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The application of supramolecular chemistry in biomedicine

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Abstract. Nowadays, with the development of the supramolecular chemistry theory, more and more products based on Supramolecular chemistry are applied in people's life. Due to the good hydrophobic/hydrophilic structure, biocompatibility, spontaneous self-assembly and other characteristics of supermolecules, these applications are particularly prominent in the field of biomedicine. In this paper, the research status, development trend and potential problems of supermolecular materials in the field of biomedicine will be reviewed from the aspects of peptide/polyamino acid self-assembled nanomaterials for cancer diagnosis and treatment and soybean protein drug carriers. The early diagnosis and treatment of tumors and the delivery of drugs have always been challenges in the medical field. However, with the dynamic, reversible and controllable characteristics of supermolecules, as well as their excellent biocompatibility, sequence controllability and high biological activity, people can develop imaging systems and drug carriers based on supermolecule theory to improve the diagnostic ability of certain diseases and the biological accessibility of certain drugs.

Keywords: supramolecular chemistry, self-assembly, tumor diagnosis and treatment, soy protein, drug carrier.

1. Introduction

The term Supermolecule was proposed as early as the mid-1930s, and the concept and term of Supramolecular chemistry were proposed in 1973 [1]. A supermolecule refers to a complex and organized aggregate, which is combined by two or more molecules by intermolecular interaction, and can maintain certain integrity, with clear microstructure and macro characteristics. Supramolecular chemistry mainly studies the interaction of non-covalent bonds between molecules, as well as the assembly, structure and function of molecular aggregates formed based on these forces. The driving forces for the formation of supermolecule structure include hydrogen bonds, coordinate covalent bonds, hydrophilic interactions, hydrophobic interactions and so on.

Supramolecular chemistry emphasizes the supermolecule system with specific structure and function, and makes the four basic chemistry become a whole [2]. Supramolecular chemistry is widely used. It plays a vital role in environmental science, information science, energy science, nano-science, material science, life science and some other fields. Therefore, the development prospect of supermolecule is very broad.

Supermolecule structure can be constructed by hydrogen bonding, π-π stacking, host guest recognition, coordination and other non-covalent bond self-assembly. Compared with the traditional amphiphile, these super amphiphilic supermolecules have the advantages of being dynamic, reversible and controllable, so they have broad application prospects in molecular recognition, drug delivery and molecular catalysis [3]. For example, due to the excellent biocompatibility, sequence controllability, and high biological activity of peptides/polyamino acid molecules, they can be used for biomedical diagnosis and treatment such as tumor diagnosis and treatment [4]; due to the excellent biocompatibility and processing characteristics of protein, it can be induced and self-assembled to form nanoparticles, serving as a nutrient carrier to solve the problem of instability of bioactive substances under physiological conditions [5].

This paper will introduce the technological development, characteristics, applications, and potential issues of peptide/amino acid self-assembled nanomaterials for the diagnosis and treatment of tumors and soybean protein drug carriers respectively.

2. Peptide/amino acid self-assembled nanomaterials for diagnosis and treatment of tumors

Peptides and polyamino acids are compounds with amino acid monomers connected by amide bonds, their chemical structures have high similarity and are widely used in the field of biomaterials. The synthetic method of peptides/polyamino acid molecules is relatively simple, with unique structural characteristics and inherent biological activity, gradually becoming a perfect building block for biomaterials and widely used in the field of tumor therapy.

2.1. Peptide/polyamino acid self-assembled nanomaterials

Similar to natural peptide self-assembly, artificially synthesized peptide/polyamino acid molecules can also rely on intramolecular/intermolecular interactions to aggregate and form micro/nano-structures [4]. Nowadays, scientists have developed various peptide/polyamino acid molecules with different functions. For example, Xu et al. used supermolecule hydrogel formed by polypeptide self-assembly as the matrix to seal heme, and prepared an artificial enzyme with a simpler structure than protein structure and higher oxidative reactivity [6].

The characteristics of different amino acids in terms of charge, hydrophobicity, and polarity enable peptides/polyamino acids to self-assemble into various structural and functional nanomaterials. The driving forces for peptide/polyamino acid self-assembly mainly include van der Waals forces, hydrophobic and hydrophilic interactions, hydrogen bonding, electrostatic interactions, π-π interactions, and metal coordination.

