Transcytosis

Transcytosis is a type of transcellular transport in which various macromolecules are transported across the interior of a cell. Macromolecules are captured in vesicles on one side of the cell, drawn across the cell, and ejected on the other side.

The blood-brain barrier (BBB) hinders therapeutic delivery to the central nervous system (CNS), thereby impeding the development of therapies for brain injury and disease. Receptor-mediated transcytosis (RMT) systems are a promising way to shuttle a targeted therapeutic into the brain.

Ye et al. developed and evaluated an RMT antibody-targeted liposomal system. A previously identified antibody, scFv46.1, that binds to the human and murine BBB and can pass through the murine BBB by transcytosis after intravenous injection was used to decorate the surface of liposomes. Using an in vitro BBB model, they demonstrated the cellular uptake of scFv46.1-modified liposomes (46.1-Lipo). Next, the biodistribution and brain uptake capacity of 46.1-targeted liposomes were assessed after intravenous administration. The results showed that 46.1-Lipo can lead to increased brain accumulation through targeting of the brain vasculature. Initial rate pharmacokinetic experiments and biodistribution analyses indicated that 46.1-Lipo loaded with pralidoxime exhibited a 10-fold increase in brain accumulation compared with a mock-targeted liposomal group, and this increased accumulation was brain-specific. These studies indicate the potential of this 46.1-Lipo system as a synthetic vehicle for the targeted transport of therapeutic molecules into the CNS [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)
Ye Z, Gastfriend BD, Umlauf BJ, Lynn DM, Shusta EV. Antibody-Targeted Liposomes for Enhanced Targeting of the Blood-Brain Barrier. Pharm Res. 2022 Feb 15. doi: 10.1007/s11095-022-03186-1. Epub ahead of print. PMID: 35169958.
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.