Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2017; 9(6): 462-472
doi: 10.25258/ijpcr.v9i6.8776

ISSN- 0975 1556

Review Article

Self-Assembling Peptides- Notion and Medical Applications: A Review

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Available Online:25th June, 2017

ABSTRACT

Peptides are the building blocks which are widely used owing to their biology as well as their chemistry. They provide a vast platform in the area of medicine. Self-assembling peptides are peptide biomaterials which are pacing in the field of diagnosis, therapeutics, tissue regeneration and vaccine. Self-assembling peptides provide an excellent alternative to the conventional methods for the drug delivery and the treatment. In this article, we discuss about the various medical applications of self-assembling peptide as they have excellent biocompatibility and resemblance with the proteins in the biological system. These are constructed and modified using various amino acid sequences depending upon the type of the application for which it is being used.

Keywords: Amino Acids, Peptides, Drug Delivery, Applications, Diagnosis, Therapy.

INTRODUCTION

Peptides

Amino acids are the building blocks of peptides which contain less than 50 amino acids. Peptides are an integral part of most biological process and are found throughout every cell and tissue in the body[1]. A wide range of functions are performed by peptides depending upon the amino acid involved. The prime reason for the fascination in peptides is that its ability to exquisitely bind to their *in vivo* targets[2].

Biologically-potent peptides are commonly designed by recombinant DNA technology. Peptides have been considered to have wide range of medical application compared to proteins owing to its smaller size for better penetrability into tissues and solid mass like tumor. Peptides have been considered as a very useful building block in creating self-assembling nanostructures for biomedical application due to their inherent biocompatible and biodegradable nature. β- sheet- forming peptides particularly demonstrate the remarkable capability to assemble into one dimensional (1D) nanostructures through intermolecular hydrogen bonding. The formation of 3D networks is as a result of interactions among 1D peptide-based nano-structure. Furthermore, the biodegradability is tunable by incorporating specific amino acid sequences or by controlling over their self-assembled structures, allows for the construction of bioactive hydrogels that can mimic the structure and function of native extracellular matrix (ECM)[3].

Peptide Drug Market

Globally the peptide market has tremendous growth in the past decade. The pharmaceutical companies have multiplied the number of research and development to gain a stronghold on the market and also owing to their wide-ranging applications in the effective management of a number of diseases. The global peptide therapeutics market was valued at US$19.98 bn in 2015 and is estimated to reach US$23.70 bn in 2020. North America currently represents the largest share of peptide drug market due to high drug pricing and presence of a large patient pool. The region is estimated to maintain its leadership until 2020 with a valuation of US$9.74 bn. However, Asia Pacific is expected to grow at most promising rate.

A high number of peptide therapeutics is in various stages of trial phases. Nearly 43% of trials are in phase II and a majority of these are related to cardiovascular and metabolic disorders.

Development of synthetic peptides for therapeutics is gaining momentum worldwide because there is rise in obesity levels and cardiovascular disorders which has fuelled the research and development activity in the development of peptide therapeutics[4].

In vivo Self-assembly

Self-assembly is a spontaneous arrangement of individual components into ordered structures as a result of inter and intra-molecular interactions. The process involves interactions with each other to form more complex structures. The balance between the attractive and repulsive forces between the molecules controls the assembling process. Several different kinds of assemblies can be formed by inter- and intra-molecular forces such as hydrogen bond formation, hydrophobic and electrostatic interactions, van der Waals forces and π–π stacking[1].

The self-assembling peptides are either formed from naturally existing proteins or proceed from novel

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biomolecular design. Moreover, the nano-structures protect the peptide against protease degradation and preserve the functionality of the individual peptides[5].

Self-assembling nanostructures are highly preferable over to their synthetic self-assembled monolayer (SAMs) alternatives because of their biocompatibility. Self-assembling peptides remain the most attractive soft biomaterial option for several reasons:

- Synthesis of peptides using solid-phase method Peptides is easy which allows for sequence-specific modifications at the molecular level[6].
- Inserting compounds such as antibodies, enzymes, magnetic particles, or fluorescent compounds to the peptide structure, further peptide functionalization can easily be performed[7].
- Peptide epitopes mediate ‘‘signaling language’’ in the extracellular matrix (ECM) and therefore act as most attractive biomaterials for regenerative scaffolds[8].
- Self-assembled peptide building blocks can be used to design the customized supra-molecular structures[6].
- Self-assembly is important in cell-penetrating peptide (CPP) mechanisms, which play a major role in introducing drugs inside cell membranes and translocation of genes inside a nucleus[9].
- The self-assembly process can be driven by naturally occurring self-assembly motifs present in proteins such as α-helices, β-sheets, and coiled-coils[10].

Through endocytosis the nano-structures enters the cell and can increase the intra-cellular drug accumulation. The accumulation of the drug doesn’t affect the healthy tissues. The peptide sequence can be designed according to the disease to be treated. It is important to understand and control peptide self-assembly to regulate the formation of peptide–drug complexes nano-/microstructure and there control their complex size. Several factors such as type, number, molecular size, peptide concentration, amino acid sequence, ionic strength, solvent, solution pH, presence of denaturation agents, temperature, time, surface and its property, and mechanical force are fruitful in peptide self-assembly. For example, in aqueous solution a β-sheet secondary structure is formed by EFK8-I. However, random coiling occurs as a result of replacing phenylalanine (F) at the same charge distribution with alanine (A). Although the reason for the occurrence is unknown, and it has been assumed that β-sheets is formed due to the steric hindrance of the hydrophobic phenylalanine.