Linear peptides/polyamino acids are the most common type, and their synthetic techniques and self-assembly behavior have also been extensively studied. However, the flexible conformation of linear peptides in the liquid phase is difficult to meet the conformational requirements of some receptors. In order to obtain peptides with stable biological properties and high receptor selectivity, transforming linear peptides into cyclic peptides is one of the most widely used and effective methods [7]. Compared with linear polypeptides, cyclic peptides have more specific fixed conformation, can fit well with receptors, do not have free carboxyl and amino groups, and are less sensitive to aminopeptidase and carboxypeptidase [8].

2.2. Application of peptide/polyamino acid self-assembled Nanomaterials in cancer diagnosis and treatment

Cancer is currently one of the diseases that pose a threat to human life and health. Bioimaging technology can be used to diagnose and treat tumors in the early stages. By endowing peptide/polyamino acid self-assembled nanomaterials with new physical and chemical properties, they can be used as new contrast agents or targeted carriers to obtain high-resolution and high-contrast images [9]. Compared with traditional contrast agents, peptide/polyamino acid self-assembled materials can modify fluorescent molecules through side chains, making the obtained images easier to observe. They can also efficiently load different contrast agents, giving them the ability to target specific lesion areas and reducing the toxicity of traditional contrast agents.

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Fluorescence imaging is simple, flexible, and non-invasive, widely used in fields such as medical diagnosis and image-guided surgery. For example, inspired by the fluorescence redshift of yellow fluorescent protein (J-type π-π stacking effect) and the fluorescence enhancement phenomenon of blue fluorescent protein (metal coordination), Fan et al. designed and synthesized self-fluorescent peptide nanoparticles with good photostability, using Trp Phe dipeptide as the unit, and self-assembled them into nanoparticles through Zn2+coordination, benzene ring stacking, and hydrogen bonding interaction. By shifting its fluorescence wavelength from the non-visible ultraviolet region to the visible light region, specific cell imaging and real-time monitoring of drug release were achieved [10]. Wang et al. prepared near-infrared fluorescent peptide materials through in situ self-assembly, which exhibit tumor-specific excretion delayed (TER) effects in tumor lesions [11]. They can improve the imaging performance of kidney tumors and achieve complete resection of tumors, ultimately reducing postoperative recurrence. Compared to the control group, the mice injected with this peptide showed stronger fluorescence signals at the tumor site, demonstrating an ideal excretion delay effect. In addition, the imaging signal-to-noise ratio of this peptide is very high (it can still reach around 0.9 after 14 days). Chen et al. designed an enzyme-activated prodrug based on a peptide (Fmoc Gly Pro Leu Gly Leu), which cascades with the drug to inhibit tumor growth and further synergizes with MMP-9 to activate doxorubicin prodrugs (MMP9-DOX-NPs) to improve chemotherapy selectivity and reduce toxic side effects [12]. In the presence of MMP-9 synergy, the treatment effect is 5.5 times that in the absence of MMP-9.

2.3. Shortcomings and development trends of peptide/polyamino acid self-assembling nanomaterials

Peptide/polyamino acid molecules still have certain defects, such as poor optical properties, short half-life, and fast clearance rate [4]. In addition, the intracellular environment is complex. So it is a major challenge for researchers to adapt peptide/polyamino acid self-assembled nanomaterials to the physiological environment within cells and let them function normally. Nowadays, researchers are trying to find ways to avoid cell rejection reactions to peptide/polyamino acid self-assembled nanomaterials and involve peptide/polyamino acid self-assembled nanomaterials in more complex life activities.

3. Soybean protein drug carrier

Functional foods play a very prominent role in preventing chronic diseases and promoting physical and mental health. One of the simplest ways to develop functional foods with different health benefits is to add biologically active substances that are beneficial to health to the food. However, many bioactive substances have disadvantages such as low water solubility, poor stability, and low biological potency, which limit their use in functional food ingredients. Therefore, developing suitable carriers to transport these bioactive substances is currently a major research hotspot.

3.1. Curcumin

Curcumin is a kind of natural plant polyphenol with a ketone structure extracted from the rhizome of curcuma longa. For a long time, curcumin has been considered to have high medical value, such as anti-aging, anti-oxidation, anti-inflammatory, antimutagenic, anti-microbial and anti-cancer functions. However, under neutral and alkaline pH values, curcumin will degrade rapidly, causing the color of curcumin to change (from yellow to red) [13]. In addition, the bioavailability of curcumin is less than 1%, it is easy to mutate and degrade, and it is insoluble in water, which makes it difficult to extract, take and absorb curcumin. Therefore, many people believe that curcumin does not actually have nutritional value.

