Nanoscale transport at the blood brain barrier: mechanism and therapy development

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The blood–brain barrier (BBB) is a highly specialized, dynamic interface that couples tight paracellular sealing with carefully regulated transcellular pathways. Rather than being uniformly impermeable, the BBB uses receptor-mediated transcytosis to move selected cargos across the brain endothelium. In this talk, I will discuss how nanoscale transport is organized by low-density lipoprotein receptor–related protein 1 (LRP1), how the F-BAR protein syndapin-2 (PACSIN2) stabilizes tubular carriers, and how multivalency and collective endocytosis can be harnessed to design therapeutic nanoparticles.

LRP1 is a key endothelial transporter for amyloid-β (Aβ) and other ligands, and its role in Aβ efflux and Alzheimer's disease (AD) pathogenesis has been established in both mechanistic reviews and in vivo models [1–2]. Recent work has shown that LRP1 does not traffic only via classical, round vesicles; instead, Aβ–LRP1 complexes can shuttle across the BBB through elongated, tubular carriers whose formation depends on a syndapin-2–driven curvature program [3, 4].

Syndapin-2 is an F-BAR–domain scaffold that senses and induces positive curvature and sculpts invaginations and tubules at the plasma membrane and along endocytic routes. Structural and cell-biological studies have shown that PACSIN/syndapin F-BAR domains can generate narrow tubules, constrictions, and caveolar or endosomal membrane remodeling [5]. In brain endothelium, syndapin-2 associates with LRP1-dependent Aβ transport, and its reduced expression with aging or AD-related stress correlates with impaired Aβ clearance [4].

A central theme of this presentation is that multivalency converts these molecular components into a collective endocytic system. Theory and simulations have shown that multivalent nanoparticles can be engineered to exhibit "super-selective" binding, where the fraction of bound particles switches sharply with receptor density, an effect arising from the combinatorics of many weak ligand–receptor bonds [6]. In our experiments, increasing ligand valency or tuning ligand spacing triggers the formation of syndapin-2–positive tubular carriers and significantly enhances LRP1-mediated transcytosis.

Finally, I will show how these mechanistic insights translate into a design framework for brain-targeted nanomedicines [7]. Multivalent, LRP1-engaging nanoparticles can be optimized to exploit tubular BBB carriers, increasing delivery of therapeutic payloads, such as Aβ modulators or neuroprotective agents, into the brain parenchyma while limiting off-target retention and degradation. By explicitly linking receptor biology, membrane curvature, and the physics of multivalent binding, this work outlines a rational route from nanoscale mechanisms to therapy development for neurodegenerative disease.

References

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