

RESEARCH HIGHLIGHT

Connexin43 in Gap Junctional Intercellular Communication in Astrocytes and Glioma Cells

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Gap junctional intercellular communication built by hemichannels on cell membrane is a functional syncytium which allows rapid transfer of ions and molecules between cells. Recent findings have shown that gap junction proteins, and specifically Cx43, can play a significant role in cell migration, tissue formation and organ development, impacting adhesion and cytoskeletal rearrangements. Some literatures have shown that Cx43 was able to contribute to the treatment of gliomas by modulation of gap junctional communication. However, the exact cellular mechanism behind those pharmaceutical efficacies on Cx43 still remains unknown. Hereby, targeting Cx43 on astrocytes in gliomas is mainly discussed.

Keywords: Connexin43; Gap junctional intercellular communication; Glioma; HSV-TK; Dexamethasone

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Although brain cancer only accounting for less than 2% of all neoplasias^[1], it is often lethal with survival rate less than 1 year after diagnosis. Surgery and chemo/radio therapy available are only palliative treatments which cannot cure this disease. Astrocytomas, the most prominent form of glioma, are the most common neoplasia of the central nervous system (CNS) in adults^[2].

Gap junctional intercellular communication (GJIC) built by hemichannels on cell membrane is a functional syncytium which allows rapid transfer of ions and molecules between cells. Recent findings have shown that gap junctions, and specifically Cx43^[3], can play a significant role in cell migration, tissue formation and organ development, impacting adhesion and cytoskeletal rearrangements. Although Cx43 expression is very heterogeneous in glioma,

most of the studies indicate that it is less expressed in glioma than normal tissue and even less with higher glioma grade^[4]. Some literatures have shown that Cx43 was able to contribute to the treatment of gliomas by modulation of gap junctional communication^[5,6,7]. Therefore, Cx43 modulations can be a promising way for treating of glioma.

HSVTK/GCV anticancer gene therapy

Herpes simplex virus thymidine kinase (HSVTK)-transduced neoplastic cells were killed when treated with ganciclovir (GCV)^[8]. However, "it was noticed that the neighboring cells that were not induced by HSV-TK were also killed after GCV therapy in animal experimental models"^[9,10]. This "bystander effect" can be explained as certain toxic metabolites were transferred through GJIC,

supported by several *in vitro* studies. For example, GJIC in C6 cells was normally low and largely increased when transfected with Cx43, accompanied with higher bystander cell death^[11]. Another study^[12] show that “the efficacy of bystander cell death was mostly dependent on the Cx43 expression of the non TK-transduced cells rather than the infected cells”, which suggested that higher GJIC could enhance the bystander effect. These findings imply that Cx43 expression in glioma cells may contribute to the HSV-TK treatment.

T-cell protein tyrosine phosphatase (TC-PTP)

Many studies have shown that Cx43 could act as a tumor suppressor gene. Zhang *et al.*^[13] investigating C6 cells transfected with Cx43 and clearly found that the channel permeability were mediated by C-terminal of Cx43, TC-PTP directly interacted with carboxyl terminus of Cx43^[8], which might eventually lead to methods to modulate the regulation of gap junction channels, with potential benefits.

Dexamethasone (DEX)

DEX is commonly used to reduce edema and inflammation for glioma patients as a symptomatic therapy^[14], and might achieve increased Cx43 and consequently bystander effect^[15,16]. Hinkerohe *et al.*^[17] found that DEX decreases both functional GJIC and Cx43 protein expression in C6 cell line. The application of DEX on three different cell lines reduced the bystander effect of HSV-TK gene therapy, as well as GJIC and sensitivity of tranfected cells to ganciclovir. It implies that DEX administration in glioma could have a negative impact on glioma treatment and further research may be needed.

Sodium valproate (VPA)

VPA is commonly used to treat seizures but it has been found to be histone deacetylase inhibitor (HDAC)^[18]. It has been documented that HDACs can modulate Cx43 in glioma cell lines. Ryu *et al.*^[19] showed that the expression of both Cx43 and Cx26 was increased by VPA treatment in HSV-TK gene therapy in U87 human glioma cells. However, Van Breemen *et al.*^[20] found no correlation between VPA use and survival rate while in Guthrie's study. The controversy in those findings might be explained by different Cx43 expressions in tumor cells or the stage of tumor.

All mentioned therapies evaluated in the above studies focused on the role of Cxs in homocellular population. However, the role of heterojunctional coupling between

astrocyte and glioma cells should be taken into account aslo^[21]. Since both glioma and astrocytes share similar Cxs which may allow them to communicate through membranes and transfer metabolites and certain molecules^[22]. “The transfer of such molecules or metabolites can be either beneficial or detrimental to cell proliferations of both glioma cells and astrocytes”^[23]. Therefore, it would be better to find Cxs specific drugs which could have selective effect on glioma cells and astrocytes. As to today, Cx43 modulations have not shown a clear advantage in glioma treatment by in favor of both astrocyte survival and tumor cell eradication. Future experiments should focus on Cxs in homocellular population during studying the mechanism of gap junctional intercellular communication in astrocytes and glioma cells.

