Transferrin receptor

The transferrin receptor is a membrane glycoprotein whose only clearly defined function is to mediate cellular uptake of iron from a plasma glycoprotein, transferrin.

Glioblastoma (Glioblastoma) remains the most common and malignant tumor of the human central nervous system. Increasing evidence has highlighted that tumor cells with high transferrin receptor (TFRC) expression show advantages in growth.

Ferritin, the natural iron storage protein complex, self-assembles into a uniform cage-like structure. Human H-ferritin (HFn) has been shown to transverse the blood-brain barrier (BBB) by binding to transferrin receptor 1 (TfR1), which is abundant in endothelial cells and overexpressed in tumors, and enters cells via endocytosis. Ferritin is easily genetically modified with various functional molecules, justifying that it possesses great potential for development into a nanocarrier drug delivery system.

Long non-coding RNAs (lncRNAs) are related to glioma progression by mediating microRNAs (MicroRNAs). However, the underlying mechanism among TFRC, MicroRNA and lncRNA in Glioblastoma is limited.

Ma et al. identified a new lncRNA-induced signaling mechanism that regulates the transferrin receptor (TFRC) levels in Glioblastoma (Glioblastoma). The TFRC level was higher in glioma cell lines, and elevated TFRC expression promoted the proliferation and survival of glioma cells. Further study showed that hsa-miR-144a-3p bound to the 3'-UTR of TFRC mRNA and inhibited its expression, preventing the malignant properties of glioma cells, such as proliferation and survival. They also found that the lncRNA RP1-86C11.7 sponges hsa-miR-144-3p to suppress its protective role in glioma. RP1-86C11.7 overexpression in glioma cells elevated TFRC expression, increased the intracellular free iron level, and deteriorated oncogenicity, with a significant reduction in hsa-miR-144-3p. By contrast, silencing RP1-86C11.7 upregulated the hsa-miR-144-3p level, resulting in decreased TFRC expression and repressed glioma progression. However, the effect of silencing RP1-86C11.7 was reversed with simultaneous hsa-miR-144-3p inhibitor treatment: the TFRC level, intracellular iron level and proliferation in glioma cells increased. Mechanistically, this data indicated that RP1-86C11.7 exacerbates the malignant behavior of glioma through the hsa-miR-144-3p/TFRC axis. RP1-86C11.7 may be a potential biomarker or target to treat glioma in the future [1)].

A unique integrin α2β1-targeting H-ferritin (2D-HFn)-based drug delivery system was developed that highlights the feasibility of receptor-mediated transcytosis (RMT) for glioma tumor treatment. The integrin targeting α2β1 specificity was validated by biolayer interferometry in real-time monitoring and followed by cell binding, chemo-drug encapsulation stability studies. Compared with naïve HFn, 2D-HFn dramatically elevated not only doxorubicin (DOX) drug loading capacity (up to 458 drug molecules/protein cage) but also tumor-targeting capability after crossing BBB in an in vitro transcytosis assay (twofold) and an in vivo orthotopic glioma model. Most importantly, DOX-loaded 2D-HFn significantly suppressed subcutaneous and orthotopic U-87MG tumor progression; in particular, orthotopic glioma mice survived for more than 80 days.

This versatile nanoparticle has established a proof-of-concept platform to enable more accurate brain tumor targeting and precision treatment arrangements. Additionally, this unique RMT based ferritin

drug delivery technique would accelerate the clinical development of an innovative drug delivery strategy for central nervous system diseases with limited side effects in translational medicine [2)].

1)
Ma Q, Wang X, Li J. LncRNA RP1-86C11.7 exacerbates the glioma progression and oncogenicity by hsa-miR-144-3p/TFRC signaling. Transl Oncol. 2021 Sep 24;14(12):101215. doi: 10.1016/j.tranon.2021.101215. Epub ahead of print. PMID: 34571345.
2)
Huang CW, Chuang CP, Chen YJ, Wang HY, Lin JJ, Huang CY, Wei KC, Huang FT. Integrin α2β1-targeting ferritin nanocarrier traverses the blood-brain barrier for effective glioma chemotherapy. J Nanobiotechnology. 2021 Jun 13;19(1):180. doi: 10.1186/s12951-021-00925-1. PMID: 34120610; PMCID: PMC8201891.

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