

Norepinephrine transporter-derived homing peptides enable rapid endocytosis of drug delivery nanovehicles into neuroblastoma cells.

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Artykuł

Streszczenie**Background:**

Currently, the diagnosis and treatment of neuroblastomas—the most frequent solid tumors in children—exploit the norepinephrine transporter (hNET) via radiolabeled norepinephrine analogs. We aim to develop a nanomedicine-based strategy towards precision therapy by targeting hNET cell-surface protein with hNET-derived homing peptides.

Results:

The peptides (seq. GASNGINAYL and SLWERLAYGI) were shown to bind high-resolution homology models of hNET in silico. In particular, one unique binding site has marked the sequence and structural similarities of both peptides, while most of the contribution to the interaction was attributed to the electrostatic energy of Asn and Arg (< -228 kJ/mol). The peptides were comprehensively characterized by computational and spectroscopic methods showing ~21% β -sheets/aggregation for GASNGINAYL and ~27% α -helix for SLWERLAYGI. After decorating 12-nm ferritin-based nanovehicles with cysteinated peptides, both peptides exhibited high potential for use in actively targeted neuroblastoma nanotherapy with exceptional in vitro biocompatibility and stability, showing minor yet distinct influences of the peptides on the global expression profiles. Upon binding to hNET with fast binding kinetics, GASNGINAYLC peptides enabled rapid endocytosis of ferritins into neuroblastoma cells, leading to apoptosis due to increased selective cytotoxicity of transported payload ellipticine. Peptide-coated nanovehicles significantly showed higher levels of early apoptosis after 6 h than non-coated nanovehicles (11% and 7.3%, respectively). Furthermore, targeting with the GASNGINAYLC peptide led to significantly higher degree of late apoptosis compared to the SLWERLAYGIC peptide (9.3% and 4.4%, respectively). These findings were supported by increased formation of reactive oxygen species, down-regulation of survivin and Bcl-2 and up-regulated p53.

Conclusion:

This novel homing nanovehicle employing GASNGINAYLC peptide was shown to induce rapid endocytosis of ellipticine-loaded ferritins into neuroblastoma cells in selective fashion and with successful payload. Future homing peptide development via lead optimization and functional analysis can pave the way towards efficient peptide-based active delivery of nanomedicines to neuroblastoma cells.

Słowa kluczowe

Homing peptide, Ferritin, Neuroblastoma, Norepinephrine transporter, Targeted therapy

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