Controlling Cellular Trafficking by Nanoparticle Avidity: From Endocytosis to Transcytosis

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Drug delivery to the brain is hindered by the presence of the blood-brain barrier (BBB), which consists in specialised endothelial cells that line brain capillaries restricting movement of molecules from blood-to-brain. Nonetheless, brain endothelial cells (BECs) rely on endogenous transport mechanisms (such as, receptors) that allow certain molecules to transverse the BBB. By using Angiopep-2(AP2)-decorated pH-sensitive polymersomes, we previously demonstrated the ability to specifically target lipoprotein receptor-related protein-1 (LRP-1) at the surface of BECs, and trigger transcytosis allowing the delivery of macromolecules into the brain parenchyma [1]. Here, we explore the mechanism of transcytosis of the polymersomes as a function of the number of AP2 ligands (i.e., avidity) using an established *in vitro* BBB model as well as *in vivo*.

AP2-poly(oligo(ethylene glycol) methyl ether methacrylate)-block-poly((diisopropylamino) ethyl methacrylate) (POEGMA-PDPA) polymersomes showed binding to LRP-1 in BECs, and significantly higher levels of apparent permeability (2.5-folds) compared to unfunctionalised polymersomes. When decorated with different numbers of AP2 ligands (I = 16 to 82), the rate of transport across a bEnd3 monolayer is affected, with the highest efficiency observed for 16 AP2 per polymersome. At the density of I = 16, the overall affinity of the nanoparticle triggers transcytosis by the formation of tubular structures, as demonstrated by live cell imaging and molecular dynamic modelling simulations. Cellular trafficking of AP2 polymersomes, I = 16 and I = 82, illustrated that, depending on the number of ligands, polymersomes undergo distinct intracellular sorting in BECs. After a tail vein administration of the polymersomes, 3.82% of the injected dose was obtained in the brain for the polymersomes with I = 16 which is significantly higher than unfunctionalised polymersomes, I = 80 AP2-functionalised polymersomes and AP2.

Together, these results elucidate the impact of the density of AP2 ligands on the intracellular trafficking of POEGMA-PDPA polymersomes at BECs. Hence, our work offers a new insight into the mechanism of transcytosis that could be explored when engineering nanoparticles for drug delivery to the delivery.

References

[1] Xiaohe Tian, Sophie Nyberg, Paul S. Sharp, Jeppe Madsen, Nooshin Daneshpour, Steven P. Armes, Jason Berwick, Mimoun Azzouz, Pamela Shaw, N. Joan Abbot, Giuseppe Battaglia, *Scientific Reports*, **5** (2015), 11990.