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Editorial Open Access

Combination Therapy for Combating Brain Tumor Stem Cells

Swapan K Ray*

Department of Pathology, Microbiology, and Immunology, University of South Carolina School of Medicine, Columbia, SC 29209, USA

The most common and malignant brain tumor is glioblastoma, which lets the patient live only for a few months and hardly for a year or longer after the diagnosis [1]. It keeps growing due to presence of brain tumor stem cells (BTSC), also called glioblastoma stem cells (GSC), which can be considered as the seeds for growth and regrowth of the tumor [2]. Complexity of a malignant brain tumor requires that it must be controlled by the application of multimodality treatments. Diagnosis of every malignant brain tumor is a new puzzle that challenges us for finding an appropriate strategy for its treatment. At present, discovery of BTSC is probably the most important piece in the complexity of malignant brain tumor. Even a small number of BTSC or GSC, left behind after surgery and therapy, can continuously replicate and regrow the tumor. After surgery, sequential combination of radiotherapy and chemotherapy is frequently used for combating the growth of glioblastoma. But various studies indicate that most of the BTSC remain radioresitant or chemoresistant and replicate to regrow the tumor [3,4]. Thus, designing an appropriate combination therapy for completely eradicating the BTSC and thereby the malignant brain tumor itself is now one of the biggest challenges to basic scientists and clinical neuro-oncologists.

It is now widely recognized that BTSC can play pivotal roles in promoting proliferation, angiogenesis, and invasion and can confer resistance to radiotherapy or chemotherapy so as to perpetuate the tumor growth. Additive or more importantly synergistic combination of therapeutic agents at low doses can be explored to maximize efficacy, minimize undesirable side effects, target multiple oncogenic pathways, overcome drug resistance, and control growth of malignant cells harboring different molecular markers. Combination therapy undeniably will be the key to keep the growth of BTSC under stringent control. Repetitive low dose administering or metronomic dosing of combination of therapeutic agents can be highly useful to increase anti-angiogenic and pro-apoptotic effects in proliferating endothelial cells, glioblastoma cells, and also BTSC in preclinical models.

There have been several thousand reports showing varying degrees of efficacy of sequential or concurrent combination chemotherapy in combating the growth of different types of glioblastoma, mostly in preclinical models [5]. Concurrent use of small interfering RNA (siRNA) technology targeted to an oncogenic molecular marker in combination with another therapeutic agent can be effective in controlling the growth of glioblastoma. For examples, use of siRNA technology for knocking down expression of hTERT or survivin in combination with another therapeutic agent showed promising therapeutic efficacy in controlling invasion, angiogenesis, and growth of different human glioblastomas in preclinical models [6,7]. Two formidable features of glioblastoma are heterogeneity and invasiveness of tumor cells that make it very hard to eradicate the residual tumor cells after surgery. Combination chemotherapy is thus almost certainly needed to control of growth of remaining heterogenic and invasive tumor cells as long as possible. Translation of some of the potential combination chemotherapeutic strategies to the clinics has been helpful in extending the life of glioblastoma patients by only a few months [8]. It is, thereby, an important lesson that the combination therapy that hardly targets or mostly ignores BTSC is definitely destined to fail in combating growth of malignant brain tumor in the patients.

In contrast, there have been only a few recent studies showing that synergistic combination of therapeutic agents can be used to induce apoptotic death not only in heterogenic glioblastoma cells but also in BTSC for abolishing the root cause of tumor regrowth [9,10]. More studies are obviously needed in this direction to explore the molecular action and efficacy of novel combination therapy that can modulate the epigenetic mechanisms and also expression of potential oncogenic or tumor suppressor microRNAs (miRs) for inducing apoptosis in glioblastoma cells as well as in BTSC. Establishment of the proof-of-principle of novel combination therapy for modulating epigenetic mechanisms and expression of miRs for inducing apoptosis in various brain tumor cells including BTSC in preclinical models may presage the path for application of this innovative approach as personalized medicine to the clinics.

In this new era of neuro-oncology, all multimodality treatments for glioblastoma need to be developed and used to make sure that these are capable of controlling the growth of BTSC as well. Future investigations in neuro-oncology field should also be directed to exploring novel epigenetic mechanisms and potential miRs in BTSC so as to design novel combination therapy for combating the growth of BTSC. It is expected that young and senior investigators in this challenging field will continue to produce exciting results working on combination therapy especially for BTSC and also use the open access Clinical & Experimental Pharmacology as a vehicle to disseminate their findings freely to the world.

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***Corresponding author:** Swapan K Ray, Department of Pathology, Microbiology, and Immunology, University of South Carolina School of Medicine, Building 2, Room C11, 6439 Garners Ferry Road, Columbia, SC 29209, USA, E-mail: swapan.ray@uscmed.sc.edu

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