Along with the type of amino acid, the length of the peptide sequence is significantly important in nano-macrostructure formation. Comparison of EAK16-II, EAK12, and EAK8-II shows that the first one, when dissolved in a salt solution, associates to form a macroscopic membrane. Even the second one can form a membrane under the same condition, but to a much lesser degree, less than 50%. The third one cannot form a membrane under these conditions. One possible reason for these phenomena is that peptides with a shorter chain length have fewer ionic-complementary pairs that can affect self-assembly.

A different charge distribution because of the arrangement of amino acids can change peptide self-assembly to different nanostructures. For example, EAK16-I and EAK16-II have a fibril-like nanostructure (as shown in Figure 1), but EAK16-IV has globular aggregates at neutral pH and forms at neutral pH[11].

The process of self-assembly is involved in the generation of several biological nano-structures such as DNA double helix formation through hydrogen bonding interactions between nucleotide bases, the formation of cell membranes upon self-assembly of phospholipids and so on.

Amino acids have various physicochemical properties because of difference in the charge, hydrophobicity and polarity of the side chain which in turn has an impact on the peptides being formed. Self-assembling peptides can be designed by modifying the type, number as well as the sequence of the amino acid. Peptides sequence may or may not serve a biological function. In the former case, they form bio-materials, while in the latter case they serve as a complement element for bio-assembly[12].

Certain peptides and protein which self-assemble in the human body are related to different disease and disorder including Type 2 diabetes mellitus and Parkinson’s disease. The pathophysiological change that can be observed during such state is the formation of protein aggregate, known as amyloid fibrils. A study shows that amyloid interaction plays a significant part in the early stages of amyloid fibril formation. This is due to the stability, order and directionality of planar aromatic systems observed in the restricted geometry of interaction[13].

The ability of the peptides to form specific secondary structures enables the engineer to design it with controllable structural features. Cyclic peptides, amphiphilic peptides, copolypeptides, surfactant-like oligopeptides, dendritic peptides, and aromatic dipeptides are few of the peptide based building block available[12].

Applications of Self-assembling Peptides

As antimicrobial agents

Antimicrobial peptide amphiphiles elicit potent and broad spectrum antibiotic activity, extended to various antibiotics resistant microbes such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), multi-drug-resistant *Pseudomonas aeruginosa* and multi-drug-resistant Mycobacterium tuberculosis. More than 2300 naturally occurring Antimicrobial peptide amphiphiles sequences have been catalogued in various antimicrobial peptide amphiphiles databases[14].

Generally, at membrane surface, positively charged antimicrobial peptide amphiphiles accumulate via electrostatic interactions with the anionic phosphate head groups of membrane lipids so as to achieve a critical concentration. Membrane disruption occurs through toroidal pore, the barrel-stave pore, carpet mechanisms or disordered toroidal if the hydrophobic moieties of interfacially active antimicrobial peptide amphiphiles is inserted into lipid bilayers which leads to cytoplasmic leakage, membrane depolarization, membrane lysis and cell death[15,16]. A schematic presentation of membrane disruption mechanisms of antimicrobial peptides (AMPs) above threshold concentrations is given in Figure 2.

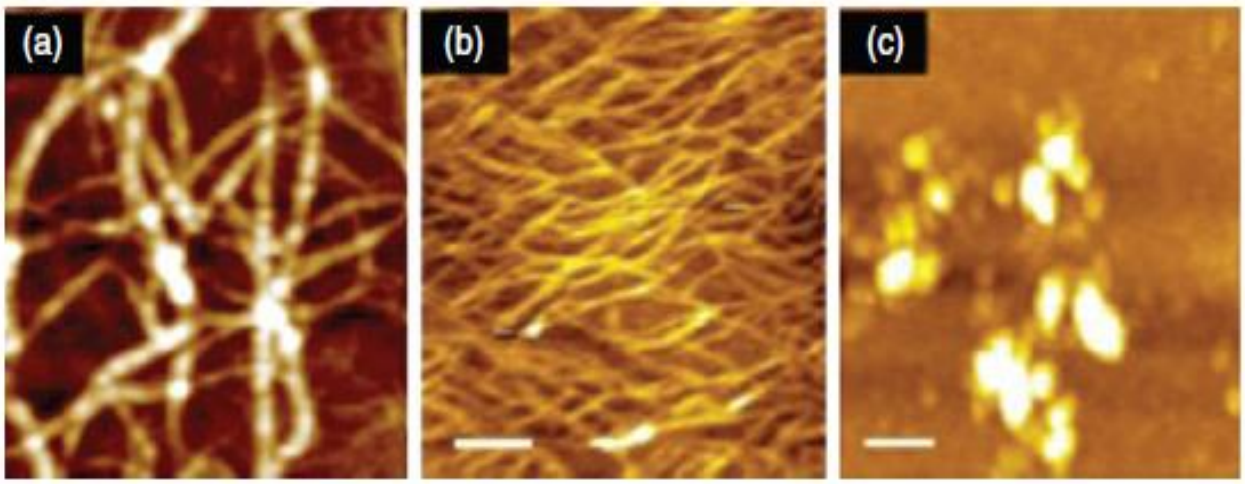

Figure 1: AFM image of peptide self-assembled nanostructures from (a) EAK16-I, (b) EAK16-II, and (c) EAK16-III. (Reproduced from reference 11).

