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A Review of Self-Assembling Peptides in Medical Applications

Self-assembling peptides are a class of biomaterials capable of spontaneously forming ordered nanostructures through noncovalent interactions. Their molecular design is typically based on amphiphilicity, charge complementarity, or repeating sequence patterns. Under specific conditions, these peptides can form stable nanofibers, hydrogels, or more complex higher-order structures, exhibiting excellent biocompatibility, customizable biological activity, and good biodegradability. With these properties, self-assembling peptides have become important research tools and potential therapeutic agents in multiple cutting-edge medical fields, including regenerative medicine, drug delivery, anti-infection, and diagnostic imaging.

I. Applications as Three-Dimensional Scaffolds in Tissue Engineering and Regenerative Medicine

Self-assembled peptide hydrogels can highly mimic the physical and biochemical characteristics of natural extracellular matrices, providing an ideal three-dimensional microenvironment for cell growth and tissue

regeneration.

1. Central Nerve Regeneration

Following spinal cord injury or peripheral nerve defects, an inhibitory microenvironment and lack of physical guidance channels impede axonal regeneration. Nanofiber scaffolds formed by peptides such as RADA16 provide physical support for neural cell adhesion and axonal extension. Integrating functional peptide segments into the peptide sequence further confers biological activity. For instance, incorporating cell adhesion signals and neurotrophic factor mimetic sequences into the scaffold significantly promotes neural stem cell migration, differentiation, and functional axonal regeneration. Animal studies demonstrate that such functionalized peptide hydrogels effectively bridge rat spinal cord defects, promoting partial recovery of motor function.

2. Bone and Cartilage Repair

Repairing bone defects requires materials that combine robust mechanical support with osteogenic induction activity. By designing peptide sequences rich in negatively charged amino acids, bone matrix proteins can be mimicked to promote in situ hydroxyapatite mineralization and enhance the scaffold's osteoconductivity. Further integration of functional peptide segments, such as those derived from osteomorphin, endows the scaffold with bone-inductive capacity, activating endogenous stem cells to differentiate into osteoblasts. In articular cartilage repair, self-

assembled peptide gels provide chondrocytes with a chondro-like ECM environment, supporting proliferation and secretion of specific extracellular matrix components to promote the formation of hyaline cartilage-like tissue.

3. Angiogenesis

Constructing pre-vascularized tissue engineering grafts is crucial for addressing post-implantation ischemic necrosis. Self-assembling peptide hydrogels serve as co-culture scaffolds for endothelial cells and pericytes. Integrating pro-angiogenic peptide segments into the gel network effectively recruits endothelial cells and promotes their assembly into tubular structures. Such bioactive gels have demonstrated efficacy in myocardial infarction and chronic skin ulcer models by facilitating functional neovascular network formation, improving tissue perfusion, and accelerating repair.

II. Applications as Smart Carriers in Drug Delivery and Controlled Release

Self-assembling peptide nanostructures can load therapeutic molecules through encapsulation, conjugation, or electrostatic adsorption, enabling targeted, controlled release in response to the disease microenvironment.

1. Anticancer Drug Delivery

The tumor microenvironment exhibits characteristics such as weak acidity and high expression of specific proteases. Designing peptide

carriers responsive to these signals enables precise drug release. For example, inserting a Linker cleavable by matrix metalloproteinases into the self-assembling peptide sequence enables specific cleavage at the tumor site, causing the carrier to disassemble and release encapsulated chemotherapeutic drugs. Furthermore, modifying the surface of nanocarriers with peptides targeting tumor cells can further enhance delivery efficiency and reduce systemic toxicity.

2. Protein and Nucleic Acid Delivery

Biomacromolecules such as growth factors, antibodies, and siRNA are prone to inactivation and struggle to penetrate cellular barriers. Self-assembling peptides can protect these molecules by encapsulating them through electrostatic interactions or specific recognition. Some self-assembling peptides with transmembrane domains can also promote the endocytosis and endosomal escape of macromolecular cargo, significantly enhancing their intracellular bioavailability. This holds potential applications in fields like gene therapy and cellular reprogramming.

