OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference and Exhibition on
Metabolomics & Systems Biology

March 24-26, 2014 San Antonio, USA

EGFR signaling regulates lipid metabolism in glioblastoma

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Abstract

Glioblastoma (GBM) is the most common malignant primary brain tumor and one of the most lethal of all cancers, with median patient survival of 12-15 months from initial diagnosis, despite wide surgical resection and improvements in radio- and chemotherapies. Recent progress in the understanding of cancer biology has demonstrated that tumor cells reprogram their metabolism in order to facilitate their rapid growth and proliferation. Therefore, directly targeting these metabolic alterations has become a very promising therapeutic strategy in cancer treatment. Our recent data have revealed a previously unrecognized tumor pro-survival mechanism by which epidermal growth factor receptor (EGFR) upregulates lipid metabolism to promote tumor growth. We found that EGFR signaling mediated by PI3K/Akt signaling upregulates the master lipogenic transcription factor, sterol regulatory element-binding protein-1 (SREBP-1). Our data show that SREBP-1 and its regulated downstream genes controlling fatty acid synthesis are significantly elevated in GBM patients, xenografts and cell lines. Using pharmacological and genetic methods, we further demonstrated that inhibiting SREBP-1 significantly suppressed GBM tumor growth. Recently, we further reveal that GBM tumor requires large amounts of cholesterol for malignant growth, and EGFR/PI3K/Akt signaling was shown to directly upregulate cholesterol uptake. Moreover, targeting cholesterol homeostasis has been shown to significantly inhibit GBM growth. Taken together, our data reveal that SREBP-1 is a central player which integrates oncogenic EGFR signaling and lipid metabolic reprogramming. We further provide a rational to targeting GBM through targeting lipid metabolism.

Biography

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