Molecular Therapy
Oncolytics
Commentary

Sodium iodide symporter-targeted gene therapy in glioblastoma

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https://doi.org/10.1016/j.omto.2022.12.004

Sodium iodide symporter (NIS) gene transfer for active accumulation of radioactive iodide (or alternative radionuclides) in tumor cells is a powerful theranostic strategy allowing for both diagnostic and therapeutic applications. In the current issue of *Molecular Therapy – Oncolytics*, Spellerberg et al.[1] designed NIS plasmid DNA polyplexes containing targeting ligands for the transferrin receptor (TfR) and the epidermal growth factor receptor (EGFR) in order to improve active transport across the blood-brain barrier, followed by targeting of glioblastoma cancer cells, an aggressive and therapeutically challenging brain tumor.[2]

NIS is an intrinsic plasma membrane glycoprotein that mediates active iodide transport into the thyroid follicular cells for thyroid hormonogenesis.[3] Remarkably, for more than 80 years, the ability of the thyroid follicular cell to accumulate iodide constitutes the cornerstone for diagnostic scintigraphy and ^{131}I-iodide therapy for differentiated thyroid carcinoma and their metastases after thyroidectomy.[4] In addition to iodide, NIS translocates other clinically relevant radionuclides, including ^{99m}Tc-pertechnectate and ^{18}F-tetrafluoroborate, which facilitate non-invasive diagnostic imaging, and ^{188}Re-perrhenate, which allows therapeutic destruction of tumor tissue through the radionuclide accumulation in NIS-expressing cells.

Polymeric nanoparticles are ideal candidates for drug delivery based on their flexible composition, allowing them to be tailored for precision medicine applications.[5] In this study, Spellerberg et al. generated nanosized polyplexes complexing a cytomegalovirus-driven NIS expression vector with sequence-defined cationic lipo-oligoaminoamides, followed by masking and surface functionalization by the addition of peptides for targeting purposes (the GE11 and TfRre peptides for EGFR and TfRre targeting, respectively). The cancer genome atlas database indicates that EGFR mRNA expression is frequently upregulated in glioblastomas. Previously, Spellerberg et al.[6] demonstrated successful EGFR-targeted systemic polyplex-mediated NIS gene therapy in glioblastoma.

A major challenge in glioblastoma targeting is the blood-brain barrier, which limits the effectiveness of systemic therapies. Receptor-mediated transcytosis emerged as an effective pathway to deliver therapeutic drugs to the brain.[7] Brain endothelial cells express the TfR to provide transferrin-conjugated iron to the brain. In the current paper, Spellerberg et al. demonstrated that TfRre peptide-functionalized NIS polyplexes are endocytosed in TfR-expressing cells, thereby leading to significant radioiodide accumulation. Moreover, the authors assessed functional NIS expression in intracranial orthotopic U87 glioblastoma cell line-derived xenografts after systemic injection of targeted polyplexes using high-resolution positron emission tomography imaging with an ^{18}F-tetrafluoroborate radiotracer. Quantitative analysis revealed that the group that received GE11-TfRre/NIS polyplexes showed higher ^{18}F-tetrafluoroborate uptake compared with those injected with GE11/NIS polyplexes. As a result, therapeutic ^{131}I-iodide administration caused a significant delay in tumor growth resulting in a significant extension of survival of mice treated with GE11-TfRre/NIS polyplexes. However, ^{131}I-iodide treatment only resulted in a non-significant increase in survival in mice injected with GE11-TfRre/NIS polyplexes over those treated with GE11/NIS polyplexes.

The authors conducted immunohistochemical analysis that demonstrated a higher number of NIS-positive cells in tumor sections of mice injected with GE11-TfRre/NIS polyplexes over those treated with GE11/NIS polyplexes. Off-target NIS expression was undetectable in non-tumoral tissues including the liver, spleen, kidney, and lung. However, NIS protein expression analysis revealed that the transfected protein was mostly expressed in the cytoplasm, suggesting a defective sorting to the plasma membrane. Recently, Castillo-Rivera et al.[8] revealed the relevance of the tumor microenvironment for successful NIS-based radioiodine therapy, as hypoxia impairs NIS expression at the plasma membrane. The metabolic characteristics of the tumor cell promote oxidative stress that may cause the oxidation of redox-sensitive NIS amino acids leading to functional inactivation of the protein due to intracellular retention. In line, the analysis of congenital iodide transport defects revealed that single amino acid substitutions render NIS expression intracellularly retained.[9] Dedicated experiments will therefore be required to uncover the molecular mechanisms underlying hypoxia-induced NIS intracellular retention.

Preclinical experimentation for cancer therapeutics hinges on the ability of the animal model system to recapitulate the local environment and characteristics of a human tumor. In the case of glioblastoma, great consideration must also be given to the blood-brain barrier within that model system. In patient tumors, intact areas of the blood-brain barrier usually coincide with areas of infiltrating tumor cells and highlights another challenge of treating this malignancy. The authors acknowledge that the U87 mouse model is widely used but that it

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has a relatively large degree of blood-brain barrier disruptions, which is not typical of many human glioblastomas.[10] There is no one optimal model system, but patient-derived xenograft, genetically engineered, and syngeneic mouse models all have attractive features for use in preclinical studies. Thus, future preclinical studies conducted in more reliable tumor models are highly awaited to further understand the potential of dual-targeted NIS polyplexes for glioblastoma gene therapy.

The dual-targeted NIS polyplexes presented in this study demonstrate potential as a novel gene therapy approach for glioblastoma treatment combining site-specific gene delivery in the brain tumor and the theranostic potential of NIS allowing molecular imaging and targeted radioiodide therapy. However, the article also highlights some of the challenges of NIS-based gene therapies, including ensuring that NIS is optimally expressed within the cancer cell plasma membrane and maximizing quantity and duration of radioiodine within the tumor cells to generate maximum therapeutic effect.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

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