3. Long-Acting Sustained-Release Systems

By modulating peptide assembly kinetics and gel degradation rates, sustained drug release spanning weeks or even months can be achieved. For instance, injectable peptide hydrogels loaded with analgesic peptides or hormones have demonstrated promising sustained-release effects in preclinical studies. These systems hold promise as alternatives to

traditional formulations requiring frequent injections, thereby improving patient compliance.

III. Application as an Antimicrobial Agent in the Field of Infection Control

Multidrug-resistant bacterial infections have become a global public health crisis. Self-assembling peptides designed to mimic natural antimicrobial peptides exert their effects through unique physical membrane disruption mechanisms, making them less likely to induce bacterial resistance.

These amphiphilic peptides assemble upon contact with bacterial cell membranes, disrupting membrane integrity and leading to leakage of contents and bacterial death. Compared to traditional antibiotics, they exhibit rapid bactericidal activity and a broad antimicrobial spectrum. More importantly, the self-assembly strategy enables the formation of localized, high-concentration networks of peptide nanofibers that sustain antimicrobial activity. Such materials have been utilized in functional wound dressings, simultaneously eliminating pathogens while maintaining a moist environment to promote wound healing.

IV. Applications of Novel Probes in Diagnostic and Imaging Fields

The conformational changes and modifiable properties of self-assembling peptides make them suitable for constructing highly sensitive biosensors and molecular imaging probes.

1. Disease Biomarker Detection

Design peptide probes whose self-assembly behavior is regulated by specific molecules. For instance, when encountering target proteases or abnormal ion levels, the probe's assembly is triggered or inhibited, inducing significant changes in solution turbidity, fluorescence, or electrochemical signals to achieve highly sensitive biomarker detection.

2. Molecular Imaging

Integrating imaging elements with self-assembling peptides enables the construction of multimodal imaging probes. Examples include conjugating fluorescent groups, radionuclides, or magnetic nanoparticles to peptides. These probes assemble upon targeting diseased regions, achieving signal concentration and amplification. This significantly enhances imaging signal-to-noise ratios and contrast, enabling early, precise localization of tumors, thrombi, or inflammation.

V. Challenges Faced and Future Outlook

Despite promising prospects, the clinical translation of self-assembling peptides still faces challenges:

1. Long-term safety and immunogenicity: The long-term in vivo fate, degradation products, and potential immune responses of novel peptide materials require systematic evaluation.

2. Large-scale production and quality control: Achieving scalable, low-cost synthesis of complex functionalized peptides while ensuring their self-assembly behavior and batch-to-batch consistency of final products is

key to industrialization.

3. Standardization and Regulatory Pathways: As novel products bridging traditional drugs and medical devices, their evaluation criteria and regulatory frameworks are still evolving.

Future development will focus on:

1. Intelligent Design: Developing next-generation smart systems capable of responding to multiple biological signals and executing complex functions (e.g., sequential release of different drugs) according to predefined spatiotemporal logic.

2. Dynamic and Adaptive Materials: Design “living” materials capable of dynamic, bidirectional information exchange with host tissues to achieve superior integration and functional regeneration.

3. Personalized Therapy: Combine patient-specific biomarkers to tailor fully individualized self-assembling peptide treatment regimens.

VI. Conclusion

Self-assembling peptides demonstrate unprecedented breadth and depth of application in medicine by integrating fundamental principles of molecular self-assembly with precise biomedical requirements. Their functions extend far beyond traditional biomaterials—ranging from physical scaffolds for cell growth to intelligent drug delivery systems, from physical weapons against drug-resistant bacteria to highly sensitive diagnostic probes. Although numerous scientific and engineering

challenges remain on the path to widespread clinical adoption, deepening insights into “material-biosystem” interactions and strengthened interdisciplinary collaboration position self-assembling peptides to play a transformative role in future precision and regenerative medicine practices. They promise to deliver novel solutions for diagnosing and treating numerous intractable diseases.