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International Journal of Bioorganic Chemistry & Molecular Biology (IJBCMB)
ISSN 2332-2756

Large Conductance, Calcium Activated Potassium (BK) Channels as New Therapeutic Target for Glioma

Editorial

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Received: February 15, 2013
Published: April 30, 2013

Citation: Shivaputra A. Patil, Renukadevi P, Miller D D (2013) Large Conductance, Calcium Activated Potassium (BK) Channels as New Therapeutic Target for Glioma. Int J Bioorg Chem Mol Biol. 1(1e), 1-2. **doi:** http://dx.doi.org/10.19070/2332-2756-130001e

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Gliomas are the most common malignant primary brain tumors that arise within the central nervous sys-tem in adults and they account for more than 80% of all brain tumors (Central Brain Tumor Registry of the United States [CBTRUS] http://www.cb-trus.org/).

These tumors remain difficult to treat because of the infiltrative growth of the tumor cells, and their resist-ance to standard therapy. Glioblastoma Multiforme (WHO grade IV) is the most aggressive of the gliomas, accounts for nearly 60-70% of malignant gliomas. A common approach for the treatment of GBM involves surgery, radiation therapy, and various chemotherapeu-tic regimens [1,2]. Despite advance standard therapy, including surgical resection followed by radiation and chemotherapy, the prognosis for patients with GBM remains poor. Even patients who are optimally treated with combined multimodal treatments have a median survival of only 12 months. This is possibly because of the poor drug delivery and the correspondingly lim-ited therapeutic response caused by partly intact blood brain barrier (BBB) and blood-tumor barrier (BTB).

Poor drug delivery significantly impairs the efficacy of chemotherapy. Thus, the main challenge of the exist-ing brain cancer therapies is enhancing the delivery of chemotherapeutic agents selectively to the tumor by noninvasive biochemical modification of the BBB/BTB [3,4].

The therapeutic efficacy of many potent anticancer drugs is limited by their poor penetration into brain tu-mor tissue and by their adverse effects on healthy cells, which limits the dose of drug that can be safely admin-istered to cancer patients. Invasive drug delivery strat-egies circumvent the BTB but require either a craniotomy or insertion of catheters into the carotid artery. Research in brain tumors should focus on strategies for improving non-invasive drug delivery to tumors. The cerebral microvessels and capillaries that form the BBB protect brain but they also pose an obstacle to the drug delivery. Microvessels supplying brain tumors retain some characteristics of BBB and form a blood brain tumor barrier and this BTB further significantly limits the delivery of chemotherapeutic drugs to tu-mors even though it is more permeable than BBB. Therefore, understanding biochemical modulation of BBB and BTB is critical for developing strategies to deliver therapeutic agents to tumors. During the past decade a considerable effort has been made on the role of certain vasoactive molecules on BBB/BTB permea-bility. Vasoactive molecules such as leukotriene, bradykinin and certain potassium channel agonists selectively increase permeability in brain tumor capillaries. These research ideas are being translated into strategies to increase drug delivery selectively to brain tumor tissue in patients in clinical studies. The modulation of critical molecules involved in selectively increasing BTB per-meability could lead to the development of effective strategy to increase chemotherapy delivery to tumors by noninvasive methods. BTB expresses certain unique protein markers that are absent or barely detectable in normal brain capillaries and one such marker is large conductance, calcium activated potassium (BK) chan-nel. Scientists can utilize selectively overexpressed BK channels to modulate the BTB to deliver the anticancer agents selectively to tumors.

BK channels play important roles in vital cellular sign-aling processes in both excitable and non-excitable cells. These channels are essential for cell prolifera-tion and appear to play a role in the development of cancer. BK channels are activated by both membrane depolarization and micromolar levels of intracellular calcium providing a link between the metabolic and electrical state of cells. BK channels are also present in cerebral blood vessels where they regulate blood vessel tone and probably BBB and BTB permeability. Recent studies suggest that BK channels are over-expressed in primary brain tumors and tumor microvessels [5]. These channels respond to agonist such as NS1619 (al-pha-subunit-selective BK opener; synthetic benzimida-zolone analog) [6], which selectively increase BTB per-meability to obtain sustained enhancement of selective drug delivery to brain tumors. This strategy exploits the responsiveness of brain tumor capillary endothelial cells that over-express these channels to specific activators such as NS1619. According to recent findings

NS1619 induce accelerated formation of transport vesicles in both brain tumor capillary endothelium and tumor cells. This mechanism allows chemotherapeutic agents to pass through BTB. Therefore, BK channels are potential promising targets for biochemical modu-lation for BTB permeability. The use of BK channels as therapeutic target for brain cancer is not designed

to stop the cancer cell growth; instead these agents will help the anticancer drug penetrate deep inside the tu-mor area by opening them in tumor environment se-lectively. This tumor specific delivery will minimize the toxicity to normal cells. Thus, the use of BK chan-nel activators in combination with other therapies could improve the brain cancer treatment if scientists provide selective and very potent BK activators. BK channels still considered as novel area of research in glioma and we hope that scientists will identify the highly potent BK activator that could be used to improve antiglioma agents to deliver across BBB/BTB selectively. A critical point is the delivery of drug to the glioma tumor. We believe that potent BK activa-tors will further enhance significantly the efficacy of antiglioma agents in tumor environment resulting in much improved treatment of the disease and life ex-pectancy of the brain cancer patients. An additional important consideration for brain cancer research in the future will be a focus on chemotherapy of both glioma and glioma stem cells (GSCs).

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