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Review

Self-Assembly Peptides-a Review

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Abstract: Self-assembling of peptides is a spontaneous process by which peptides are self-organized to form well-ordered structures by intramolecular and intermolecular interactions. This process is controlled by the balance of the forces (attractive and repulsive) within the peptide molecules. Notable methods used for the synthesis of self-assembly peptides are solid-phase synthesis, liquid-phase synthesis, recombinant technology, and the use of external fields. The self-assembled nanostructure-based peptides offer remarkable advantages; such as mild synthesis conditions, relatively simple functionalization, fast synthesis, and low cost, resulting in their remarkable potential for use in biosensors, imaging tools, antimicrobial agents, drug delivery systems, bioelectronics, tissue reparation. Herein, we present the origin of self-assembled peptides, synthesis of novel materials produced through self-assembly of peptides, structural elucidation, applications, recent trends, and the future outlook of self-assembly peptides.

Keywords: Biomolecules, Self-Assembled Peptide, Nanostructure, Nanotechnology

Introduction

Peptides and proteins have the potential to self-assemble to form elongated solid nanostructure known as nanofibrils. These nanofibers are well ordered with significant uniformity and have been useful in quite a several fields such as tissue engineering, wound healing, antimicrobial agents, imaging tools, drug delivery, and biosensors to nanoelectronics. Self-assembly for the synthesis of novel material is currently been exploited by virtual the manners in which supramolecular structures are assembled in nature. Biomolecules such as peptides and proteins are useful building blocks for assembling materials, they interact and self-organize to yield well-defined structures (Zhang, 2003). Some of the physical stimuli used to control peptide self-assembly are light, enzymes, pH, temperature, and sonication (Rasale and Das, 2015). Self-assembly is a bridge between the bottom-up and top-down assembly of nanostructured materials, although, it could be assemblies of any size (de Wild *et al*., 2002). It is a method that can be used to synthesize nanomaterials that are not feasible by the top-down techniques. In self-assembly, materials are synthesized bottom-up into regular patterns (Whitesides *et al*., 2005), it involves fabrication from the nanoscopic scale to allow for ordering into highly organized micro and/or macro structures to give appropriate materials for a wide array of applications. Figure 1 illustrates the self-assembly nanostructures form by diphenylalanine.

Self-assembled peptides are usually synthesized at room temperature, in aqueous environments without the need for a specialized gadget. The development of self-assembled peptides can take a few seconds, days, or several weeks. Furthermore, the shapes of self-assembled peptides could be tailored, depending on the building block used (Castillo-León *et al*., 2011). Molecular self-assembly is one in which the constitutive components are molecules and can also be divided into intramolecular (known as folding) and intermolecular self-assembly. It could also be categorized into static or dynamic self-assembly due to the dissipation of energy during the assembling processes. For the static self-assembly process, the well-organized assembly is in equilibrium and does not dissipate energy, conversely, the self-organized structure dissipates energy in a dynamic

self-assembly process (Maheswari, 2013). Molecular self-assembly, a method for the synthesis of new supramolecular materials is facilitated by weak, non-covalent bonds, hydrophobic and van der Waals interactions, stacking interactions, and ionic and water-mediated hydrogen bonds (Zhang, 2003). Surfactant-like oligopeptides, dendritic peptides, aromatic dipeptides, cyclic peptides, amphiphilic peptides, and polypeptides are examples of peptide-based building blocks that have been developed for generating supramolecular structures include (Mandal *et al*., 2014).

Self-assembly permits the buildup of structures that are minute to be tailored suitably or independently into the well-ordered patterns that generally determine the function of the materials (Whitesides *et al*., 2005). It is suitable for nanostructures starting from their atomic or molecular components, applicable to materials with a large number of small components, and works well in 3D assemblies. Self-assembly of nanostructured materials is inexpensive, characterized by a higher yield, and has been reported to display higher scientific and industrial applications. It has been widely studied in drug delivery due to better loading capacity, high biocompatibility levels, extended circulation, and localization in the required target site (Roy *et al*., 2013). The application of self-assembled peptides in medicine, as well as in biomedical sciences can be grouped into two, namely, the natural and non-natural systems. In the natural system category, the basic conformational unit of the peptide acts as a building block providing the possibility for a range of peptide arrangements by changing the respective amino acids. Whereas, the amino acids are covalently linked to other molecules to form amphiphile-like structures or π-π interactions between the aromatic amino acids in the non-natural system of classification (Ravichandran *et al*., 2014).

The simplest peptide block for self-assembly is the diphenylalanine peptide, facilitated through hydrogen bonding and π–π stacking of aromatic residues. Yan *et al*. (2008) projected the self-assembly mechanism of the dipeptide as shown in Fig. 2. The authors stated that the aromatic groups of diphenylalanine peptides stack via π-π interactions, the molecular stacks may subsequently assemble to give nanofibrils and the nanofibrils could tangle to produce the peptide organogel Fig. 2.

