Short Communication

Integrating NOTCH Inhibitors with Standard Chemotherapeutic Drugs in Glioblastoma Multiforme Treatment: A Synergistic Approach

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Abstract

Glioblastoma Multiforme (GBM) presents a significant obstacle in the field of cancer because of its aggressive nature and limited treatment options. Despite advances in surgical resection, radiation therapy, and chemotherapy, the median survival rate remains dishearteningly brief at 15 months. Glioblastoma Stem Cells (GSCs), particularly those expressing the CD133 marker, are acknowledged for their pivotal role in tumor growth and resistance to conventional therapies. The NOTCH signaling pathway is a crucial regulator of GSCs and plays a significant role in the induction of tumor heterogeneity and radioresistance. In this review, we explore the therapeutic potential of the NOTCH signaling pathway and evaluate various classes of NOTCH inhibitors inhibitors such as Gamma-Secretase Inhibitors (GSI), small interfering RNA (siRNA), and monoclonal antibodies. Although recent trials have suggested improved outcomes by integrating GSIs with standard treatments, the challenge persists in sparing $CD133^+$ cells. This review also emphasizes the role of Chk1 and Chk3 inhibitors in reversing radioresistance in $CD133^+$ cells. In conclusion, this review explores the nuances of NOTCH signaling inhibition in GBM treatment, emphasizing precision in targeting the tumor microenvironment and addressing therapeutic resistance associated with $CD13^+$ cells.

Keywords: Glioblastoma multiforme; Glioblastoma stem cells; CD133 marker; NOTCH signaling pathway; Chemotherapeutic resistance; Therapeutic Intervention.

Description

Glioblastoma Multiforme (GBM) is a highly aggressive grade IV glioma of the astrocytic lineage and is associated with a high mortality rate and limited treatment options [1]. Despite current treatment modalities involving surgical resection, radiation therapy, and chemotherapy, GBM remains an incurable disease with a median survival of only 15 months [2,3]. Glioblastoma Stem Cells (GSCs), characterized by their stem-like properties, have been identified in GBM and contribute to tumor growth and therapy resistance. CD133 has emerged as a marker for some GSCs, enabling the isolation of a subpopulation with enhanced tumor-initiating potential. The notch signaling pathway implicated in GSC regulation facilitates engraftment and long-term proliferation of malignancies [4-6].

NOTCH signaling occurs when transmembrane ligands on one cell engage NOTCH receptors on an adjacent cell, resulting in the γ-secretase-mediated proteolytic release of the NOTCH Intracellular Domain (NICD), with subsequent release of *HES* and *HEY* genes, resulting in differentiation of neurons and glial cells [7-9]. This differentiation and growth of tumor cells enhances the heterogeneity in the tumor microenvironment, making it difficult to target. Targeting this signaling mechanism could significantly enhance the treatment scope of this malignant tumor along with standard treatment. Various classes of NOTCH inhibitors have been developed, including Gamma-Secretase Inhibitors (GSI), small interfering RNA (siRNA), and monoclonal antibodies, to restrain the NOTCH signaling mechanism [10]. However, the efficacy with which it suppresses tumor progression and halts tumor growth remains unclear.

Recent clinical trials have proposed that clinical outcomes have improved because of the rational integration of GSIs with already-used treatment modalities [11]. However, common chemotherapeutic drugs, including temozolomide, carboplatin, paclitaxel (Taxol), and etoposide (VP16), as well as traditional radiation therapy, predominantly target the $CD133^-$ population, while sparing or enriching the $CD133^+$ population [6,12]. One reason for the sparring of the $CD133^+$ cell population is its chemotherapeutic resistance, which is induced by DNA damage checkpoints in these cells. Targeting Chk1 and Chk3 DNA damage checkpoint kinases by specific inhibitors can reverse the radioresistance of $CD133^+$ tumor cells, which in turn reduces the chances of tumor recurrence after radiation and provides a therapeutic approach for malignant tumors [6].

Gamma-Secretase Inhibitors (GSI) induces apoptosis and differentiation in $CD133^+$ stem-like cells isolated from medulloblastoma and impairs their tumorigenic activity by blocking the NOTCH signaling mechanism [13]. In addition, dynamic contrast-enhanced magnetic resonance imaging showed that GSI alone reduced glioma perfusion and drastically decreased $CD133^+$ cells in tumor explants [14]. However, gastrointestinal toxicity has been a serious concern with NOTCH blockade, leading to goblet cell proliferation in intestinal

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transit amplifying cells, resulting in severe diarrhea. However, gastrointestinal toxicity has been a serious concern with NOTCH blockade, leading to goblet cell proliferation in intestinal transit amplifying cells, resulting in severe diarrhea [15]. In addition, NOTCH blockade reduced the tumor-forming $CD133^+$ cell population 5-fold. The importance of the NOTCH signaling pathway and CD133 marker in the growth and recurrence of malignant tumors and in promoting radioresistance specifically in GBM is evident in the current literature. Future research should focus on blocking the NOTCH pathway specific to the tumor environment and investigating the therapeutic resistance induced by the CD133 marker. By focusing on therapeutic modalities that target the NOTCH pathway and $CD133^+$ tumor cells, a novel therapeutic strategy can be created to suppress these cancers.

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