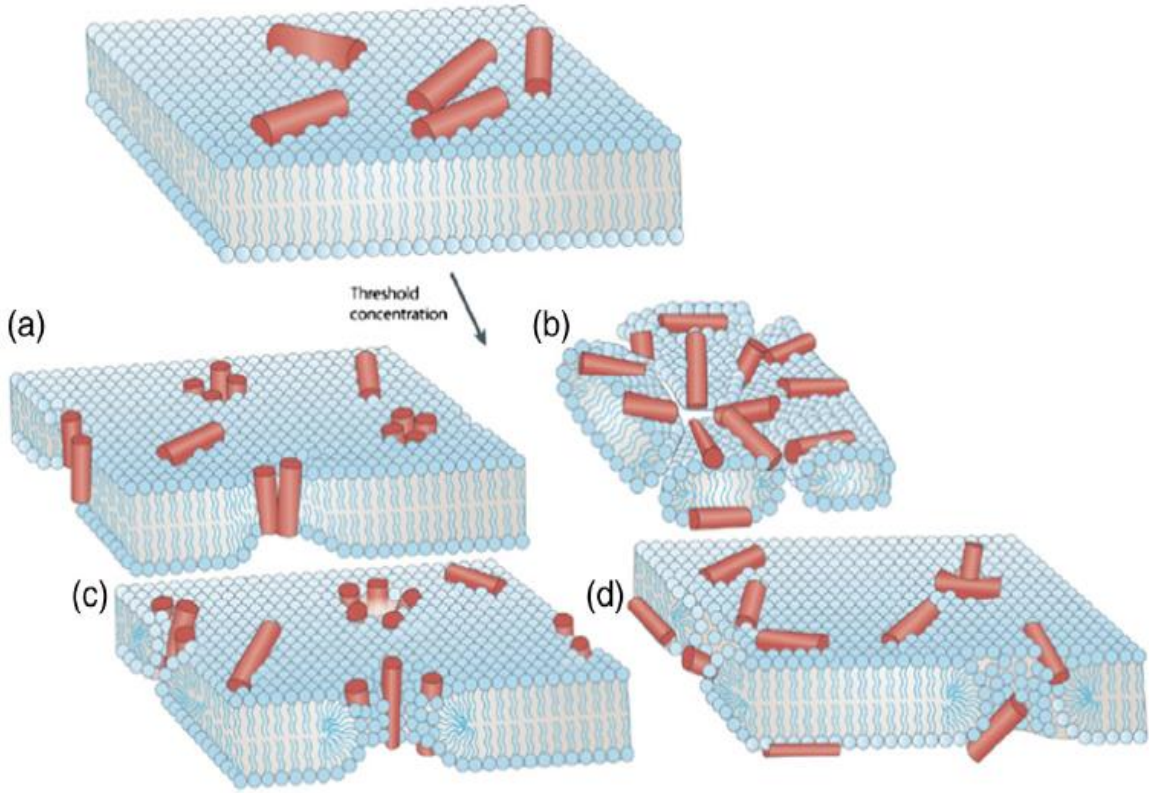

Figure 2: Proposed membrane disruption mechanism of antimicrobial peptides (AMPs) above threshold concentrations include (a) barrel-stave model, (b) carpet or detergent mechanism, (c) toroidal pore model and (d) disordered toroidal pore model.

Self-assembling peptide for diagnosis

Magnetic resonance imaging (MRI) is a reliable non-invasive method which is used in clinical as well as medical field which allows evaluating of opaque deep tissues at higher cellular level resolution[17]. Contrasting agents (CAs) are utilized in the MR scan. Higher concentration of the CAs is employed to improve the sensitivity and also to reduce the signal-to-noise ratio of the images. However, the higher concentration exhibit higher cytotoxicity[18]. Thus, peptide-based molecules have been employed to design gadolinium (Gd) containing molecules that condense into amphiphilic dimers post intra-cellular disulfide reduction, and in order to increase the sensitivity in the region of interest they subsequently self-assemble into Gd-containing nanoparticle while unaltered condition the surrounding tissue[19].

Self-assembled peptide structures are used as targeted fluorescent imaging *in vivo*. A self-assembly of

