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Review

Spatiotemporal control of the creation and immolation of peptide assemblies

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ABSTRACT

Peptides are excellent building units to construct supramolecular biomaterials for diverse biomedical applications. A vast amount of research effort over the past two decades has focused on the rational design of peptidic building units and the formulation protocols required to create supramolecular assemblies that can chemically and structurally emulate the functions of naturally occurring nanostructures. A rapidly growing interest in the field is the spatiotemporal regulation of the formation and immolation pathways of peptide assemblies, an essential characteristic to control if these constructs are to fulfill their roles as biologically active and compatible materials. In this review, we discuss the necessity for control over the assembly and morphological transformation of peptides and peptide conjugates, the critical role of these properties for their ultimate biological application, as well as the methods by which this can be programmed into the molecular structure. A particular focus will be on recent advances in the use of enzyme and redox processes for exerting spatiotemporal control over a variety of peptide-based nanostructures.

1. Introduction

Peptides are relatively short sequences of amino acids and can perform a wide range of biological functions to mediate many intercellular, cellular, and subcellular activities. As structural units, they are able to assemble into a variety of supramolecular

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nanostructures that expand their functional space for use as biomaterials [1–11]. Extensive efforts in peptide research over the past two decades have led to the development of peptidic biomaterials with precisely tailored mechanical, biological, and structural properties [5,6,8,12]. However, for any specific biomedical setting, it has been increasingly recognized that not only the well-tailored, initial properties but also the materials' adaptability (the change of properties with time and in response to biology) as well as their immolation pathways, are equally essential to achieve the desired biological/biomedical functions. For example, in the design of biomaterials to assist in wound healing, it is crucial to tailor their mechanical properties and payload release rates to deliver cells and growth factors to accelerate the wound healing process. After the delivery function is fulfilled, it is hoped that these materials will break down in a timely manner for effective clearance and also to make room for the growth of new tissues. Similarly in the context of drug delivery, the nanostructure carrier should be able to hold its size and shape during circulation for a robust and predictable pharmacokinetic profile, but upon arriving at the target site it should rapidly disassociate to release its payload, enabling a specific treatment of pathogenic cells [10]. Indeed, the formation and immolation of many structural units in living organisms are highly regulated biologic events that take place only in a particular period of time and at a particular site. Dysregulated formation and immolation of protein aggregates could lead to function disorders. For example, the deposition of amyloid β-peptide (Aβ) plaques in the brain are implicated in neurodegenerative diseases such as Alzheimer's and Parkinson's, and this abnormal amyloid aggregation results from an imbalance between Aβ production and clearance [13–15]. Therefore, from the perspectives of both biomedical applications and bioinspired materials design, spatiotemporal control has become an increasingly important guiding principle for the development of peptidic biomaterials to specifically interface with biology.

To spatiotemporally control the creation and immolation of peptide assemblies, the principle of design is to create molecular building blocks that can be specifically responsive to changes in environmental factors, such as pH, ionic strength, temperature, light, ultrasound, redox state, and/or enzymatic activities [16–25] Among all these factors, pH, ionic strength, redox state, and enzyme catalysis are the four most common bio-factors dispersed widely and uniquely in living systems. First of all, body fluid or interstitial fluid surrounding cells contains proteins, electrolytes, fatty acids, and a myriad of other types of bioactive molecules, and its high ionic strength could screen electrostatic interactions of charged peptides so as to induce their self-assembly into supramolecular nanostructures. Second, pH differences in various subcellular compartments such as lysosomes can be used to trigger release of payload from pH-sensitive carriers. Also, the lower pH value of the extracellular environment of tumorous tissues (~6.8 *vs.* 7.4), as a result of hypoxia-induced glycolysis that increases lactate production, can be exploited to design cancer therapeutics and diagnostics for controlled release. Third, enzymes are an important class of biological triggers for many important reactions. Tumor progression and invasion are often accompanied by the abnormal activities of various enzymes, and in some cases these tumor-relevant enzymes show a difference in intracellular and extracellular distribution, thus serving as a potential biochemical trigger for both peptide aggregation and immolation. Lastly, some disease-related reductive/oxidative agents represent another group of potential stimuli to regulate peptide assembly. For example, glutathione (GSH) is an important antioxidant to prevent damage caused by reactive oxygen species such as free radicals, peroxides, and heavy metals. In tumorous tissues, the intracellular GSH levels were found to be up to ten times higher than that in normal cells, providing the cancer cells with protection against oxidation and cytotoxic compounds.

In this context, we will describe recent progress in the programmed assembly of peptides and peptide conjugates, as well as the specific immolation of their supramolecular nanostructures. Since peptide materials responding to pH and ionic strength have been systematically reviewed elsewhere [19,26–28], we highlight the strategies for using enzymatic activities and redox processes to achieve spatiotemporal control of peptide-based assembly (Fig. 1). It is not our intention to provide a comprehensive review of the field, but rather, we will focus on several representative examples to illustrate the importance of the spatiotemporal control of peptide assembly and immolation.

2. Principles of controlled peptide assembly

Appropriately designed peptides and their derivatives possess the capacity for self-assembly into a variety of nanostructures, with one dimensional (1D) nanostructures being the most easily attainable ones [1,4]. The self-assembly process can be promoted and stabilized by several associative interactions, including intermolecular hydrogen bonding, π–π stacking, hydrophobic collapse, van der Waals, and crystallization. These can be provided from the amino acid side-chains and/or from various chemical segments covalently linked to the peptide backbone. The correlation among the driving forces, chemical moiety, and the type of peptide-based building blocks is summarized in Table 1. As a result of the remarkable structural and functional diversities offered by the various building blocks, peptide-based nanomaterials have broad applications in the area of regenerative medicine [12,29,30], drug and gene delivery [20,31–33], molecular imaging [34], cancer detection [35], cancer therapy [7], antimicrobial agents [36], and immune therapies [37].

In addition to the associative interactions as driving forces, other contributions like electrostatic repulsions [38,39], elasticity [40], and steric effects [41] can also have an impact on the formation and transformation of these self-assembled supramolecular morphologies. Repulsive and attractive electrostatic interactions can be introduced through charged amino acids and hydrophilic molecules [42]. Electrostatic repulsions tend to cause the disassociation of supramolecular nanostructure into monomeric units while having a limited effect when charged groups are screened by the opposite charges or the electrolytes from the solution. In general, individual peptide molecules first associate into one dimensionally linked tapes (often in the form of β-sheets) through directional, intermolecular hydrogen bonding. The pitch length of the β-sheet tapes plays an important role in their lateral stacking, acting in concert with other interactions to define the final assemblies as either finite structures such as fibrils and ribbons or infinite structure such as belts [39]. Electrostatic interactions have a significant effect on the β-sheet tape's twisting degree and pitch length. For example, Mezzenga and coworkers quantified the nanomechanical properties of various polymorphic forms of amyloid fibrils based on the theory of elasticity [40]. Steric effects always act as an adverse force countering the associative interactions in peptide self-assembly, and influence the degree of molecular packing and stability [41]. Therefore, the final assemblies, including micelles, nanofibers, amyloid fibrils, twist ribbons, helical ribbons, tubes, and belts [4,42–53], represents the culmination of all the attractive and repulsive interactions, and is a delicate balance between the benefits of aggregation and the detriments of adverse effects. Enzymatic activities and redox reactions can break the balance of associative and repulsive interactions in peptide assemblies by forming new chemical bonds to link several parts together or to cleave off hydrophilic or hydrophobic segments from the parental molecule [9,35,54–57].