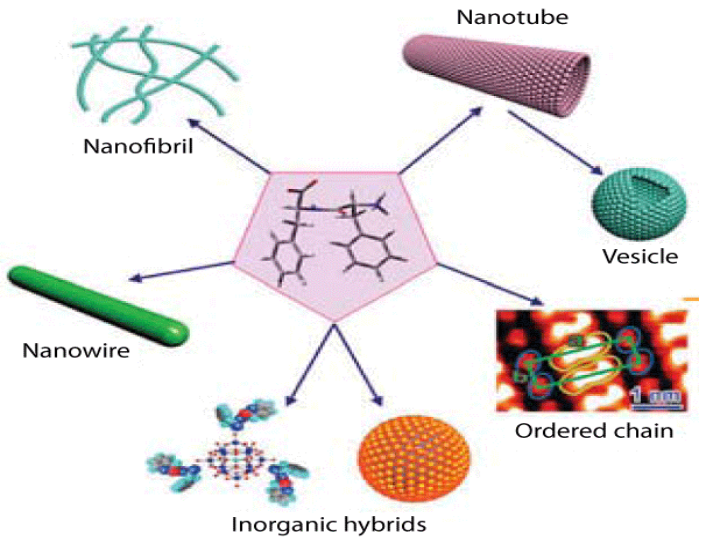

Fig. 1: Self-assembly nanostructures form by diphenylalanine (Yan *et al*., 2010)

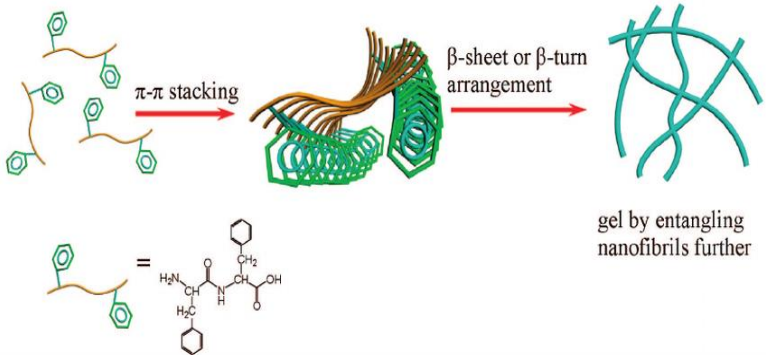

Fig. 2: Mechanism of self-assembly of dipeptide (Yan *et al*., 2008)

Ghadiri *et al*. (1993) pioneer the cyclic peptide nanotubular structures. Deming (1997) developed amphiphilic copolypeptides. The development of artificial proteins that undertake self-assembly to give hydrogels responsive to pH and other environmental changes were carried out by Petka *et al*. (1998); Aggeli *et al*. (2001) reported that other β-sheet peptide systems can form regular nanofiber structures via self-assembly, while, the fabrication of simple amphiphilic peptides that solely comprise of natural L-amino acids was described by Zhang *et al*. (2002). The authors established the self-assembly of surfactant-like peptides and also developed RADA-16I [Ac-(RADA)4-CONH2], this gave rise to a fibrillar hydrogel that has been reported to have great potential in stimulating cell growth and tissue scaffolding (Zhang, 2003; Ellis-Behnke *et al*., 2006). Cui *et al*. (2010) expounded on the features of self-assembly of peptide amphiphiles into β-sheet containing nanofibrils. Hamley (2011) reviewed the self-assembly of surfactant-like peptides with amphiphilicity resulting from the sequence of natural amino acids and peptide amphiphiles in which lipid chains are attached to hydrophilic peptide sequences containing charged residues. Castillo-León *et al*. (2011) presented the advantages, challenges, and possible solutions of self-assembled peptide nanostructures in biomedical applications. Concerns such as controlling the size of self-assembly peptides during synthesis, the stability of self-assembled peptides in liquid environments, and handling the integration of these nanostructures in sensing devices or drug-delivery systems are some of the challenges identified in their article. Bowerman and Nilsson (2012) considered the review of the self-assembly of amphipathic β-sheet peptides. Bowerman and Nilsson mentioned in their study that self-assembled amphipathic peptide fibrils are biocompatible, biodegradable, and non-immunogenic and that the fibrillar network offers an exceptional framework for use in ex vivo tissue culture, display of immunostimulants, bacteria aggregation, drug and protein delivery, hemostasis and as antibiotics and microbicides. Marchesan *et al*. (2015) reported the potential of the diphenylalanine motif as a simple, strong, and valuable building block to drive molecular self-assembly into diverse nanostructured materials. Furthermore, the authors discussed in detail the synthesis, distinctive nature, features, as well as uses of the diphenylalanine motif.

Synthesis of Self-Assembly Peptides

The basic building blocks of peptides are the amino acids; their structure presents functional groups that are open to non-covalent forces that favor self-assembly. Self-assembling peptides are categories of peptides that assume extemporaneous assembling, serving as a building block, to form supramolecular nanostructures. A plethora of building blocks exists with which peptides can combine and they include nucleic acids, lipids, sugars, metallic nanocrystals, etc., (Griffin *et al*., 2015; Gopalan *et al*., 2015; Whaley *et al*., 2000; Zhang *et al*., 2002). Utilization of simple building blocks to build nanostructures by allowing them to self-assemble allows for the incorporation of specific and desired features. Hence, the function of the peptides formed can be controlled when necessary, either by direct interactions or by subjecting it to an external influence (Singh *et al*., 2014; Zhang, 2002). The challenge, however, is to be able to design building blocks that can self-assemble spontaneously into an ordered and stable polypeptide (Zhang *et al*., 2002) using hydrogen bonds, hydrophobic interaction, ionic bonds, and van der Waals interaction. The mutual interactions of these forces can lead to a stable macrostructure, irrespective of the weak nature of the forces. Thus, the various building blocks must be compatible physically and structurally to facilitate and ensure the stability of the self-assembled nanostructures.