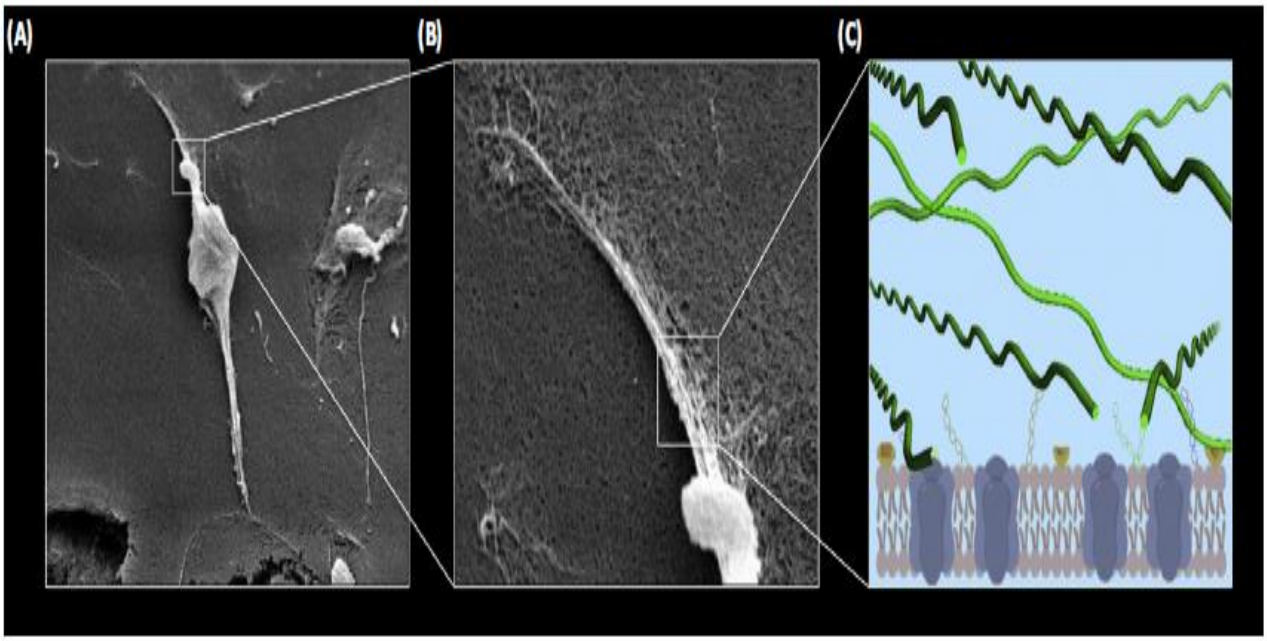

Figure 3: Self-assembling peptides- Synthetic extracellular matrix-like biomimetic materials. (A) Scanning electron microscope image of a single neural stem cell cultured on a self-assembling peptide (SAP) scaffold (cell body and branches are clearly visible) made of Ac-$(RADA)_4$-$CONH_2$. In general, this SAP forms β-sheet structures in water, which are stable across broad ranges of temperature and pH. Peptide nanofibers are approximately 6 nm wide and 0.8 nm thick. Furthermore, the Ac-$(RADA)_4$-$CONH_2$ nanofiberous scaffold contains 5-200 nm pores allowing for high hydration of the gel (>99.5%). (B) At a higher magnification, a cellular protrusion interacts with the nanostructured milieu. (C) Cartoon scheme of self-assembled nanofibers interacting with the cell membrane proteins of the selected cell. (Reproduced from reference 25).

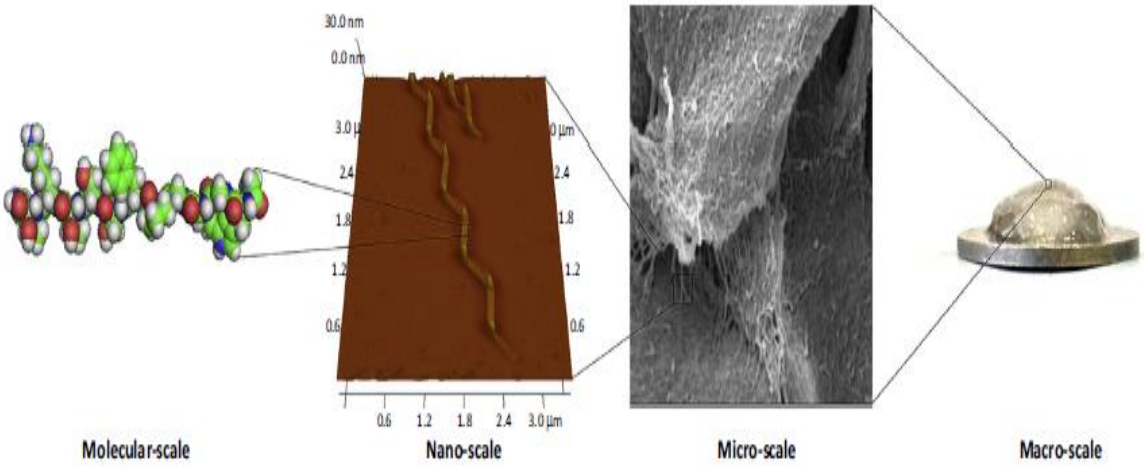

Figure 4: Self-assembling peptides- Nanoscale to macroscale. The 'Lego bricks' peptides, approximately 5 nm in size, form stable β-sheet structures and self-assemble into twisted nanofibers (AFM image at the nanoscale level). At the microscale, nanofibers bundle together, yielding an interconnected network (SEM image) with nonpolar residues placed inside and polar residues exposed to the aqueous environment that macroscopically leads to the formation of a hydrogel scaffold. (Reproduced from reference 25).

fluorophore containing small molecules into nanostructures which causes the fluorophores to come closer, which results in fluorescence resonance energy transfer (FRET) effect to quench the fluorescence signal[21]. To detect the activity of enzymes enhanced quenching has been employed by researchers. The process of enzymatic hydrogelation is used for self-assembly of nanofibers which upon enzymatic reaction with a hydrogelator precursor induce peptidic self-assembly inside the cells. This process was exploited in numerous studies. One such precursor was employed by Gao *et al*., i.e., the growth of nanofibers inside the cell was illustrated by a combination of 4-nitro-2,1,3-benzoxadiazole (NBD), and a phosphorous ester on the tyrosine residue of a small peptide. The nanofibers also facilitated the confirmation of the endoplasmic reticulum as the location of the enzymatic

