**Therapeutic Targeting of the Notch Pathway in Glioblastoma Multiforme**

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**Background**

Glioblastoma (GBM) is the most common and deadly form of brain tumor. After standard treatment of resection, radiotherapy, and chemotherapy, the 5-year survival is <5%. In recent years, research has uncovered several potential targets within the Notch signaling pathway, which may lead to improved patient outcomes.

**Methods**

A literature search was performed for articles containing the terms “Glioblastoma” and “Receptors, Notch” between 2003 and July 2015. Of the 62 articles retrieved, 46 met our criteria and were included in our review. Nine articles were identified from other sources and were subsequently included, leaving 55 articles reviewed.

**Results**

Of the 55 articles reviewed, 47 used established human GBM cell lines. Seventeen articles used human GBM surgical samples. Forty-five of 48 articles that assessed Notch activity showed increased expression in GBM cell lines. Targeting the Notch pathway was carried out through Notch knockdown and overexpression and targeting d-like ligand, Jagged, g-secretase, ADAM10, ADAM17, and Mastermindlike protein 1. Arsenic trioxide, microRNAs, and several other compounds were shown to have an effect on the Notch pathway in GBM. Notch activity in GBM was also shown to be associated with hypoxia and certain cancer-related molecular pathways such as PI3K/AKT/mTOR and ERK/MAPK. Most articles concluded that Notch activity amplifies malignant characteristics in GBM and targeting this pathway can bring about amelioration of these effects.

![Diagram of Notch Pathway](image)

**Conclusions**

A multitude of recent and ongoing research shows the connection between Notch signaling activation and the pathophysiology of GBM. Four clinical trials (NCT01122901, NCT0119599, NCT0126941, and NCT01192149) exploring the relationship of the Notch pathway to GBM survival have been undertaken using the g-secretase inhibitor RO4929097. Of these trials, only 1 phase 1 trial was completed and the other 3 were terminated because of the manufacturer’s decision to terminate drug supply. Future clinical trials targeting the Notch pathway in GBM may be a productive endeavor.