Various design approaches have been adopted in the self-assembling of molecules, these approaches include copolymerization and micelles aggregation. Others are surfactant-like materials to scaffolds for three-dimensional cell culture, DNA-based structures, and models to study protein folding and protein conformational disease (Hosseinkhani *et al*., 2013; Park and Champion, 2014). The sequence of amino acids (both natural and non-natural amino acids) provides the template for peptides synthesis. Amino acids are organic compounds that contain amines ($-NH_2$), carboxyl (-COOH), and side-chains as functional groups which influence and facilitate the reactions of amino acids particularly their conversion by self-assembling into polypeptides (Lu *et al*., 2014; Deng *et al*., 2014).

Moreover, the flexibility of the structure of the amino acid tolerates the alternation of the amines and carboxyl functional groups, which leads to the development of hydrogen bonds Fig. 3. The formation of the metastable structure by non-covalent interactions soon gives rise to the formation of polypeptides and consequently supramolecular nanostructure by combining two or more different chains of the polypeptide (Biasini *et al*., 2014).

Solid-Phase Synthesis

The pioneering work on Solid Phase Peptide Synthesis (SPPS) by Robert Merrifield (Merrifield, 1963), led to notable advances in the synthesis of peptides and has become the standard laboratory method for synthesizing peptides and proteins. This method promotes the preparation of natural peptides that are problematic to express in microorganisms, integration of synthetic amino acids, and alteration of the peptide building block. SPPS method has been reported to synthesize a self-assembly polypeptide-P11-4 (Ace-Gln-Gln-Arg-Phe-Glu-Trp-Glu-Phe-Glu-Gln-Gln-NH2) (Aggeli *et al*., 1997).

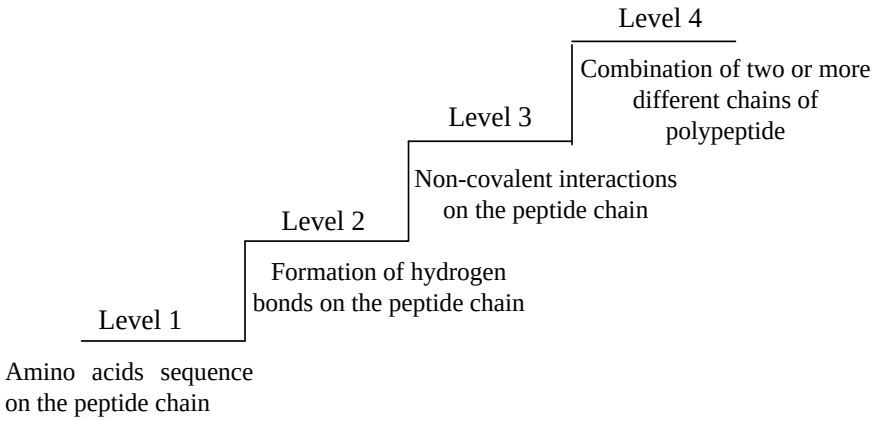

Fig. 3: Structural levels for the formation of supramolecular nanostructure from peptide

The synthesized peptide can be immobilized on a solid support, which enhances its recoverability during the filtration process (Kirkham *et al*., 2007). This is a particular advantage of SPPS over the liquid-phase treatment where a significant quantity of the product is washed away. In addition, other nanostructures have been synthesized by this method by dissolving dipeptides in hexafluoro-2-propanol (Zhang *et al*., 2014; Sanders *et al*., 2017) and from the diphenylalanine motif of Alzheimer's β-amyloid peptide (Schnölzer *et al*., 1992). Another method is the synthesis of peptides on solid support by linking the carbonyl group of one amino acid to the amino group of another amino acid molecule (Lay and Bannwarth, 2015). The approach often begins at the carboxyl end of the peptide and continues to the amino terminus. However, it is necessary to protect the groups to avoid unintended reactions. The two majorly used groups in SPPS are Boc (tert-Butyloxycarbonyl) and Fmoc (9-Fluorenylmethoxycarbonyl) (Behrendt *et al*., 2016). Boc is often preferred for complex syntheses and for synthesizing non-natural peptides which are base-sensitive. However, the use of Hydrofluoric acid (HF) to remove Boc from the resin after the completion of the synthesis has been restricted due to its possible danger. Meanwhile, the foremost benefit of Fmoc chemistry is that the HF is not required (Gates *et al*., 2016); hence, it is used for most routine synthesis. There is the availability of automated synthesizers for the two procedures, nonetheless, a lot of researchers have continued to manually carry out SPPS. For instance, a 12-amino-acid peptide consisting of an MMP-2-sensitive sequence with a cell-adhesive sequence (GTAGLIGQRGDS) was produced via the standard Fmoc chemistry on an Advanced Chemtech Apex 396 peptide synthesizer (Karmakar *et al*., 2016). Advances in the use of protecting groups have limited the occurrence of undesirable side reactions, while epimerization has decreased by activating side chains on the carboxyl group of amino acids. However, certain challenges have been observed with the use of the SPPS method. These challenges are low yield, synthesis complexity, and product sequence dependency. To circumvent these challenges, some techniques have been deployed such as elongation of peptide chain or synthesis of long-chain peptides, conjugation, and cleavage of C-terminal amino acid and resins. These are discussed briefly here under various subheadings.