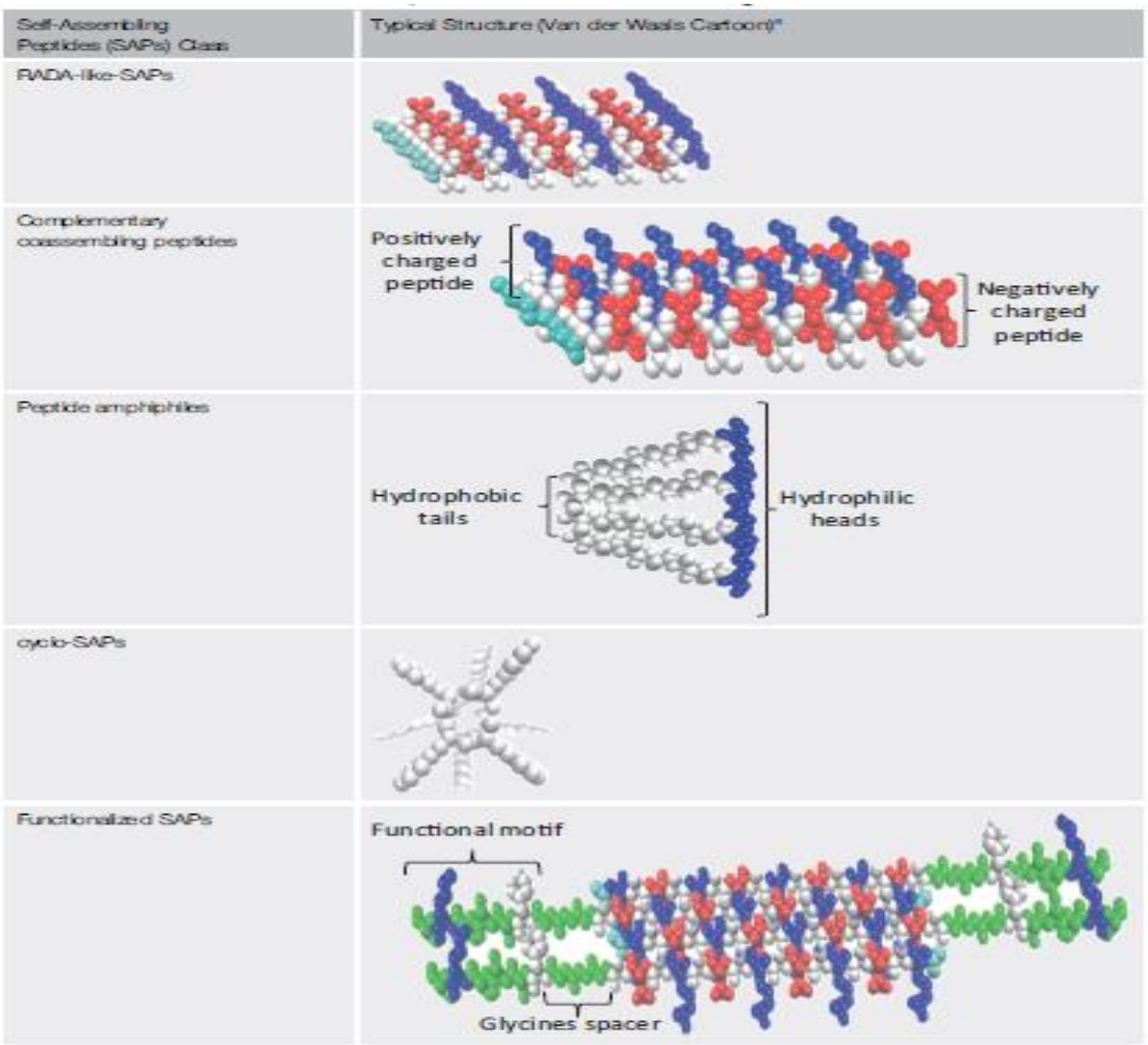

Figure 5: Self-assembling peptides class and typical structure (Van der Waals cartoon).

activity through in vitro spatiotemporal fluorescence measurements. Aromatic–aromatic interactions is involved in the self-assembly of the nanofibres and produces slightly hydrophobic regions inside the fibers, thus leading to enhanced fluorescence of the probes. Thus, Fluorescence imaging can be employed to understand the interactions of peptides with various enzymes[21].

As anticancer drug carrier

Cationic amino acids are known for their cell penetrating abilities though they cannot self-assemble due to the repletion of their high charge. Transactivator of transcription (TAT) is one of the most popular examples of cell-penetrating peptides (CPPs) and has been widely used in the treatment of cancer so as to enhance cellular uptake along with intracellular retention in cervical cancer cells.

Even with non-cationic amino acids cell membrane penetration is possible through self-assembly on the cell membrane. Artificial transmembrane nanochannels are formed by self-assembly of cyclic peptide (cyclo[Gln-(D-Leu-Trp)4-D-Leu]) CP on the cell membrane for the permeation of anti-cancer drugs, which are smaller than 1 nm. The *in vivo* study with these nano channels in a grafted solid tumor model in mice showed that tumor growth was greatly inhibited by the combination of anti-cancer drugs with the cyclic peptide nano channels[22].

Tissue Regeneration

The extracellular microenvironment (ECM) is one of the most influential factors for cellular differentiation, proliferation, migration, or apoptosis. The extracellular microenvironment surrounding the cells of a tissue or an organ, through insoluble proteins such as collagen, elastin, fibrillin and soluble proteins such as growth factors, hormones, chemokines regulates the morphogenesis and cell processes that lead to tissue formation, homeostasis, and regeneration[23]. However, morphogenetic processes mediated by ECM fail during tissue injuries, with some exceptions. A synthetic ECM-like biomimetic material is therefore required for tissue regeneration[24]. This can be achieved by self-assembling peptides which has highly defined structures and molecular interactions. SAPs are able to form fibrillar intricate nano structures that are

