

Connexin 43 (Cx43)

Connexin 43 (Cx43), a protein that forms [gap junction channels](#) and hemichannels in [astrocytes](#).

Gap junction alpha-1 protein (GJA1), also known as [connexin 43 \(Cx43\)](#), is a protein that in humans is encoded by the [GJA1](#) gene on [chromosome 6](#).

As a connexin, GJA1 is a component of gap junctions, which allow for gap junction intercellular communication (GJIC) between cells to regulate cell death, proliferation, and differentiation.

As a result of its function, GJA1 is implicated in many biological processes, including muscle contraction, embryonic development, inflammation, and spermatogenesis, as well as diseases, including oculodentodigital dysplasia (ODDD), heart malformations, and cancers.

Yang et al. aimed to explore the role of connexin 43 on exosomal uptake and [angiogenesis](#) in glioma under hypoxia. [U251](#) cells were exposed to 3% oxygen to achieve hypoxia, and the expression levels of HIF-1 α and Cx43, involved in the colony formation and proliferation of cells were assessed. Exosomes were isolated by differential velocity centrifugation from U251 cells under normoxia and hypoxia (Nor-Exos and Hypo-Exos), respectively. Immunofluorescence staining, along with assays for CCK-8, tube formation, and wound healing along with a transwell assay were conducted to profile exosomal uptake, proliferation, tube formation, migration, and invasion of HUVECs, respectively. Our results revealed that Hypoxia significantly up-regulated the expression of HIF-1 α in U251 cells as well as promoting proliferation and colony number. Hypoxia also increased the level of Cx43 in U251 cells and in the exosomes secreted. The uptake of Dio-stained Hypo-Exos by HUVECs was greater than that of Nor-Exos, and inhibition of Cx43 by 37,43gap27 or lenti-Cx43-shRNA efficiently prevented the uptake of Hypo-Exos by recipient endothelial cells. In addition, the proliferation and total loops of HUVECs were remarkably increased at 24 h, 48 h, and 10 h after Hypo-Exos, respectively. Notably, 37,43gap27, a specific Cx-mimetic peptide blocker of Cx37 and Cx43, efficiently alleviated Hypo-Exos-induced proliferation and tube formation by HUVECs. Finally, 37,43gap27 also significantly attenuated Hypo-Exos-induced migration and invasion of HUVECs. These findings demonstrate that exosomal Cx43 contributes to [glioma angiogenesis](#) mediated by Hypo-Exos, and suggest that exosomal Cx43 might serve as a potential therapeutic target for glioblastoma ¹⁾.

[Astrocytes](#) are crucial in neural [protection](#) after [traumatic brain injury](#) (TBI), a global health problem causing severe [brain tissue](#) damage. Astrocytic [connexin 43 \(Cx43\)](#), encoded by the [GJA1](#) gene, has been demonstrated to facilitate the protection of astrocytes to neural damage with unclear mechanisms.

A study aimed to explore the role of the GJA1-20K/Cx43 axis in the astrocyte-neuron interaction after TBI and the underlying mechanisms. Primarily cultured cortical neurons isolated from embryonic C57BL/6 mice were treated by compressed nitrogen-oxygen mixed gas to simulate TBI-like damage in vitro. The transwell astrocyte-neuron co-culture system was constructed to recapitulate the interaction between the two cell types. Quantitative PCR was applied to analyze the mRNA level of target genes. Western blot and immunofluorescence were conducted to detect target protein expression. GJA1-20K overexpression significantly down-regulated the expression of phosphorylated Cx43 (p-Cx43) without affecting the total Cx43 protein level. Besides, GJA1-20K overexpression

obviously enhanced the dendrite length, as well as the expression levels of function and synthesis-related factors of mitochondria in damaged neurons. GJA1-20K up-regulated functional Cx43 expression in astrocytes, which promoted mitochondria transmission from astrocytes to neurons which might be responsible for the protection of astrocyte to neurons after TBI-like damage in vitro ²⁾.

Small Interference RNA Targeting Connexin-43 Improves Motor Function and Limits Astrogliosis After Juvenile Traumatic Brain Injury ³⁾.

