Chapter 11

Design and construction of protein and peptide-based self-assembled nanostructures

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11.1 Introduction

In biological processes, inorganic structures are formed hierarchically with the help of a template composed of biomolecules. These processes, which may provide milder manufacturing conditions, yield assembled nanostructures that are precisely controlled and difficult to obtain with the traditional material engineering approaches. Because biomolecules possess recognition and self-assembly features, they can direct highly ordered inorganic material synthesis in nature.

Among the biomolecular building blocks of self-assembling structures, peptide- and protein-based materials gained attention in the last decade since the material characteristics propose many advantages compared to other building blocks [1]. Self-assembling properties of biomolecules can be used to develop new nanostructures with superior chemical and physical properties. In this chapter, we discuss peptides and proteins such as β-sheets, β-hairpins, α-helices, amyloid, capsids, ferritin, and albumin that are used to form nanostructures with desired functions. In addition, we explain how these biological molecules are involved in the design and construction of superior nanostructures.

11.2 Short peptide-based nanostructures

Peptides are short chains of amino acids that follow the basic structural rules for protein folding and submolecular interactions. As observed in protein secondary structure, peptides can also form α-helices and β-sheets by the same amino acid and chemical bond interactions. The resulting structures could be self-assembled into the coupling, energetically favorable structures by the rules of non-covalent interactions [2]. Among those secondary structures, β-sheets facilitate the formation of macroscopic fibrils as also observed in nature. The literature highly investigates many self-assembling fibril structures also show β-sheet rich monomeric subunits as observed in biofilm formation and nanotube generation [3].

Considering their property of forming complex, biocompatible structures with easily manipulated and synthesized building blocks, peptide-based materials have a large selection of highly reviewed applications. Hydrogels are advanced 3D structures that can also arise from peptide-based fibrillar structures and contain water. In a recent review, peptide-based hydrogels were reviewed extensively, and possible applications with peptide hydrogels were investigated [4]. In addition, drug molecules can also incorporate with peptide nanostructures and can be easily delivered to desired space by controlled disassembly of building blocks. In the review by Habibi et al. [5], drug delivery strategies with peptide-based materials were investigated [5]. Apart from the natural design, peptide nanomaterials can also be designed from scratch, which means that the design principle harbored from nature could be applied to obtain unnatural peptides with desired properties. Designer peptides with chemical modifications have been investigated to show possible applications ranging from biosensing and nanofabrication [6]. On a different note, peptide-based nanostructures gained attention in medicine due to their biocompatibility and exceptional in vivo traits, including the ability to traverse through cellular membranes and tunable assembly dynamics from external stimuli. In the Lee et al. [7] review, a possible approach to using peptide-based materials in medicine and disease treatment was investigated [7].

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Later in this chapter, examples of peptides and proteins in bio-templated structures, scaffolds, and nanocarrier systems are given.

11.3 Bio-templated nanostructures

Taking advantage of the self-assembly feature of biomolecules, bio-templating makes it possible to design innovative nanostructures that can find applications in different fields, including electronics and medicine. Their varying sizes and shapes give nanostructures superior properties; controlling these elements are critical in producing precisely designed and engineered innovative nanostructures [8]. Bio-templating allows the size and shape of nanostructures to be controlled during the fabrication process. The use of biomolecules in bio-templating facilitates overcoming the challenges of producing nanostructures with superior chemical and physical properties that accommodate the designed functions. Both natural and engineered protein-based bio-templating can make nanostructures with desired functionality in mild environmental conditions such as the use of non-toxic solvents and low temperatures. More specifically, these proteins include cage-shaped proteins, amyloid proteins, virus, and bacterial subunits proteins.