3.2. Soybean protein and its nanostructures

Soybean protein is an important plant protein that can serve as the main source of high-quality protein in the diet. It is composed of four major proteins: 2S, 7S, 11S, and 15S. Among them, the most important are 11S globulin and 7S β- Paraglobulin, which account for over 80% of the total protein content [5]. The 7S molecule is a trimer, composed of α Subunit, α' Subunit and β Subunit; 11S is a hexamer, with acidic subunit A and alkaline subunit B connected by electrostatic and hydrogen bonding to form two hexagonal rings, forming a hollow cylinder. 7S protein and 11S protein can transform into each other at a certain pH value and temperature.

As a plant protein, soybean protein can increase the total intake of dietary protein, reduce the intake of carbohydrates or fats, improve the proportion of nutrients consumed, and have extremely high nutritional value. The raw material of soybean protein is soybean, which has low production cost, can be well absorbed by organisms, and is easy to process. Therefore, it has gradually become a research hotspot in the field of the food industry.

In the food industry, soybean protein is an important functional component, which has a variety of functional properties, such as emulsification, foaming and gel formation [5]. Food-grade nanoparticles are easy to manipulate, and have large specific surface areas and stable structures within the size range. Therefore, they can be used to load bioactive ingredients and construct nutrient delivery system carriers [14]. Using soybean protein to construct nanostructures to carry some bioactive substances, can improve their biological accessibility and bioavailability.

3.3. *Soybean protein self-assembled drug carriers*

The formation process of soy protein self-assembly depends on the synergistic effect of non-covalent interaction between molecules, including hydrogen bonding, hydrophobic interaction, π - π stacking, electrostatic interaction and Van der Waals force [5].

Hydrogen bond is an important driving force for self-assembly to form supermolecule structure. Hydrogen bonds play an important role in the formation and stabilization of protein-protein secondary structure. Hydrogen bonds are directional and selective, so peptide self-assembly driven by hydrogen bonds can selectively form different nanostructures. Hydrophobic interaction is one of the main driving forces in the self-assembly process. When non-polar molecules enter the water (solvent), the hydrogen bond network is disrupted, and surrounding water molecules rearrange to form a cavity, causing non-polar molecules to undergo self-assembly. Hydrophobic interactions do not have directionality, and when only hydrophobic interactions exist during the self-assembly process, soybean proteins tend to self-assemble into micelles. The π - π interaction occurs between aromatic amino acids containing benzene rings, which are basically parallel or vertical, and are stabilized by the attraction of the Electron cloud between benzene rings, thus promoting the self-assembly of soybean protein. When charged ions exist during self-assembly, they can be driven by electrostatic interactions. The electrostatic interaction is formed by the Zwitterion between polypeptides through the coulomb force between opposite charges. Generally speaking, the stronger the polarity of the solvent, the stronger the electrostatic effect. Van der Waals force is relatively weak and generally has an effect only when the action area is very wide. Under the influence of different chemical environments and driving forces, soybean protein can self-assemble into different nanostructures, such as nanoparticles, nanofibers, nanotubes, micelles, etc.

Because of its good foaming and emulsifying properties, soybean protein is widely used as a stabilizer for foam and lotion in the food industry. Soybean protein is an amphiphilic biological macromolecule that can interact with solvents and bioactive compounds. Therefore, it is considered an ideal material for preparing nanoparticles. Soybean protein has hydrophobic amino acids that can self-assemble into nanoparticles through hydrophobic interactions. The driving force of this process is mainly hydrophobic interaction. Zhang et al. obtained soybean peptide aggregates (SPA) by hydrolyzing soybean protein isolate (SPI), which further self-assembled under the effect of ultrasound to obtain soybean peptide nanoparticles as the stabilizer of lotion. The prepared lotion has a thick interface layer and good stability, the self-assembled SPN is spherical with a small particle size (104.10 nm) and uniform particle size distribution (PDI~0.20) [15].

In the food industry, when researchers want to prepare hydrogels or drug delivery systems, protein fibrils are one of their best choices due to the high aspect ratio structure, good gel performance and interfacial adsorption of protein fibrils. The structure of protein fibril is affected by many factors, such as pH, Ionic strength, temperature, etc. [5]. Soybean protein isolate, which can be obtained while processing soybean protein, is rich in glutamic acid and Aspartic acid and has good conditions to form protein fibrils. The driving force of this process is mainly electrostatic interaction [5]. Ji et al. used soy protein isolate to form soy protein fibril (SPF), which can explore the structural changes of SPF under different Ionic strength and temperature conditions, improve the functional properties of soy protein fibril, and provide a theoretical basis for its application in the food system. The SPF formed at 80 ℃ is more flexible than it at 95 ℃. As the concentration of NaCl increases, the diameter of the SPF formed at 80 ℃ thickens, and at high salt concentrations (>80 mmol/L), the original fibers become entangled together. The transparent local gel of the raw fiber was observed at 95 ℃, giving it higher viscosity [16].