Conflict of interests

The authors have declared that no conflict of interests exists.

References

1. Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001;2: 533-543.
2. Louis DN. Molecular pathology of malignant gliomas. *Annu Rev Pathol* 2006; 97-117.
3. Dermietzel R, Spray DC. Gap junctions in the brain: where, what type, how many and why? *Trends Neurosci* 1993; 16:186-192.
4. Rong Y, Durden DL, Van Meir EG, Brat DJ. ‘Pseudopalisading’ necrosis in glioblastoma: a familiar morphologic feature that links vascular pathology, hypoxia, and angiogenesis. *J Neuropathol Exp Neurol* 2006; 65:529-539.
5. Asklund T, Appelskog IB, Ammerpohl O, Ekström TJ, Almqvist PM. Histone deacetylase inhibitor 4-phenylbutyrate modulates glial fibrillary acidic protein and connexin 43 expression, and enhances gap-junction communication, in human glioblastoma cells. *Eur J Cancer* 2004; 40:1073-1081.
6. Bates DC, Sin WC, Aftab Q, Naus CC. Connexin43 enhances glioma invasion by a mechanism involving the carboxy terminus. *Glia* 2007; 55:1554-1564.
7. Brand-Schieber E, Werner P, Iacobas DA, Iacobas S, Beelitz M, Lowery SL, *et al.* Connexin43, the major gap junction protein of astrocytes, is down-regulated in inflamed white matter in an animal model of multiple sclerosis. *J Neurosci Res* 2005;80:798-808.
8. Li H, Spagnol G. TC-PTP directly interacts with connexin43 to regulate gap junction intercellular communication. *J Cell Sci* 2014;127:3269-3279.
9. Leten C, Trekker J. Monitoring the Bystander Killing Effect of Human Multipotent Stem Cells for Treatment of Malignant Brain Tumors. *Stem Cells Int* 2016; 4095072.
10. Moolten FL, Wells JM. Curability of tumors bearing herpes thymidine kinase genes transferred by retroviral vectors. *J Natl Cancer Inst* 1990; 82: 297-300.

11. Touraine RL, Vahanian N, Ramsey WJ, Blaese RM. Enhancement of the herpes simplex virus thymidine kinase/ganciclovir bystander effect and its antitumor efficacy in vivo by pharmacologic manipulation of gap junctions. *Hum Gene Ther* 1998;9:2385-2391.
12. Robe PA, Princen F, Martin D, Malgrange B, Stevenaert A, Moonen G, et al. Pharmacological modulation of the bystander effect in the herpes simplex virus thymidine kinase/ganciclovir gene therapy system: effects of dibutyl adenosine 3',5'-cyclic monophosphate, alpha-glycyrrhetic acid, and cytosine arabinoside. *Biochem Pharmacol* 2000; 60:241-249.
13. Zhang YW, Kaneda M, Morita I. The gap junction-independent tumor-suppressing effect of connexin 43. *J Biol Chem* 2003; 278:44852-44856.
14. Wong ET, Lok E, Gautam S, Swanson KD. Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma. *Br J Cancer*. 2015;113:232-241.
15. Zhuo YH, He Y. Dexamethasone disrupts intercellular junction formation and cytoskeleton organization in human trabecular meshwork cells. *Mol Vis*. 2010;16:61-71.
16. Robe PA, Nguyen-Khac M. Dexamethasone inhibits the HSV-tk/ganciclovir bystander effect in malignant glioma cells. *BMC Cancer* 2005;5:32.
17. Hinkerohe D, Wolfkuhler D. Dexamethasone differentially regulates functional membrane properties in glioma cell lines and primary astrocytes in vitro. *J Neurooncol* 2011;103: 479-489.
18. Rempel E, Hoelting L. A transcriptome-based classifier to identify developmental toxicants by stem cell testing: design, validation and optimization for histone deacetylase inhibitors. *Arch Toxicol* 2015;89:1599-1618.
19. Ryu CH, Park KY, Kim SM, Jeong CH, Woo JS, Hou Y, et al. Valproic acid enhances anti-tumor effect of mesenchymal stem cell mediated HSV-TK gene therapy in intracranial glioma. *Biochem Biophys Res Commun* 2012;421:585-590.
20. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurol* 2007;6: 421-430.
21. Roxane Oliveira, Christo Christov, Jean S'ebastien Guillamo, Sophie De Bo'uard, St'ephane Palfi, Laurent Venance, et al. Contribution of gap junctional communication between tumor cells and astroglia to the invasion of the brain parenchyma by human glioblastomas. *BMC Cell Biol* 2005;6:7.
22. Lin Q, Balasubramanian K. Reactive astrocytes protect melanoma cells from chemotherapy by sequestering intracellular calcium through gap junction communication channels. *Neoplasia* 2010;12:748-754.
23. Zahra Moifar, Hannes Dambach, Pedro M. Faustmann. Influence of drugs on gap junctions in glioma cell lines and primary astrocytes in vitro. *Front Phys* 2014;5:1-10.