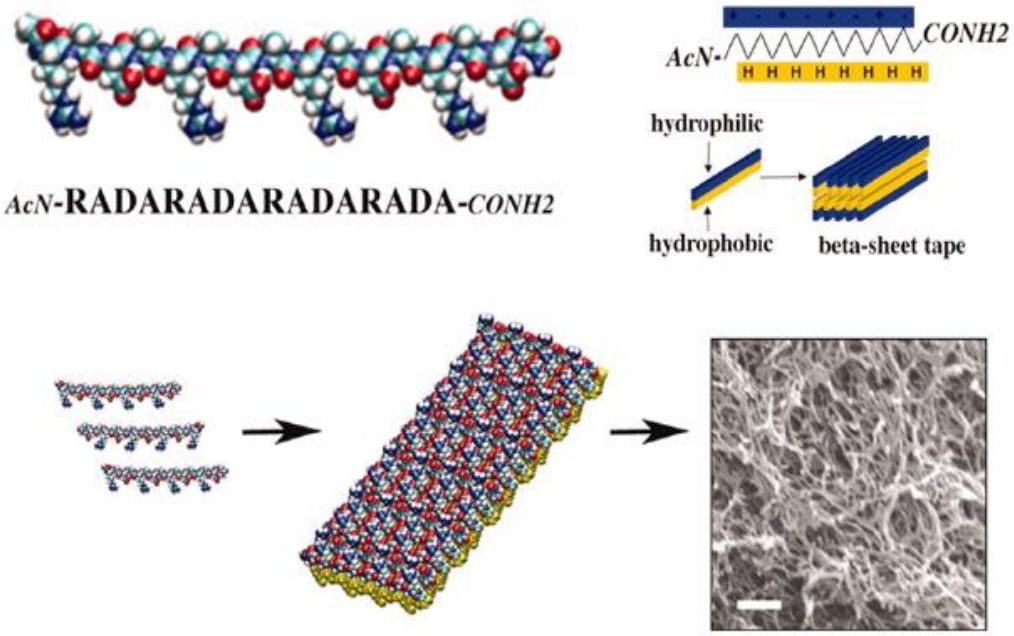

Figure 6: Illustration of RADA16-I hydrogel formation by parallel β-sheet alignment of peptides.

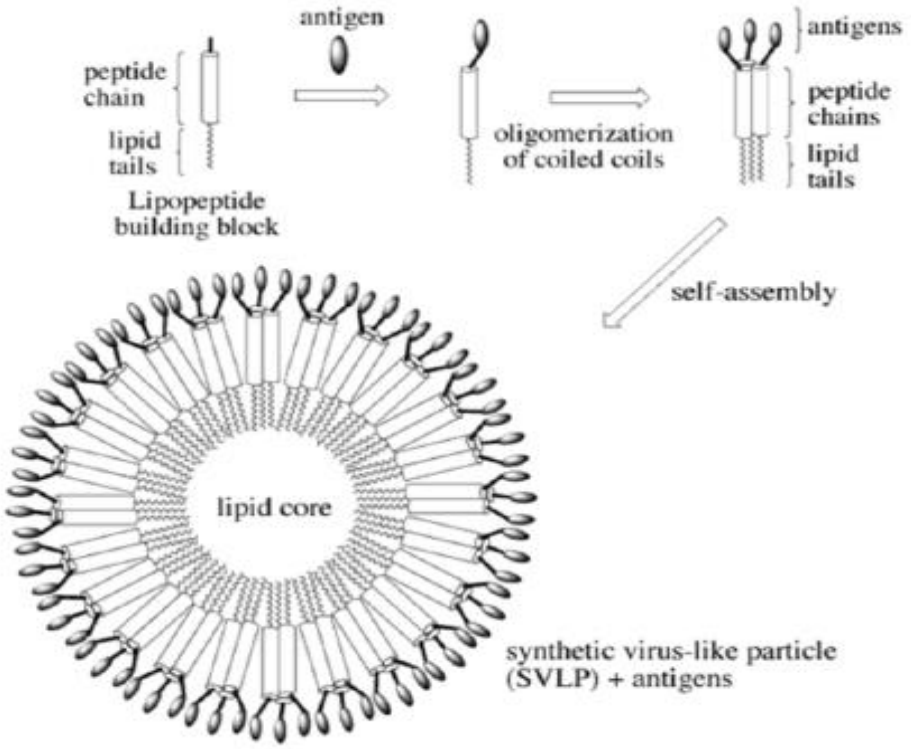

Figure 7: Synthetic virus-like particle (SVLP) formation through self-assembly of a trimeric coiled-coil helical structure and hydrophobic interaction of lipophilic tails.

similar in shape, size and porosity to the natural fibrillar proteins of ECM (Figure 3). They have the capability of forming a porous network providing a tissue like but fully synthetic extracellular microenvironment. SAPs can display cell-biding sites similar to natural fibrillar structures, also named functional motifs (short peptide capable of interacting with cells and/ or cytokines), specifically interacting with cells and influencing some of their biological functions. SAPs potentially provide microenvironments similar to the natural ECM[25].

The presence of monovalent or divalent electrolyte ions triggers the shift in pH of the self-assembly of peptides used in regenerative medicine. Generally, the basic concept is that SAP molecules are like 'Lego bricks' with

the ability to spontaneously self-assemble upon exposure to an external stimulus to form nano-fibrous structures. At the microscale and macroscale, they usually look like mats of fibers with random orientation and hydrogel scaffolds respectively.

Peptides containing alternating charged hydrophilic and hydrophobic amino acid residues (also called RADA-like-SAPs) are known to have a strong propensity to create cross β-sheet structures. When soluble electrolytes screen electrostatic repulsions, hydrophobic forces lead assembly and orientation of nanofibers. This orientation is in such a manner that their charged hydrophilic residues are exposed to aqueous environment; whereas their hydrophobic residues are placed in an inner hydrophobic pocket. As per the distribution of charge on their hydrophilic surfaces, SAPs are classified into diverse moduli as: modulus I (– + – + – + – +), modulus II (– – + + – – + +), modulus III (– – – + ++), and modulus IV(– – – – + +++). Among aforementioned, several SAP variants have been modified, designed and extensively studied, including Ac–$(RADA)_4$–$CONH_2$[4], Ac–$(KLDL)_3$–$CONH_2$[5], and Ac–$(RADADADA)_2$–CONH[9].