It is downregulated in high-grade gliomas. Its relevance for glioma therapy has been thoroughly explored; however, its positive effects on proliferation are counterbalanced by its effects on migration and invasion. Here, we show that a cell-penetrating peptide based on CX43 (TAT-Cx43266-283) inhibited c-Src and focal adhesion kinase (FAK) and upregulated phosphatase and tensin homolog in glioma stem cells (GSCs) derived from patients. Consequently, TAT-Cx43266-283 reduced GSC motility, as analyzed by time-lapse microscopy, and strongly reduced their invasive ability. Interestingly, we investigated the effects of TAT-Cx43266-283 on freshly removed surgical specimens as undissociated glioblastoma blocks, which revealed a dramatic reduction in the growth, migration, and survival of these cells. In conclusion, a region of CX43 (amino acids 266-283) exerts an important anti-tumor effect in patient-derived glioblastoma models that includes impairment of GSC migration and invasion ⁴⁾.

Human and mouse breast and lung cancer cells express [protocadherin 7](#) (PCDH7), which promotes the assembly of carcinoma-astrocyte gap junctions composed of [connexin 43](#) (Cx43). Once engaged with the astrocyte gap-junctional network, brain metastatic cancer cells use these channels to transfer the second messenger [cGAMP](#) to astrocytes, activating the [STING](#) pathway and production of inflammatory cytokines such as interferon- α (IFN α) and [tumor necrosis factor](#) (TNF). As paracrine signals, these factors activate the STAT1 and NF- κ B pathways in brain metastatic cells, thereby supporting tumour growth and chemoresistance. The orally bioavailable modulators of gap junctions [meclofenamate](#) and [tonabersat](#) break this paracrine loop, and we provide proof-of-principle that these drugs could be used to treat established brain metastases ⁵⁾.

Hypotrichosis with keratosis follicular and hyperostosis: a new phenotype due to GJA1 mutation ⁶⁾.

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Yang ZJ, Bi QC, Gan LJ, Zhang LL, Wei MJ, Hong T, Liu R, Qiu CL, Han XJ, Jiang LP. Exosomes Derived from Glioma Cells under Hypoxia Promote Angiogenesis through Up-regulated Exosomal Connexin 43. *Int J Med Sci.* 2022 Jul 4;19(7):1205-1215. doi: 10.7150/ijms.71912. PMID: 35919821; PMCID: PMC9339413.

²⁾

Ren D, Zheng P, Zou S, Gong Y, Wang Y, Duan J, Deng J, Chen H, Feng J, Zhong C, Chen W. [GJA1-20K](#) Enhances [Mitochondria](#) Transfer from [Astrocytes](#) to [Neurons](#) via [Cx43](#)-TnTs After [Traumatic Brain Injury](#). *Cell Mol Neurobiol.* 2021 Mar 16. doi: 10.1007/s10571-021-01070-x. Epub ahead of print. PMID: 33728536.

³⁾

Ichkova A, Fukuda AM, Nishiyama N, Paris G, Obenaus A, Badaut J. Small Interference RNA Targeting

Connexin-43 Improves Motor Function and Limits Astroglia After Juvenile Traumatic Brain Injury. ASN Neuro. 2019 Jan-Dec;11:1759091419847090. doi: 10.1177/1759091419847090. PubMed PMID: 31194577.

4)

Jaraíz-Rodríguez M, Tabernero MD, González-Tablas M, Otero A, Orfao A, Medina JM, Tabernero A. A Short Region of Connexin43 Reduces Human Glioma Stem Cell Migration, Invasion, and Survival through Src, PTEN, and FAK. Stem Cell Reports. 2017 Jul 3. pii: S2213-6711(17)30270-9. doi: 10.1016/j.stemcr.2017.06.007. [Epub ahead of print] PubMed PMID: 28712848.

5)

Chen Q, Boire A, Jin X, Valiente M, Er EE, Lopez-Soto A, Jacob LS, Patwa R, Shah H, Xu K, Cross JR, Massagué J. Carcinoma-astrocyte gap junctions promote brain metastases by cGAMP transfer. Nature. 2016 May 18;533(7604):493-8. doi: 10.1038/nature18268. PubMed PMID: 27225120; PubMed Central PMCID: PMC5021195.

6)

Bursztejn AC, Magdelaine C, Mortemousque B, Zerah M, Schmutz JL, Leheup B. Hypotrichosis with keratosis follicular and hyperostosis: a new phenotype due to GJA1 mutation. J Eur Acad Dermatol Venereol. 2019 Feb 27. doi: 10.1111/jdv.15405. [Epub ahead of print] PubMed PMID: 30811667.

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