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Intracellular and Transcellular Targeting of Nanocarriers in the Vasculature

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Extended Abstract

Apart from their activity, many factors govern the efficacy of therapeutic agents, including solubility in body fluids, circulation half-life, clearance, degradation, etc. Nano-scale drug delivery systems (drug nanocarriers) can be designed to modify these parameters and enhance the therapeutic efficacy of agents than otherwise would render suboptimal effects. Yet, even when these properties are improved, an additional requirement to achieving an efficient therapeutic outcome is the transport of drugs to sites of the body where their action is needed. In this regard, directing drugs or drug carriers to endothelial cells lining the vasculature is critically relevant since these cells represent an important target for intervention in a plethora of pathologies and they also pose a barrier hindering access of therapeutics to the underlining tissues. Our laboratory focuses on these aspects by targeting drug delivery systems to markers expressed on the surface of endothelial cells, capable of inducing endocytic transport. Addressing drug carriers to these markers facilitates intraendothelial uptake as well as transport between the circulation and tissues, which represents one of the greatest challenges to successful therapeutic interventions. These approaches are being optimized through mechanistic studies that aim at deciphering and optimizing key parameters governing the efficacy of transport of endothelial-targeted nanomedicines. Our results highlight that endothelial transport of drug carriers is subjected to a highly complex regulation, where not only extrinsic factors of carrier design are important, but also intrinsic factors related to the biological machinery and patho-physiological state rule the final outcome. These effects are influenced by cross-signaling between the endothelium and the surrounding tissue, modulation of the endocytic pathways involved, cellular mechanosensing elements, biophysical properties, etc. Importantly, some of these regulatory elements are altered in cells affected by various diseases, resulting in an unpredictable regulation of said transport. Novel drug delivery strategies based on combination targeting to different receptor and/or epitopes, as well as decoupling of receptor-targeting from the subjacent endocytic signaling, offer new means to overcome these obstacles. Altogether, our studies are beginning to highlight the relevance of the diverse biological parameters to which cells are subjected in the body and the impact on their capacity to transport drug carriers. Understanding such complex interactions will help guide design of meaningful and effective drug delivery systems into and across the endothelium.

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