Riluzole for Glioblastoma

In advanced grades of glioblastoma, glutamate and glutamine are reported to be increased in concentration in the extracellular fluid. It has been reported that glutamate acts as an extracellular signaling molecule for facilitating local spread of advanced grades of glioblastoma.

Glioblastomas exploit various molecular pathways to promote - glutamate- dependent growth by activating the AMPA (2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid) receptor, the group II metabotropic glutamate receptor, mGluR, and the epidermal growth factor receptor, EGFR. Yelskaya et al. hypothesized that targeting more than one of these pathways would be more effective in inhibiting glutamate-dependent growth. Using a model of U87 cell line, Yelskaya et al. showed that blocking glutamate release by Riluzole inhibits cell proliferation. Glutamate-dependent growth is effectively inhibited by a combination of Iressa, an inhibitor of EGFR activation and LY341495, a group II mGluR inhibitor. Treatment of U87 cells with a combination of Iressa and LY341495 inhibits proliferation as indicated by Ki-67 staining, induces apoptosis and inhibits migration of U87 cells more effectively than the treatment by Iressa or LY341495 alone. These results demonstrate that a combinatorial therapy with Iressa and LY341495 is more effective due to synergistic effects of these drugs in inhibiting the growth of glioblastoma [1)].

Tong et al. aimed to examine whether glutamate uptake mechanisms is impaired in advanced glioblastoma. The possible downregulated mechanisms of glutamate uptake would facilitate persistence of glutamate in the extracellular environment, rather than intracellular uptake. We obtained biobanked human specimens of glioblastoma and tested expression of proteins belonging to the solute carrier families of proteins that are known to function as membrane-located excitatory amino acid like glutamate transporters. The present study provides preliminary evidence of the downregulation of membrane expression of excitatory amino acid transporters solute carrier family 1 member 3 (SLC1A3) and its palmitoylated form in gliosomes, as well as SLC1A2 in the glio-synaptosomes. Compounds like riluzole used in the treatment of amyotrophic lateral sclerosis and the antibiotic ceftriaxone have the potential to facilitate glutamate uptake. These medications may be examined as adjunct chemotherapy in the massively aggressive tumor glioblastoma multiforme [2)].

Sperling et al. reported that riluzole treatment inhibits the growth of brain tumor stem-like cells enriched cultures isolated from two human glioblastomas. The effects of riluzole on these cells were associated with an inhibition of a poor prognostic indicator: glucose transporter 3 (GLUT3). A decrease in GLUT3 is associated with a decrease in the p-Akt/HIF1α pathway. Further, downregulation of the DNA (Cytosine-5-)-methyltransferase 1 (DNMT1) gene that causes hypermethylation of various tumor-suppressor genes and leads to a poor prognosis in Glioblastoma, was detected. Two hallmarks of cancer cells-proliferation and cell death-were positively influenced by riluzole treatment. Finally, we observed that riluzole reduced the tumor growth in in vivo CAM assay, suggesting it could be a possible synergistic drug for the treatment of glioblastoma [3)].

Viability of U87 MG and 11ST patient-derived GMB cell lines, after valproic acid, tranylcypromine or riluzole alone, in different combinations, as well as combined with standard temozolomide

chemotherapy was examined using the MTT assay. Proliferation, mRNA level of tissue factor pathway inhibitor 2 (TFPI2), and cell invasion were evaluated using anti-Ki-67 antibody staining, reverse transcriptase-polymerase chain reaction and xCELLigence system.

The strongest effect on cell viability was achieved by the combination of riluzole with valproic acid (U87MG: 27.2%, 11ST: 25.99%). Tranylcypromine significantly enhanced the effect of temozolomide when used in combination, as did valproic acid. The normally high proliferation of Glioblastoma significantly declined under treatment with valproic acid with tranylcypromine (p=0.01). Finally, we observed reduction of invasion comparing single tranylcypromine to its combination with valproic acid or riluzole [4].

Khan et al. demonstrated that pretreatment with the glutamate-release inhibitor riluzole sensitizes glioma cells to radiation and leads to greater cytotoxicity [5].

In a riluzole-bead coupled binding assay and in surface plasmon resonance imaging analyses, riluzole was found to directly bind to hnRNP A1 and inhibited IRES activity via effects on ITAF/RNA-binding. Riluzole also demonstrated synergistic anti-glioblastoma (Glioblastoma) affects with mTOR inhibitors in vitro and in Glioblastoma xenografts in mice. These data suggest that repurposing riluzole, used in conjunction with mTOR inhibitors, may serve as an effective therapeutic option in glioblastoma [6].

Riluzole attenuates TMZ-induced MGMT promoter methylation upregulation and enhances the antitumor effect of TMZ in MGMT-positive Glioblastomas. Therefore, combinatorial TMZ/riluzole treatment is a potentially promising novel therapeutic regimen for MGMT-positive Glioblastomas [7].

Dučić et al. exploited synchrotron radiation-based soft X-ray tomography and hard X-ray fluorescence for elemental microimaging of the shock-frozen Glioblastoma cells. The present study focused instead on the biochemical profiling of live Glioblastoma cells and provides new insight into tumor heterogenicity. They studied bio-macromolecular changes by exploring the live-cell synchrotron-based Fourier-transform infrared spectroscopy (SR-FTIR) microspectroscopy in a set of three Glioblastoma cell lines, including the patient-derived glioblastoma cell line, before and after riluzole treatment, a medicament with potential anticancer properties. SR-FTIR microspectroscopy shows that Glioblastoma live cells of different origins recruit different organic compounds. The riluzole treatment of all Glioblastoma cell lines mainly affected carbohydrate metabolism and the DNA structure. Lipid structures and protein secondary conformation are affected as well by the riluzole treatment: cellular proteins assumed cross β-sheet conformation while parallel β-sheet conformation was less represented for all Glioblastoma cells. Moreover, they hoped that a new live-cell approach for Glioblastoma simultaneous treatment and examination can be devised to target cancer cells more specifically, i.e., future therapies can develop more specific treatments according to the specific bio-macromolecular signature of each tumor type [8].

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