SPPS involves the use of three primary types of solid supports, they include (1) surface-type supports, (2) gel-type supports, and (3) composites (Albericio, 2000). Efficient solid support has this characteristics-rapid filtration of excess reagents; physical stability; inertness to all the reagents; spread broadly in the solvents used to permit the permeation of the reagents. Efficient solid support must tolerate the incorporation of the first amino acid. Gel-type support is the most common type because it dissolves easily in the solvents, with an equal functional group distribution. Examples of gel-type supports are polystyrene, polyacrylamide, polyethylene glycol, etc., (Behrendt *et al*., 2016). Materials such as highly cross-linked polystyrene, controlled pore glass, and cellulose fibers have been advanced for surface functionalization. Peptides can undergo cyclization on a solid support and thereafter cleaved from the resin by acidolysis and purified (Lay and Bannwarth, 2015; Petersen *et al*., 2014). This is one of the strategies to enhance the yield of peptides. The cyclization of peptides on solid supports is limited to side chains; it is an approach for the synthesis of major intermediates. Cyclization in the solid phase is often followed by treatment in the liquid phase, which seems to undermine the advantage of SPPS in that there is the possibility of loss in the solution phase (Petersen *et al*., 2014).

Liquid-Phase Synthesis

The liquid phase is a conventional technique for the synthesis of peptides, most especially when it involves the manufacturing of peptides on a large scale for industrial

applications. Several techniques can be used for the liquid-phase synthesis of self-assembly peptides. The aggregation of the building blocks in this method is made possible by lowering the interfacial tension (Tsuzuki *et al*., 2016). Surfactants are usually used to achieve surface tension reduction. The foremost narrative of self-assembling processes for cellulose nanomaterials was carried out in polar solvents by Heux *et al*. (2000). In this study, surfactant coating was utilized for the dispersion of cellulose nanocrystals to achieve a chiral-nematic structure. For a surface containing particles of different shapes and orientations, factors including surface properties, solvent evaporation rates, aspect ratio, and concentration, can affect the effectiveness of the surfactant coating (Böker *et al*., 2007; Grzelczak *et al*., 2010). The liquid-phase technique has been used to synthesize some commercial peptides. For instance, RAD16 (RADARADARADARADA) is one of the leading commercially obtainable peptides, which can self-assemble into a nanofiber network. This self-assembling peptide was marketed under the name of Pura Matrix TM (Kyle *et al*., 2009). Similarly, Gelain *et al*. (2006) synthesized a new category of self-assembling peptide via liquid-phase synthesis that is capable of mimicking the 3-D nanostructure of the extracellular matrix. However, control measures need to be placed on the self-assembly process to design peptide systems that can assemble and disassemble when necessary. The physicochemical properties and the factors that are needed to be controlled include temperature, pH, light, concentration, and ionic strength. For instance, the switching of pH is a simple technique for controlling the assembling process. P11-4 (QQRFEWEFEQQ) is an example of a self-assembling b-peptide that is highly sensitive to pH. The advantage of peptides amphiphiles is the possession of both hydrophilic and hydrophobic moieties. For example, Cui *et al*., 2010 reported that the incorporation of the hydrophobic alkyl tail into a synthesized nanofiber allows the self-assembly of the nanostructure to impact peptide signals on the nanofiber. Other important features of amphiphilic peptide molecules are the design of hydrophobic peptide sequence and incorporation of charged amino acids. Generally, monomeric molecules comprising a separate hydrophobic and hydrophilic moiety can aggregate/assemble in an aqueous solution to produce giant molecules known as micelles.

Methods for the Synthesis of Long-Chain Peptides

The most commonly used methods in the synthesis of long-chain peptides are stepwise elongation, fragment condensation, and chemical ligation (Malins and Payne, 2014). In a stepwise elongation method, the amino acids are coupled step-by-step in turn, it is a perfect method for small peptides involving 2-100 amino acid residues. It can be used to synthesize long-chain peptides without racemization. However, the yield reduces when utilized to synthesize highly polar peptides. The synthesis of sophisticated long peptides is often preferred by fragment condensation, but its use is limited because of the possibility of racemization. Another drawback to fragment condensation is that the coupled fragment can be in excess, thereby causing a restraint subject to the length of the fragment. The most recent approach for the production of long chain peptides is chemical ligation, whereby the unguarded peptide chains react selectively in an aqueous medium (Malins and Payne, 2014). Peptide thioester is often used in the common chemical ligation method. Other applicable methods include the covalent linkage of polypeptides in the liquid phase, which employs spontaneous isopeptide bond formation (Haridas *et al*., 2014; Reddington and Howarth, 2015).

Microwave irradiation has been employed in peptide synthesis to produce long peptide sequences characterized by high yield and low racemization. When amino acids are coupled to a growing polypeptide chain, the increase in temperature, as well as the alternating electric field of the microwave irradiation, catalyze the reaction (Palasek *et al*., 2007). As the electric field of the microwave alternates, the peptide backbone tries to align itself accordingly; this enhances the solid phase reaction and consequently the yield of the final peptide products (Collins *et al*., 2014; Mahindra *et al*., 2014). Heating above 55°C can speed up coupling by preventing aggregation. Regardless of the significance of microwave irradiation in the synthesis of peptides, racemization may occur during coupling which is a major challenge.