Regeneration of damaged optic tissue

In another study conducted by Rutledge G. Ellis-Behnke *et al.,* self-assembling peptide nanofiber scaffold (SAPNS) was used in the regeneration of damaged optic tissue. The study involved injecting a peptide scaffold into the wound site in both young and adult animals. The optic tract of the hamster was completely severed at the brachium of the SC. Before using SAPNS, several surgically implanted segments of sciatic nerve collected from one of the animal's leg was used for the reconnection of the optic tract was accomplished. However, it often resulted in leg disabilities in experimental animals. It was reported that when SAPNS was used, it not only permitted significant axonal growth through the site of the treated lesion, partially restoring the optic tract, but also in brachium transected experimental adult animals it helped in the reoccurrence of functional vision. It was shown that use of this biological nanofiber scaffold is an effective approach to facilitate the reconstruction of a continuous tissue substrate after CNS injury[28].

Self-assembling peptide for neural regeneration

Peripheral nerve repair is clinically challenging task, which takes addition of different strategies including physical, structural guidance as well as for effective functional axon regeneration bioactive components are also incorporated[29]. Nanofibrous scaffolds have been extensively used in neural tissue engineering applications due to their similarity to the extracellular matrix and high surface area to volume ratio. For nanofiber production, the most widely used techniques are Electrospinning and self-assembly for their neural applications[30].

Electrospinning has a upper hand than that of other techniques for the production of nanofibers.It can produce long and continuous fiber with various diameters with tailorable properties like orientation, porosity, mechanical properties, etc.[31].

Self-assembly is another technique of nanofiber production which is natural molecular phenomena of organising smaller building blocks to larger structures[32]. Among several self-assembling peptides, a class called 'molecular lego' finds applications in tissue engineering. RADA16, a class of ionic self-complementary peptide has extensively promoted neurite outgrowth in studies by several groups[33]. Recently, Gelain *et al.,* carried out a experiment in order to improve neural regeneration, in order to do that they introduced 'PFSSTKT' a sequence motif called bone marrow homing peptide sequence (BMHP1), into RADA16-I.

integration and migration of self-assembling peptides into deep layers of the electrospun nanofibrous scaffolds is showed when they are incorporated with polymers before electrospinning[34].

Unmodified self-assembly peptide

Peptides consisting of natural L-amino acids with or without standard N-(acetylation) or C-terminal (amidation) modifications to remove unwanted terminal charges are majorly used to engineer the self-assembling peptides. The properties of the amino acid sequence are responsible for Self-assembly of such peptides entirely. This class of self-assembling peptides can be easily synthesized using standard solid phase synthesis techniques without the need for laborious chemical modifications. This is considered as a main advantage of this class. Indefinite structures such as fibers or hydrogel-based networks are formed the majority of unmodified peptides used for self-assembly. The best example of a self-assembling peptide that form hydrogels is RADA16-I. RADA16-I constitutes 4 repetitive units of arginine (R), alanine (A), aspartic acid (D) and alanine (A). Hydrophobic interactions of the alanines among 2 peptide molecules in aqueous solution expose the negatively charged aspartate residues and positively charged arginine residues towards the exterior face (Figure 6). Consequently, complementary charge interactions between the formed pieces result in nanofiber formations with a width of 3-8 nm. Large number of Nano fibers generates nanoporous hydrogels at such high concentrations.

Hydrogels are frequently studied for the controlled release of the drugs because of its properties. Koutsopoulos *et al.* studied the release profile of different proteins with different molecular weights which were loaded in RADA16-I hydrogels. They found that the release was governed by diffusion which the diffusion coefficients are dependent on the molecular weight of proteins and the concentration of peptide used to form the geometrically uniform hydrogel[35].

Peptide as Vaccine

In order to reconstruct virus like structure, self-assembling peptides have been considered for vaccination as well by making use of β-sheet or alpha helical coiled-coil forming peptides for assembly into well-defined nanostructures. Self-assembling peptide particles have several advantages over other antigen carrier systems such as ease of production, biodegradability, high density of surface-exposed antigen epitopes, control on particle size, direct conjugation of ligands or imaging probes to the peptides and increasing of antigen uptake by antigen-presenting

Table 1: Different types of self-assembled peptides with biomedical application.

Peptide Type	Nanostructure	Biomedical Application	References
Peptide amphiphilic (PA)C16-Cysteine-Glycin-Serine-RGD	Nanofibers	Mineralization of hydroxyapatite	41
L-Phe-L-Phe (FF)	Nanotubes, β-sheets, nano vesicles, nano fibrils, ordered chains, peptide-nanoparticle hybrids, dendrite nanostructures	3D cell culture, gene delivery, anticancer drug delivery, bioimaging, biosensors, guest encapsulation	42-44
C12-PPPPRRRR-NH2	Nanofibers	Doxorubicin and paclitaxel delivery with intracellular uptake	45
PA-IKVAV C16-(A4G3)(Isoleucine-lysine-valine-alanine-valine)	Nanofibers	Artificial 3D scaffold, Encapsulation and differentiation of neural progenitor	46
RADA16 I(AcRADARADARADARADA-CONH2)	Hydrogels	Controlled release of small molecules, functional proteins and anticancer drugs	47, 48
Poly(L-lysine) poly(L-leucine)	Dendritic vesicles	pH-triggered responsive smartnano-vesicles for controlled intracellular drug delivery	49
(ELP) I	Elastin-like polypeptide	Inhibitor of tumor growth	50
RGD-PANTFR-PA	Nanofibers	Cell response studies, Melanoma and endothelial cell adhesion, Enhanced liposome uptake, Mineralization of hydroxyapatite, Pyreneen capsulation	8, 41, 51, 52
(Trp-D-Leu)4-Gln-D-Leu	Cyclic nanotubes	Delivery of anticancer drug(5-Fu)	53
C16-V3A3F3	Nanofibers	Cell encapsulation	54
KLDL3(AcN-KLDLKLDLKLDL-CNH2)	Hydrogels	Controlled release of doxorubicin and Smac-derived pro-apoptotic peptide, Protease sensitive hydrogel	55-57
Collagen mimetic self-assembled peptidesIV-H1 peptide-amphiphiles(Gly-Pro-Hyp)4-[IV-H1]	Triple-helix structure	Targeting fibroblast cell lines,Enhanced uptake of liposomes	58, 59

