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Commentary

Connexin 43 peptidic medicine for glioblastoma stem cells

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The role of connexin 43 (Cx43) in glioblastoma (GBM) is perplexing, making it difficult to develop Cx43-based therapies to treat this deadly brain cancer. For instance, Cx43 has long been considered as a tumor suppressor in glioma, because Cx43, as a gap junction (GJ) protein, forms membrane channels to enhance cell-cell communication, which suppresses the formation of glioma [1]. Indeed, reduced GJ intercellular communication (GJIC) is a hallmark of cancer [2]. However, recent research—that highlights the importance of Cx43 in intertumoral and intratumoral heterogeneity in GBM—has challenged this model. A side population of GBM cells, called GBM stem cells (GSCs), has displayed considerably different traits compared to other GBM cells, one of which is the unusually strong ability to propagate a tumor in mice [3]. This helps explain why GBM patients often succumb to a progressive and recurrent disease because GSCs, spared by surgical resection, radiation, and chemotherapy, can grow another tumor in the brain. Eliminating GSCs is therefore an appealing therapeutic approach; however, targeting GSCs is challenging given their idiosyncratic nature that makes GSCs metabolically resilient compared to differentiated tumor cells and endows GSCs survival advantages particularly under unfavorable growth conditions. Recent research from Pelaz and her colleagues has provided possible answers to this challenge and offered a new therapeutic opportunity that allows us to eliminate dormant and resilient GSCs [4].

This research stems from the finding from the Tabernero laboratory that Cx43's carboxyl terminus (CT), located inside of cells, activates SRC proto-oncogene, non-receptor tyrosine kinase (c-SRC) in patient-derived GSCs [5]. The activation of c-SRC subsequently promotes the motility, growth, and tumorigenicity of GSCs in vitro and in vivo [6]. Given that c-SRC plays a vital role in regulating metabolism in cancer, Pelaz et al., tested the hypothesis that Cx43-CT regulates GSCs' metabolic activity [4]. By treating GSCs with TAT-$Cx43_{266-283}$, a Cx43 CT-mimetic peptide that inactivates c-SRC [6], they have demonstrated that TAT-$Cx43_{266-283}$ decreases the hexokinase-dependent/glucose transporter-independent uptake of glucose and induces a temporal and spatial change of mitochondria localization and function. Expected from these observations, TAT-$Cx43_{266-283}$ reduces the metabolic adaptability and plasticity in GSCs, thereby disabling these malignant stem cells from surviving in nutrient-limiting conditions (e.g. low glucose or amino acids), a key characteristic of GSCs that contributes to GBM progression. This finding is important because, as described above, dormant GSCs are expected to be more resistant to current therapies and the culprit of GBM recurrence, a progressive disease that leads to the low rate of 5-year survival in GBM. More critically, TAT-$Cx43_{266-283}$ does not change the metabolic activity of differentiated GBM cells, astrocytes, and neural stem cells, which makes this Cx43-mimetic peptide an appealing drug target.

Peptidomimetics of Cx43-CT have attracted attentions from different researchers given the multifaceted functions of Cx43 [7]. For instance, the juxamembrane2 (JM2) peptide (231-VFFKGVKDRVKGRSD-245) that encompasses a microtubule-binding site (KGVKDRVK) located at the Cx43-CT enhances the binding between microtubules and Cx43 and decreases the ATP-releasing activity of Cx43 hemichannels and GJs in endothelial cells; as such, JM2 negates the innate immune response during inflammation. Recently, this Cx43-mimetic peptide has been found to disrupt microtubule dynamics in GSCs and suppresses GSCs' survival [8]. Another well-studied Cx43-CT mimetic peptide αCT1 comprises of nine amino acids (RPRPDDLEI) at the very end of Cx43-CT, which binds to zona occludens-1 (ZO-1), a well-known tumor suppressor. Intriguingly, this peptide inhibitor blocks Cx43 hemichannel activity, while enhancing GJIC. Moreover, αCT1 selectively inactivates phosphoinositide 3-kinase catalytic subunit β (PIK3CB, also called PI3Kβ or p110β) in temozolomide-resistant GSCs [9] and a combination of αCT1 and temozolomide obstructs the self-renewal and tumorigenicity of GSCs [10]. In line with the results of TAT-$Cx43_{266-283}$ in GSCs described above [4, 5], Cx43-CT is vital to GSCs. Because JM2 and αCT1 exhibit negligible toxicity to normal neural stem cells, same as TAT-$Cx43_{266-283}$ [8-10], targeting Cx43-CT represents a powerful and feasible therapeutic approach for selectively eliminating GSCs. Among these Cx43-CT mimetic peptides, only TAT-$Cx43_{266-283}$ targets metabolic plasticity in GSCs, making this peptide even more important in the development of effective therapeutics to slow down or prevent GBM progression associated with dormant and resilient GSCs.

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Whist Pelaz and her colleagues have uncovered how TAT-$Cx43_{266-283}$ alters metabolic adaptation in dormant GSCs, it remains elusive whether this activity depends on Cx43-formed hemichannels or GJIC or whether TAT-$Cx43_{266-283}$ inactivates c-SRC independent of Cx43-channels. Addressing these questions is important because it necessitates the use of Cx43 peptidomimetics, rather than GJ channel inhibitors which often have severe side effects, as cancer treatments. Other unaddressed questions that are also essential for using Cx43 peptidomimetics as cancer drugs include whether systemically delivered TAT-$Cx43_{266-283}$ induces any undesired immune responses, how stable TAT-$Cx43_{266-283}$ is in the blood stream and brain, and how to overcome blood-brain barrier to effectively deliver TAT-$Cx43_{266-283}$ into the brain. Future research on Cx43 peptidic medicine should focus on answering aforementioned questions and converting previously identified Cx43 therapeutic peptides into effective cancer medicine.

Contributors

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Declaration of Competing Interests

Dr. Sheng has no conflicts of interest to disclose.

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