Orientation of Self-Assembly Peptides under External Fields

Sugiyama *et al*. (1992) reported that the suspensions of crystalline cellulose from the marine invertebrate animal were able to orient when exposed to a magnetic field of 7 T. Similarly, an aqueous suspension of a cellulose nanocrystal was found to reorient when subjected to both magnetic and electric field (Habibi *et al*., 2010). Chemically speaking, the forces responsible for initiating self-assembly or the interactions between interfacial molecules depend on certain parameters such as electromagnetic radiation, solvent polarity, pH, and temperature. Hence, these factors are the major limiting criteria for chemically assisted direct self-assembly (Zhang, 2002). Furthermore, diphenylalanine nanotubes have been found to align horizontally when subjected to strong magnetic fields (Gazit, 2007; Lakshmanan *et al*., 2012).

Self-Assembling Peptides from Natural Amino Acids

A self-assembling peptide system made from natural amino acids has been reported (Gelain *et al*., 2006). It was stated that the peptide can go through spontaneous assembly into nanofiber scaffolds with pores of 5-200 and 10 nm in fiber diameter. These groups of peptides have

been chemically manufactured on a large scale by the use of standard solid phase synthesis and purified to homogeneity. The nanofibers produced by these peptides could be controlled at physiological pH by varying the salt concentration. Self-assembling peptides obtained from natural systems diphenylalanine is reported to be the shortest self-assembling peptide (Gilead and Gazit, 2005; Lakshmanan *et al*., 2012). Diphenylalanine nanotubes are worth the attention they have received due to metal depositions that are made probable within and outside the hollow cores of the nanotube to form electromagnetic nanowires (Niu *et al*., 2007). Additionally, standard chemical synthesis could be used to produce short peptides, thereby, evading the total intricacies involved in the synthesis of large proteins. In what appears to be a pioneering work, a genetically modified self-assembling N-terminal and yeast prion protein was used as building blocks for metal nanowires (Scheibel *et al*., 2003). Likewise, a self-assembling polypeptide obtained from fiber protein was used to produce conductive nanowires (Lakshmanan *et al*., 2012). Enzymes as natural proteins and catalysts have been used to tune the self-assembly of peptide-based materials as well as regulate the hydrophobicity of peptide conjugates such that they self-assemble into fibrils (Shu *et al*., 2013).

Chemical synthesis and recombinant production are part of the major approaches for peptide synthesis from plants and animals. Quite several readily available self-assembling peptides are synthesized via chemical synthesis, this is because the process allows the incorporation of a range of amino acid analogs. The advantages of these methods include process sustainability through sustainable biomaterials resources, rapid and effective production of designer peptides, ability to produce easily modified bioactive motifs. However, chemical synthesis can be expensive and complicated in terms of process scale-up. Generally, amino acids with sequence lengths above 35 amino acids are considered to be economically impracticable (Sato *et al*., 2006). Although recombinant technology is preferred for the synthesis of long-chain peptides, a major challenge lies in the ability to efficiently purify short peptides (Kyle *et al*., 2009).

It is necessary to determine the three-dimensional structure of proteins to understand their functions at a molecular level. Thus, the use of cryo Electron Microscopy (cryo-EM), x-ray crystallography, and NMR spectroscopy to investigate the structure of proteins have been employed over the years (Kryshtafovych *et al*., 2019). X-ray crystallography is the most commonly used technique for the determination of the molecular and atomic structure of macromolecules (Dobson, 2019).

Uses of Self-Assembled Peptides

Self-assembled peptide nanostructures find a wide array of applications in biosensors, drug delivery, cell cultures, hydrogels for tissue reparation, etc., (Rasale and Das, 2015). The different uses of self-assembled peptides are presented in Fig. 4.

Self-assembled peptides serve as an important substitute to traditional biomaterials for the manufacturing of scaffolds for use in regenerative medicine. The scaffolds obtained through the self-assembled peptide have greater benefits over other polymeric biomaterials, this is due to their natural nanofibrous morphology which mimics the *in vivo* extracellular matrix, the scaffolds are highly biocompatible and their biodegradation products are usually not toxic to the surrounding cells and tissues (Ravichandran *et al*., 2014).

Self-assembly peptides have been very useful in drug delivery to the bone tissue, cancer cells, brain, cardiovascular system, and eye (Eskandari *et al*., 2017). Nevertheless, these delivery systems necessitated additional examination before clinical use. Self-assembling peptide hydrogels have been widely reported for use as carriers in the delivery of therapeutic agents (Altunbas *et al*., 2011).

