Targeting Macromolecular Transport for Alzheimer's Therapy

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The intricate regulation of the blood-brain barrier (BBB) significantly impacts neurological processes, often playing a pivotal role in the pathogenesis of dementia and Alzheimer's disease (AD). Recent research has highlighted the key involvement of low-density lipoprotein receptor-related protein 1 (LRP1) in the clearance of amyloid-β (Aβ) and phosphorylated tau (p-tau) [1]. Dysfunctions in these processes, compounded by disruptions in the transcription factor NRF2, lead to chronic inflammation, synaptic dysfunction, and cognitive impairment in AD [2]. Building on these insights, we are exploring the intricate relationship between BBB dysfunction and AD, particularly focusing on the involvement of LRP1/syndapin-2 transcytosis in inflammation and cellular stress [3,4].

We have successfully manipulated BBB transport using LRP1-targeting polymersomes (POs). In an Alzheimer's mouse model, the administration of these POs led to a significant reduction in brain Aβ levels. Notably, the POs not only reinitiated the LRP1-mediated transport of misfolded proteins but also influenced several BBB markers, effectively counteracting the negative trends associated with Alzheimer's disease. The consequential impact on the cognitive decline of APP/PS1 animals was substantial. These results underscore the potential of leveraging multivalent nanoparticles to elevate LRP1 levels and proficiently eliminate Aβ from the brain. This approach demonstrates the scalability of drug design through the integration of multiple ligands into multivalent scaffolds. Additionally, the supramolecular nature of these structures introduces an additional dimension, enabling further functionalities. We have engineered biodegradable scaffolds derived from Krebs' cycle diacids, capable of transforming into bioactive compounds. These materials introduce an added therapeutic dimension, exhibiting promise as potent anti-inflammatory agents by enhancing antioxidative gene transcription and influencing the NRF2 pathway.

References

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