin may also confer the survival and proliferative cues to CSCs independent of exogenous EGF.13 However, it appears that the auto- or paracrine stimulation is only partially responsible as explained by the more significant reduction in proliferation after lapatinib treatment compared to cetuximab treatment. Second, many reports have shown that neuregulin ligands may be potential activators of ERBB-dependent cancers.14,15 Neuregulin ligands activate ERBB3 or 4, which subsequently dimerize with other family members while simultaneously activating their own downstream signaling.16 And thirdly the possibility of “off-target” effects of lapatinib; the nonspecific activity of lapatinib or paracrine stimulation is only partially responsive as explained by the more significant reduction in proliferation after lapatinib treatment compared to cetuximab treatment. Sec- ondly, these “off-target” effects may all play a role in reducing proliferation, and the role of neuregulin, ERBB2 and ERBB3 in signaling progression and resistance are still largely unknown and need to be clarified to further understand the mechanism of GBM resistance and progression, in order to develop efficacious treatment modalities. In addition to providing new insights on the resistance mechanism of GBM CSCs, Clark et al’s results provide explanation for previously confounding reports illustrating the importance and critical need of aberrant EGFR activation for the survival and propagation of GBM.5,13 Furthermore, Clark et al’s results help to explain why we see minimal improvement in clinical trials that use targeted EGFR therapies. ERBB family members have been shown in various cancers to play an important role, particularly in breast cancer.16 As Clark et al showed multi-targeted therapy with lapatinib provided significant reduction in proliferation of CSCs with and without exogenous mitogenic factors. This fact combined with the observation that only GBM CSCs proliferated while the normal NSCs did not survive in the absence of EGFR signaling implicates the compensatory ERBB2/3 signaling as a tumorigenic mechanism, ergo it may be worthwhile to explore multi-EGFR receptor family-inhibiting treatment modalities as a strategy against GBM.

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REFERENCES

Having the Brain Participate in Spinal Cord Injury Recovery

Every year in the US, about 12,000 new spinal cord injuries occur, nearly half of which are complete injuries. Despite decades of active research, few effective treatment strategies exist to help in functional recovery, aside from aggressive rehabilitation. The mechanism of recovery in fortunate patients is also unclear, making it difficult to know how best to target therapeutic options.

Under certain conditions, the spinal cord has the capacity to maintain locomotion even after a complete transaction (ie, the “stepping cat”). This phenomenon has been attributed to local spinal circuits within the distal spinal cord that can continue to function despite disconnection from cortical input. In 2009, Courtine and Edgerton demonstrated that the threshold to engage this local spinal motor circuitry in locomotion can be lowered with epidural stimulation and serotonergic agonist infiltration.1 Under those conditions, rats with complete spinal cord injury recovered amazing stepping capacity on treadmills after training. However, it also became clear that the regained stepping capacity was completely treadmill dependent. The rats did not gain any voluntary control of locomotion and returned back to complete paraplegia without the treadmill.

Courtine’s recent study, published in the June 2012 issue of Science, confirms the importance of overground training in reorganizing supraspinal control and voluntary locomotion recovery after paralyzing spinal cord injury.” Staggered lateral hemisections, disrupting most of the direct supraspinal control of the lower extremity movement, were performed in rats with no spontaneous recovery of lower limb function even after 2 months. A robotic neuroprosthetic training system was then used to encourage and enforce the active participation of the rats in goal oriented locomotion training, assisted with epidural stimulation and serotonergic agonist