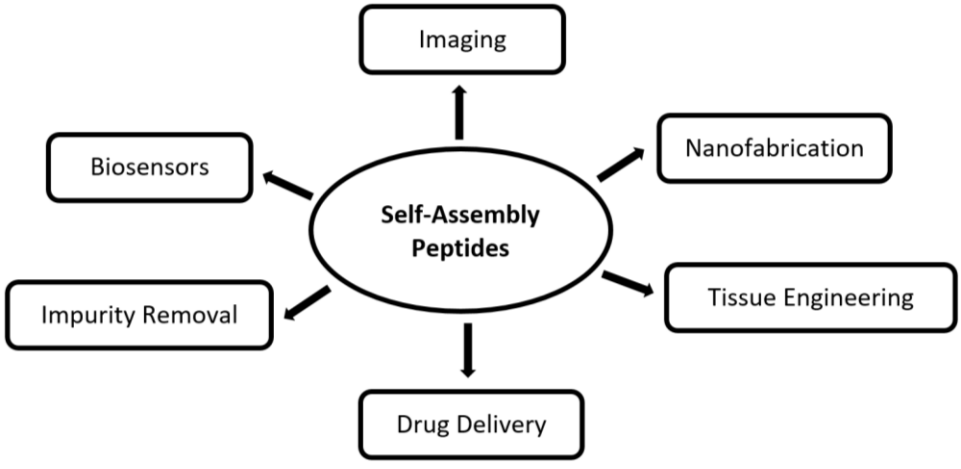

Fig. 4: Applications of self-assembled peptides

Self-assembling peptide amphiphiles have been extensively utilized in biomineralization, nanocircuits, nucleation, and nanowires, besides, self-assembled nanofibers have been reported for use as models for the nucleation and growth of nanocrystals (Rasale and Das, 2015). Although a self-assembling approach for the production of peptide-based vaccines has been demonstrated, there are currently no commercial peptide subunit vaccines. A possibility of highly immune efficient and low toxic peptide-based vaccines is expected in the future (Zhao *et al*., 2017). Peptide scaffolds have been applied to support neural growth in damaged optic nerves, resulting in the recovery of visual functions in model animals (Ellis-Behnke *et al*., 2006). Self-assembled peptide hydrogels have been used in therapeutics as wound dressing agents for the management of second-degree burns in rats (Meng *et al*., 2009), as an extracellular matrix to grow primary human dermal fibroblasts (Kyle *et al*., 2010), as a 3D scaffold to stimulate pre-osteoblast cell attachment and growth (Zhang *et al*., 2009) and implantation of cardiac progenitor cells (Tokunaga *et al*., 2010). Self-assembled peptide nanotubes have been applied in immunosensor and for the detection of pathogens, hydrogen peroxide, and neurotoxins (Cho *et al*., 2008; Cipriano *et al*., 2010; de la Rica *et al*., 2010; Kim *et al*., 2011). Moreover, the application of self-assembled peptides in nanofibers for Yersinia pestis (Men *et al*., 2010), copper (Viguier *et al*., 2011) and dopamine (Sasso *et al*., 2012) detection has been widely investigated.

Recent Trends

Recent trends in nanotechnology have inspired the synthesis and application of novel biomaterials that can undergo self-assembly to form regular nanostructured materials. Among the very many advancements in self-assembly peptides, we present the following: Eskandari *et al*. (2017) discussed the nanostructures of self-assembly peptides and their use in drug targeting and vaccine delivery. The authors highlighted recent advancements in drug delivery, centered on the fabrication of peptides that formed nanostructures for the delivery of therapeutics. The application of self-assembly peptides for the advancement of peptide subunit vaccines was also drawn. Likewise, the significance of self-assembly peptide nanostructures in the development of subunit vaccines was presented by Zhao *et al*. (2017). The application of self-assembly peptides in gasotransmitter (nitric oxide, carbon monoxide, and hydrogen sulfide) delivery as a result of their tunable mechanical properties, inherent biodegradability, and easy chemical modification was described by Qian and Matson (2017). The role, therapeutic potential as well as efforts toward a controlled gasotransmitter delivery were stressed. The authors opined on the expectation of more small molecules for the release of gasotransmitters in the future. Shirazi *et al*. (2016) synthesized linear and cyclic peptides involving an alternative sequence of cysteine and arginine residues. The authors reported the evaluation of the peptides as intracellular molecular transporters and it was revealed that the cysteine and arginine-rich peptides could undergo well-ordered self-assembly and aggregation, with which drugs can be entrapped by the self-assembled structures. Mustata *et al*. (2016) presented a method for the designed self-assembly of peptides into two-dimensional monolayer crystals on the surface of graphene and graphite. They reported that the modeling approach and stability of these peptide-based assemblies suggest applications in heterogeneous green catalysis, bioimaging, and drug delivery in nanomedicine. Self-assembly peptides act as a good receptor for anions, this is because they can bind guests, therefore, the synthesis of self-assembling asymmetrical tripodal-like peptides as anion receptors were carried out by Bhardwaj and Haridas (2016). The aspartic and glutamic acid-based branched peptides were characterized and were reported that the vesicles and the Wiffle-ball-like supramolecular self-assemblies offer opportunities for use as containers for guests encapsulation and release. Nune *et al*. (2016) synthesized an innovative hybrid nanofiber scaffold of polymer poly (L-lactide-co-glycolide) and RADA16-I-BMHP1. The scaffolds were duly characterized by modern analytical techniques, thus, the synthesized hybrid nanofiber scaffold was suggested as a good candidate for peripheral nerve tissue engineering applications. In cancer nano-medicine, Kalafatovic *et al*. (2016) reported the MMP-9 triggered self-assembly of doxorubicin nanofiber as an effective inhibitor of tumor growth in the animal. In their report, they stated that MMP-9 responsive peptide amphiphiles were able to self-assemble into spherical aggregates that undergo enzyme-triggered micelle to fiber transition and are capable of encapsulation and controlling the release of doxorubicin at the site of action. The application of a self-assembling peptide EAK16-II based platform to realize the co-delivery of CD8+T cells epitope and TLR7/8 agonists for augmenting DCs maturation and HIV-1 specific CTL response was investigated by Ding *et al*. (2016). In this study, EAK16-II was conjugated with an HIV-1 specific CTL epitope SL9 (SLYNTVATL) to obtain SL9-EAK16-II, which further co-assembled with TLR7/8 agonist to form a tripartite formulation (CTL epitope, immune potentiator, and delivery carrier). It was proposed that the self-assembling peptide EAK16-II is useful as a new delivery system for peptide-based HIV-1 vaccines. A generalized drug delivery platform for the intravenous application of hydrophobic drugs was developed by Pacheco *et al*. (2016).

