Folic Acid-Conjugated Brush Polymer

Over the past decades, evidence has consistently shown that treatment of central nervous system (CNS)-related disorders, including Alzheimer's disease, Parkinson's disease, stroke, multiple sclerosis, and brain cancer, is limited due to the presence of the blood-brain barrier (BBB). To assist with the development of new therapeutics, it is crucial to engineer a drug delivery system that can cross the BBB efficiently and reach target cells within the brain. In this study, we present a potentially efficient strategy for targeted brain delivery through utilization of folic acid (FA)-conjugated brush polymers, that specifically target the reduced folate carrier (RFC, SLC19A1) expressed on brain endothelial cells. Here, azide (N3)-decorated brush polymers were prepared in a straightforward manner coupling a heterotelechelic α-NH2, ω-N3-poly(2-ethyl-2-oxazoline) (NH2-PEtOx-N3) to N-acylated poly(amino ester) (NPAE)-based brushes. Strain-promoted azide-alkyne cycloaddition (SPAAC) 'click chemistry' with DBCO-folic acid (FA) yielded FA-brush polymers. Interestingly, while azide functionalization of the brush polymers dramatically reduced their association to brain microvascular endothelial cells (hCMEC/D3), the introduction of FA to azide led to a substantial accumulation of the brush polymers in hCMEC/D3 cells. The ability of the polymeric brush polymers to traverse the BBB was quantitatively assessed using different in vitro BBB models including static Transwell and microfluidic platforms. FA-brush polymers showed efficient transport across hCMEC/D3 cells in a manner dependent on FA composition, whereas nonfunctionalized brush polymers exhibited limited trafficking under the same conditions. Further, cellular uptake inhibition studies suggested that the interaction and transport pathway of FA-brush polymers across BBB relies on the RFC-mediated pathways. The potential application of the developed FA-brush polymers in brain cancer delivery was also investigated in a microfluidic model of BBB-glioblastoma. Brush polymers with more FA units successfully presented an enhanced accumulation into U-87 MG glioma cells following its BBB crossing, compared to controls. These results demonstrate that FA-modified brush polymers hold a great potential for more efficient delivery of future brain therapeutics [1)].

1)
Mazrad ZAI, Refaat A, Morrow JP, Voelcker NH, Nicolazzo JA, Leiske MN, Kempe K. Folic Acid-Conjugated Brush Polymers Show Enhanced Blood-Brain Barrier Crossing in Static and Dynamic In Vitro Models Toward Brain Cancer Targeting Therapy. ACS Biomater Sci Eng. 2024 Mar 31. doi: 10.1021/acsbiomaterials.3c01650. Epub ahead of print. PMID: 38556768.