Functionalized hybrid nanoparticles for glioblastoma targeting

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Effective drug delivery to the brain remains a major challenge due to the restrictive nature of the blood–brain barrier (BBB), which severely limits the penetration of therapeutic agents into the central nervous system. Strategies enabling selective brain targeting are therefore crucial to improve treatment outcomes in neurological diseases, including glioblastoma multiforme (GBM). GBM is the most common and aggressive primary brain tumor in adults, characterized by rapid progression, high recurrence rates, and resistance to standard therapy with Temozolomide (TMZ) [1]. Current treatments are limited by poor BBB penetration, systemic toxicity, and the rapid development of drug resistance, underscoring the need for advanced nanotechnology-based delivery systems. Hybrid lipid–polymer nanoparticles (HLPNs) have emerged as a promising platform, combining high drug encapsulation efficiency, controlled release, and surface functionalization for targeted delivery. Several ligands such as antibodies, gangliosides, peptides can be used to functionalize the nanomedicine surface and improve the brain targeting. Among them, tumor-penetrating peptides (TPPs) represent one of the most promising strategies. These short molecules, typically composed of fewer than 30 amino acids, preferentially accumulate within tumor tissues and can be exploited both for targeted therapy and diagnostic applications. Compared to other targeting agents, they offer several advantages, including superior tissue penetration compared to conventional antibodies, low-cost and straightforward synthesis, greater selectivity than small molecules such as aptamers, and lower immunogenic side-effects.
In particular, LinTT1, a linear derivative of the TT1 peptide, accumulates and penetrates tumors through a sequential targeting mechanism. Upon binding to its receptor p32, which is overexpressed on the surface of many tumor-associated and facilitate the extravasation, the peptide is cleaved by the serine protease urokinase-type plasminogen activator (uPA). This cleavage exposes the C-terminal CendR motif (AKRGAR in LinTT1), which interacts with Neuropilin-1 (NRP-1) that is aberrantly exposed on tumor cells [2]. The interaction with NRP-1 receptors promotes transcytosis and uptake, enabling the peptide and its associated nanoparticles to penetrate deeply into the tumor parenchyma. We developed LinTT1-functionalized HLPNs and evaluated their performance in vitro and in vivo. In vitro findings demonstrated an efficient multistep targeting of LinTT1-functionalized HLPNs and enhanced cytotoxic effect of TMZ-loaded functionalized nanoparticles than free drug. These results were further confirmed in vivo, demonstrating an improved brain penetration and deep delivery within the GBM parenchyma, highlighting this strategy as a promising precision nanomedicine approach for GBM therapy.

References

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