This was achieved by combining self-assembling peptide, amino acid, and a low concentration of co-solvent. The authors proposed that the approach successfully permits the optimization of vehicle components for drugs, their formulation strategy may be applied to any hydrophobic compound and the screening method extrapolated and may be modified to suit another clinical context.

The influence of arginine-glycine-aspartic acid-containing peptides (V6KRGDY, G6KRGDY, and A6KRGDY) on the physical characteristics of alginate in aqueous solutions was investigated by Ochbaum and Bitton (2017). In their method, conjugation of peptide to the alginate was performed by the use of carbodiimide chemistry and the small angle x-ray scattering, circular dichroism, zeta potential, and viscosity were investigated. They reported that the capacity of peptides to self-assemble in an aqueous solution is a significant factor in determining the mechanical properties of the resulting hybrid. The development of novel water-soluble amphiphilic polytyrosine-g-poly (2-ethyl-2-oxazoline) graft copolymer conjugates was reported by Bose *et al.* (2017). The conjugates were prepared by two different controlled ring-opening polymerization techniques and were characterized by the ESI-mass spectroscopy, Fourier transforms infrared spectroscopy, Matrix Assisted Laser Desorption Ionization-Time of Flight (MALDITOF) mass spectroscopy, ^{1}H NMR spectroscopy, etc. The authors confirmed polytyrosine-*g*-poly(2-ethyl-2-oxazoline) graft copolymer conjugates micelles to be a good candidate in drug delivery systems. There has been significant interest in the synthesis of peptide-polymer bioconjugate materials, thus, Dule *et al.* (2017) examined the synthesis of a water-soluble amphiphilic peptide-poly (1-vinylimidazole) bioconjugate. The bioconjugate was synthesized by the "grafting from" method based on thiol-mediated radical polymerization and was investigated using 1H-NMR spectroscopy, field emission scanning electron microscopy, ESI mass spectrometry, dynamic light scattering, transmission electron microscopy, MALDITOF, fluorescence spectroscopy, zeta potential, and critical aggregation concentration measurement. This bioconjugate was reported to have the necessary abilities and qualities in biomedical and pharmaceutical applications. Gyurova *et al*. (2017) described the self-assembly of four- and two-antennary oligoglycines in an aqueous medium. They investigated tectomers formed from four-antennary, two-antennary with octyl chain, and two-antennary with heptyl chain synthetic oligoglycines. It was reported that tectomers from oligoglycines might be beneficial in water purification devices, drug encapsulation and release, capturing bacterial endotoxins, etc. Taking into consideration the possibility of an anticancer drug delivery system, Garriga *et al.* (2016) also proposed the application of some two-antennary oligoglycines.

An innovative self-assembled peptide biosensor was produced by Zhang *et al*. (2017), the biosensor is composed of gold nanoparticles functionalized with graphene oxide for the detection of thrombin. The authors identified the biosensor as a convenient and sensitive detector for the protease of thrombin. The research is a promising prospect for cancer-related diseases. Cui *et al.* (2017) developed and applied a highly sensitive and selective electrochemical DNA hybridization biosensor for breast cancer marker BRCA1. This was believed will be helpful in clinical point of care analysis. In what they described as easy, sensitive, biocompatible next-generation cytosensors, Lian *et al*. (2017) employed the self-assembly of dipeptide monomers in a chitosan aqueous solution to prepare a unique Peptide Nanotube and Chitosan composite (PNT-CS). The authors reported that the 3D nanostructured composite had favorable stability, high surface area, and better hydrophilicity. He *et al.* (2017) stated that the D-Form and L-form peptide nanofiber scaffolds can spontaneously form stable β-sheet secondary structures and nanofiber hydrogel scaffolds, which are essential in hemostasis and wound healing. Therefore, the authors developed a D-RADA16 peptide hydrogel scaffold, L-RADA16 peptide hydrogel scaffold, and bFGF-encompassed D-RADA16 peptide hydrogel scaffold for bone repair and regeneration. The importance of D-RADA16 peptide hydrogel in releasing growth factors was also examined.