cells. Self-assembling peptide particles have shown hardly any cytotoxicity in contrary to virus like-particles (VLPs) and genetic vaccines based on viruses.

A synthetic virus-like particle (SVLP) was developed by Boato *et al*., comprising a lipo-peptide that has a coiled–coil sequence. A trimeric coiled-coil helical structure was formed by peptide monomers, which in turn formed micelles with a mean diameter of about 20-30 nm[35].

In order to understand the immune responses associated with self-assembling peptides, Rudra *et al.* investigated the mechanisms through which Q11 nanofibers activate the immune system and elicit robust antibody responses. The study involved investigating the mechanism of immunogenicity and the quality of antibody responses raised by a peptide epitope from *Plasmodium falciparum* circumsporozoite (CS) protein, (NANP)3; which was conjugatively linked with Q11 i.e. self-assembling peptide domain. By impairing the NALP3, MyD88, TLR-5, or TLR-2 function, adjuvant action mechanism in knockout mice was investigated. For malarial infection, transgenic sporozoite neutralizing (TSN) assay was implied to assess the quality of antibodies raised against (NANP)3-Q11. It has been reported that (NANP)3-Q11 were self-assembled into nanofibers, and in C57BL/6 mice MyD88 and T cell dependent antibody responses lasted up to 40 weeks. Mice sera primed with either a synthetic peptide (T1BT*)4-P3C or irradiated sporozoites, followed by boosting with (NANP)3-Q11 exhibited significant increase in antibody titers along with significant inhibition of sporozoite infection in TSN assays. Without harming the strength or duration of the antibody responses, two different epitopes could be self-assembled together which makes these materials promising platforms for self-adjuvanting multiantigenic immunotherapies[36].

For drug delivery

Christina Karavasili *et al.*, worked on lipid liked self-assembling peptide so as to enhance the permeability of the drug. Amphiphilic, lipid-like, self-assembling peptides are functional biomaterials with surfactant properties. These lipid-like peptides were developed to have aspartic acid or lysine composing hydrophilic and a six alanine residue hydrophobic domain with length similar to that of biological lipids[37]. CONH2, ac-A6D-COOH, and DA6-COOH lipid-like peptides were studied to examine the

potential of using ac-A6K-CONH2, KA6- as permeability enhancers to facilitate transport through the intestinal barrier. *In vitro* transport studies of the macromolecular fluorescent marker fluorescein isothiocyanate (FITC)-dextran (4.4 kDa) through Caco-2 cell monolayers show the permeation enhancement ability of the lipid-like peptides. It was observed that there was increase in the FITC-dextran transport across the epithelial monolayer up to 7.6-fold in the presence of lipid-like peptides[38]. Furthermore, we monitored the transepithelial resistance and performed immunofluorescence studies of the cell tight junctions. *In vitro* studies showed increased mucosal to serosal absorption of FITC-dextran in rat jejunum in the presence of the ac-A6D-COOH peptide. Additionally, a small increase in the serosal transport of bovine serum albumin was observed upon addition of ac-A6D-COOH. Lipid-like peptides are biocompatible and they do not affect epithelial cell viability and epithelial monolayer integrity. The outcome suggests that short, lipid-like peptides may be used as permeation enhancers to facilitate oral delivery of diagnostic and therapeutic molecules[39].

In a study by Xiaofei Liang *et al.*, they designed rational vectors for efficient drug and gene delivery which is essential for cancer treatment. To construct ultra-stable self-assembling peptide nanovesicle (SPV), epidermal growth factor receptor (EGFR)-binding peptide amphiphile (PA) were used as the primary bilayer skeleton material. The resulted EGFR-targeted SPV (ESPV) could efficiently encapsulate therapeutic cargos (drugs or small interfering RNAs [siRNAs]) or labelled fluorescent cargo (quantum dots [QDs]) and exhibited excellent affinity for EGFR-positive cancer cells. Additionally, ESPV could deliver more drug or plasmid DNA to tumour sites and promote gene expression (a three-fold ratio of ESPVs vs cationic liposomes). Excellent drug/gene delivery both in vitro and in vivo by the individual delivery or co-delivery of doxorubicin (DOX) and the acetylcholinesterase (AChE) gene via the ESPVs and exerted a significant growth-suppressing effect on a liver cancer xenograft[40]. Examples of different types of self-assembled peptides along with their biomedical applications are quoted in Table 1.

CONCLUSIONS

The self-assembling peptide has vast medical applications including drug delivery, diagnostics, vaccination, and tissue engineering. In this era of personalized medicine, peptide-based self-assemblies open a wide range of opportunities in the health care service. This shows how far the medical technologies have evolved for the betterment of the patients. From drug delivery to efficacious treatment of various ailments such cancer and neurodegenerative disorders. For the effective clinical translation of these therapies, collaboration of biologists, chemists and engineers are highly important.

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