Nanotubes formed through non-covalent interactions have the advantages of easy synthesis, self-assembly, controllable diameter, and high efficiency. Usually, high aspect ratio tubular nanocarriers can generate more friction force, increase system viscosity, and have higher stability compared to other structured nanocarriers. The main driving force of this process is hydrophobic interaction.

The micelles formed by soybean protein self-assembly are an important nanocarrier that can encapsulate functional substances, improving their stability and bioavailability and are excellent carriers for hydrophobic active substances. Due to the edible and biodegradable nature of soybean protein, it is widely used as a matrix material for preparing micelles. The main driving force for the formation of micelles is hydrophobic interactions. Zhao et al. prepared Lycopene micelles by emulsification solvent evaporation method using soy protein isolate combined with sodium alginate, which can improve the antioxidation and stability of Lycopene, and has a good release effect and slow release capacity. The encapsulation efficiency of SPI-SA and SPI+SA Lycopene micelles for Lycopene can reach 90.1% and 90.3% respectively. After the preparation of Lycopene micelles, the antioxidant capacity of SPI+SA Lycopene micelles and SPI-SA Lycopene micelles increased by 16.0% and 53.0% respectively [17].

3.4. Factors affecting soybean protein self-assembly

The system temperature, pH value, and protein concentration all have an impact on the self-assembly of soybean protein molecules.

When the pH value of the protein solution is far from the pH value of globulin and the ionic strength is low, the charge carried by protein molecules cannot be effectively shielded by salt ions. At this time, electrostatic repulsion is dominant, and highly ordered self-assembled fibrous aggregation will occur, forming beaded linear aggregates. On the contrary, hydrophobic interactions dominate, leading to irregular and disorderly self-assembly, fibrosis, and aggregation, forming spherical aggregates.

3.5. The shortcomings and development trends of soybean protein drug carriers

In the process of soybean protein self-assembly to form nanoparticles, nanofibers, nanotubes, and micelles, the main driving forces are hydrophobic and electrostatic interactions, which have no directionality compared to hydrogen bonds. Therefore, the self-assembly products of soybean protein have a certain degree of randomness. The self-assembly ability of soybean protein is also influenced by other components. When soybean protein coexists with other food components such as polysaccharides, lipids, and other proteins, its self-assembly ability is affected. The use of soy protein drug carriers also needs to consider the groups allergic to soy products. When soy protein is used as a carrier to transport bioactive substances, it may lead to allergic reactions in these groups.

But the different self-assembly structures of soybean protein can be widely applied in the food industry. In order to produce rapidly, Fu et al. reported a simple and environmentally friendly self-assembly method for manufacturing advanced 3D nanostructured electrodes [18]. Jin et al. used ultrasound-induced self-assembled soy protein/dextran nano gel to deliver curcumin, so as to improve the encapsulation efficiency [19]. In addition, utilizing soybean protein self-assembly can not only improve its functional characteristics but also enhance the nutritional value of food.

Currently, research is mainly focused on developing functional foods, in which bioactive substances are incorporated into proteins in the form of self-assembly. At the same time, how to reduce the instability of bioactive substances in neutral and alkaline environments (physiological environments) is also one of the research focuses. Dai et al. formed a ternary complex of corn Prolamin, surfactant and

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sugar to carry Curcumin, which enhances the nutritional functions of protein, and can be used for the development of functional food [20].

4. Conclusion

Supramolecular chemistry is widely used. The emergence and development of supramolecular chemistry provide new directions for people's development, as well as new opportunities and challenges. Various products based on supramolecular chemistry have been widely used in people's lives. In the future, with the deepening of supramolecular chemistry research, supermolecular functional materials will be more widely accepted and applied. Nowadays, supermolecular materials are developing in the direction of intelligence and environmental protection, and challenge the dominant position of traditional materials at the same time. The development and application of supermolecular materials will certainly promote the rapid development of the economy and technology. But supermolecule products also have problems, such as difficult preparation and low activity. However, with the development and improvement of 3D printing, ultrasonic induction and other related technologies, the application of supermolecules will become more and more simple for people.

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