Future Insights

In the past years, much has been done and many benefits have been utilized from research and applications of self-assembly peptides. Self-assembly peptides as an aspect of supramolecular chemistry have found much application in the field of biomedicine nanotechnologies, such as drug delivery and tissue regeneration. The design and synthesis of self-assembly peptides have resulted in advanced nanomaterials such as nanotubes, nanofibres, nanoparticles, nanotapes, and gels. Nonetheless, these advances are not without challenges, drawbacks, and gaps. These gaps and drawbacks present the spots for future research in this field. Some of the challenging areas of the investigation and application of self-assembly peptides are stability in an aqueous medium, size control, manipulation, and immobilization (Castillo-León *et al*., 2011). Other areas that are challenging in this field include issues such as predicting precise molecular structures, functional properties (Sun *et al*., 2017), yield, and biosafety of self-assembly peptides.

The control of the size of self-assembled peptide nanostructures is crucial, especially in drug delivery and tissue generation. This is because a difference between the host and guest molecular size will greatly hinder and hamper drug delivery and tissue regeneration. Though several works to name a few have been carried out

concerning this challenge, the inclination is usually towards structural control, morphological control, and growth behavior, rather than size control (Park *et al*., 2009; Castillo-León *et al*., 2011; Mason *et al*., 2014).

Just as the products of macroscopic processes are dependent on instrumental fabrication and handling, so is the manipulation of the peptide assembly process and immobilization of the product for target delivery. Nanostructures from self-assembly peptides intended for integration into devices for biomedical applications should be guided in such a way that leaves them with minimal process and product interference. Though contact methods are applied; in this respect, more attention should be given to the development of research methods that utilize non-contact methods to manipulate the assembly process and products to avoid damage (Castillo *et al*., 2008; 2011). The solvent environment in which peptide self-assembling takes place has a great influence on the stability of the product and its workability in biomedical applications. Some nanostructures have been found to lose their stability in commonly used liquids (Knowles *et al*., 2014). This challenge puts a tag on a deeper understanding of solution dynamics and mechanisms for the stability of self-assembly peptides in processing liquid media. Despite the volume of successes in the design, synthesis, and application of self-assembly peptides in drug delivery and tissue regeneration, there are more to be exploited.

Biomedical self-assembly peptides have been adduced to occur by design or conformational changes in molecules or incidental physical processes (McManus *et al*., 2016). Many diseases such as Parkinson's and Alzheimer's diseases and other protein condensation diseases have been linked to such conformational changes (Uversky and Eliezer, 2009; Cohen *et al*., 2013; Knowles *et al*., 2014). Peptides have been developed as "molecular switches" in which the peptides can undergo self-assembly and disassembly (Tan and Richmond, 1998) or change their conformations under the appropriate conditions (Minor and Kim, 1996). Therefore, therapeutic investigations and applications of self-assembly peptides should be directed towards molecular switches that disassemble the pathogenesis of peptide or protein conformational diseases such as those mentioned previously and others. In this regard, applications of "molecular switches" could be utilized in the disassembly of the pathogenesis of tumor conformations. An aspect of this application in tissue engineering and regenerative medicine could be in the early detection and conformational switch of nephritic or renal failure where transplant could be an expensive alternative.

The self-assembled peptide in nanomedicine will have significant therapeutic applications for humans in the nearest future. The success of self-assembled peptides in biomedicine points to the fact that therapy for all diseases may be available shortly. However, biodegradation is the setback of self-assembled peptides. It is, therefore, crucial to have this factor inserted in further investigations and applications. Future studies should be directed towards a complete study of the stability and biosafety of these materials in biomedical applications. Another possible exploratory research is the use of self-assembly for the fabrication of supramolecular electronics, sensors, and analytical systems. However, the fundamental thermodynamics, kinetics, mechanisms, biocompatibility, immunogenicity, and the costs for the scale-up production of self-assembly peptides necessitate crucial attention, Moreso, the mechanism by which self-assembled peptides undergo self-assembling should be studied extensively. Lastly, it is important to investigate how structural changes of self-assembly peptides affect their function in biological systems.

Conclusion

Self-assembly is the spontaneous orientation of molecules into specific structures without external interference. Peptides have the chemical diversity and biocompatibility that are found in proteins, nevertheless, peptides are considerably more chemically and physically stable, robust, diverse in sequences and shapes, and can be easily produced on a large scale. Peptides can form macroscopic assemblies such as hydrogels with the nanoscale order, in addition, short peptides can naturally orient to form nanospheres, nanotubes, nanofibrils, nanotapes, and other ordered nanostructures (Gazit, 2007). The fabrication and application of self-assembled peptides are important aspects of nanoscience and nanotechnology. Self-assembled peptide nanostructures offer quite several potential in biomedical applications due to their stability under specific chemical conditions, amenability to high precision processing, remarkable recognition capabilities, and mechanical rigidity (Lakshmanan *et al*., 2012; Roy *et al*., 2013). They can be easily functionalized with different functional compounds and can be synthesized rapidly under mild conditions and at a low cost. This review article has been able to provide readers with comprehensive details of self-assembled peptides.

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Author's Contributions

Olushola Sunday Ayanda: Initiated the concept of the article and wrote the introduction section and the synthesis of self-assembly peptides.

Olusola Solomon Amodu: Contributed to the use of

self-assembled peptides.

Cyprian Yameso Abasi: Initiated the concept of the article and contributed to the recent trends and future insights of self-assembled peptides.

Michael John Klink and Simphiwe Maurice Nelana: Contributed to the writing and proofreading of the manuscript.

Olatunde Stephen Olatunji: Contributed to the recent trends and future insights of self-assembled peptides.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues are involved.

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