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Biofunctionalization of Nanocarriers with Peptide Ligands for Targeted Drug Delivery in the Tumor Microenvironment: Mechanistic Insights and Therapeutic Potential

Ewa Kowalska, Mei Li, Antonio Russo, Rosa Pérez

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ABSTRACT

The emergence of biofunctionalized nanocarriers with peptide ligands offers a promising strategy for selective drug delivery within the tumor microenvironment (TME). The dynamic and heterogeneous nature of the TME presents challenges to conventional chemotherapy, necessitating the development of ligand-functionalized nanoparticles (NPs) that enhance tumor targeting, cellular uptake, and therapeutic efficacy. This research article explores the principles of nanocarrier biofunctionalization, peptide ligand selection, nanoparticle design strategies, and their impact on tumor-specific drug delivery. We discuss advancements in peptide-functionalized NPs, including liposomes, polymeric nanoparticles, and inorganic nanocarriers, along with their potential for clinical translation. Finally, we highlight challenges and future perspectives in peptide-mediated targeted cancer therapy.

INTRODUCTION:

Targeted drug delivery aims to enhance therapeutic efficacy while minimizing off-target effects, a critical challenge in cancer therapy. Nanocarriers functionalized with peptide ligands offer a sophisticated approach for tumor targeting due to their specificity in recognizing overexpressed receptors in the tumor microenvironment. Peptide-functionalized nanoparticles can penetrate tumor tissues, interact with cancer cells, and facilitate controlled drug release, leading to improved treatment outcomes. This section introduces the rationale behind peptide biofunctionalization and the need for tumor-targeted drug delivery systems.

Nanocarrier Biofunctionalization with Peptide Ligands

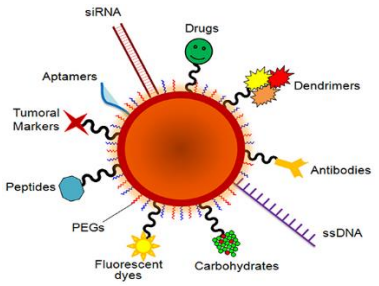

Fig.Nanocarrier Biofunctionalization

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The biofunctionalization of nanocarriers involves surface modification with targeting moieties, enabling enhanced specificity and binding to tumor-associated receptors. Peptide ligands are preferred due to their small size, high specificity, and low immunogenicity. Several strategies for biofunctionalization include:

- **Covalent conjugation:** Peptides are chemically linked to nanoparticle surfaces using carbodiimide chemistry or click chemistry.
- **Non-covalent functionalization:** Electrostatic interactions and hydrophobic forces allow peptide attachment without altering nanoparticle properties.
- **Self-assembly:** Peptides and nanoparticles co-assemble to form stable, functionalized delivery systems.

These methods enhance the targeting efficiency, biodistribution, and therapeutic potential of nanocarriers in tumor therapy.

Biofunctionalization Strategy	Mechanism	Advantages
Covalent Conjugation	Chemical bonding of peptides to NPs	Stable, long-lasting interaction
Non-Covalent Functionalization	Electrostatic/hydrophobic forces	Preserves peptide functionality
Self-Assembly	Spontaneous complex formation	Simple and scalable synthesis

Peptide Ligand Selection for Tumor Targeting

The success of peptide-functionalized nanocarriers depends on the careful selection of peptide ligands that recognize tumor-specific receptors. Common peptide ligands used for tumor targeting include:

- **RGD peptides** (Arg-Gly-Asp): Target integrin receptors overexpressed in tumor vasculature.
- **TAT peptides** (Transactivator of transcription): Enhance cellular uptake by interacting with heparan sulfate proteoglycans.
- **iRGD peptides** (Internalizing RGD): Mediate tumor penetration and intracellular drug delivery.
- **NGR peptides** (Asn-Gly-Arg): Bind to CD13 receptors in angiogenic tumor blood vessels.

Advancements in computational modeling and phage display technology have enabled the identification of novel tumor-homing peptides with enhanced affinity and stability, further improving the specificity of targeted drug delivery systems.

Nanoparticle Design Strategies for Peptide Functionalization

Different nanocarrier systems have been explored for peptide-mediated drug delivery in the TME, each with distinct properties:

- **Liposomes:** Biocompatible and capable of encapsulating both hydrophilic and hydrophobic drugs.
- **Polymeric Nanoparticles:** Provide controlled drug release and tunable surface properties.
- **Gold Nanoparticles:** Facilitate photothermal therapy and peptide-mediated targeting.
- **Silica-Based Nanoparticles:** Offer stability and high drug-loading capacity.

Each nanoparticle type presents advantages and limitations in terms of stability, drug-loading efficiency, and targeting capabilities, making them suitable for different therapeutic applications.

Nanoparticle Type	Properties	Advantages
Liposomes	Biocompatible, encapsulate diverse drugs	Long circulation time, enhanced permeability
Polymeric NPs	Biodegradable, controlled release	Tunable surface charge and stability
Gold NPs	Optical properties, functionalizable	Enables photothermal therapy
Silica NPs	High stability, porous structure	High drug-loading capacity

Peptide-Mediated Drug Delivery in the Tumor Microenvironment

The tumor microenvironment consists of hypoxic regions, acidic pH, and abnormal vasculature that influence drug delivery efficiency. Peptide-functionalized nanoparticles overcome these challenges by:

- Enhancing **tumor penetration** via receptor-mediated endocytosis.
- Promoting **controlled drug release** triggered by TME conditions (e.g., pH-responsive peptides).
- Reducing **off-target effects** by selectively binding tumor-associated receptors.

Recent in vivo studies have demonstrated the ability of peptide-functionalized nanocarriers to improve tumor accumulation and therapeutic efficacy, validating their potential for clinical applications.

Clinical Translation and Challenges

Despite promising preclinical success, several challenges must be addressed before peptide-functionalized nanocarriers achieve clinical translation:

- **Peptide stability:** Enzymatic degradation in the bloodstream limits in vivo efficacy.
- **Scalability:** Large-scale synthesis of peptide-functionalized NPs requires cost-effective manufacturing techniques.
- **Regulatory approval:** Safety and biocompatibility assessments must meet stringent regulatory standards.

Future advancements in peptide engineering, nanocarrier optimization, and clinical trial design

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will play a crucial role in overcoming these barriers and advancing peptide-functionalized drug delivery systems to clinical use.

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