11.3.1 Amyloids

As a result of peptide assembly, peptide strands can form β sheets, which can then be further assembled into amyloid fibrils. Due to their resistance to harsh physical and chemical conditions, amyloid fibrils are of great interest in nanobiotechnological studies. In addition to pathological amyloids associated with neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, two other groups can be classified as artificial and functional amyloids. Pathological amyloids are produced due to misfolding and aggregation of proteins in disease conditions, while artificial amyloids are produced under artificial conditions from non-toxic proteins. Functional amyloids, such as biofilm building blocks, highlight the beneficial properties of naturally occurring amyloids. The use of self-assembled amyloid as biotemplate to produce ultrathin silver nanowires was described in a study. Amyloid fibrils were produced using hen egg-white lysozyme and were then used to construct bio template metal nanowire of 1 nm in diameter and 2 μm in length [9]. Reches and Gazit have reported the nanotube formation by the self-assembly of the Alzheimer's β-amyloid diphenylalanine structural motif (Fig. 11.1) [10]. In addition to their usage as a cage protein, as mentioned below, apoferritin protein was used to form amyloid fibrils by applying different temperatures and pH than physiological conditions, and it was used as a bio-template to assemble and synthesize metal nanoparticles [11].

Ng et al. reported biofilm-templated production of catalytic nanocomposites [12]. Functional amyloids are among the main components of bacterial biofilm matrix and can produce bio-templated nanostructures (Fig. 11.2). In this respect, a previous study characterized the interaction of functional bacterial amyloids as potential biotemplates with various surfaces [13].

11.3.2 Cage proteins

Nanoparticles can be synthesized or patterned within the interior or on the surface of protein cage structures. Different protein cage-derived nanomaterial self-assemblies have been shown in a variety of studies. Here, viral capsid, ferritin-based units will be discussed. Viruses consist of multiple copies of capsid protein subunits which self-assemble into a coating structure that protects the genetic material and enables the delivery of genetic material during the virus infection of the host cell [14,15]. Natural and engineered virus subunits constitute an essential field of study for the production of nanostructures with superior properties. Natural capsids which have various geometries can be genetically modified in terms of surface properties and structure. Nucleic acid sequences encoding capsid subunits have been identified and

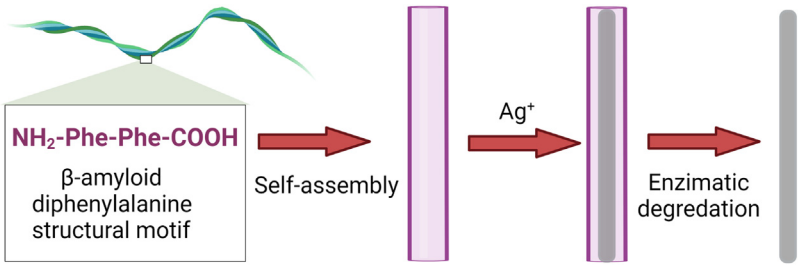

FIGURE 11.1 Silver nanowire formation using self-assembled peptide nanotubes. *Silver ions are reduced within the nanotube which is formed by the self-assembly of the Alzheimer's β-amyloid diphenylalanine structural motif. Further, the peptide tube is enzymatically degraded by proteinase K to produce silver nanowire.*

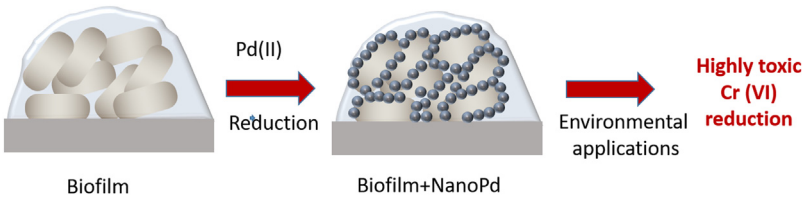

FIGURE 11.2 Biofilm-templated catalytic C − Pd nanocomposite fabrication. *Bacterial biofilm reduces Pd(II) to Pd(0). Pd(0) nanocrystals in the bacterial biofilm matrix can be used for the reduction of highly toxic pollutant Cr (VI). C − Pd nanocomposite is produced to stabilize Pd catalysts (Adapted from C. K. Ng, H. E. Karahan, S. C. J. Loo, Y. Chen, and B. Cao (2019) Biofilm-templated heteroatom-doped carbon−palladium nanocomposite catalyst for hexavalent chromium reduction.* ACS Appl. Mater. Interfaces *11 (27):24018−24026. Doi:10.1021/acsami.9b04095).*

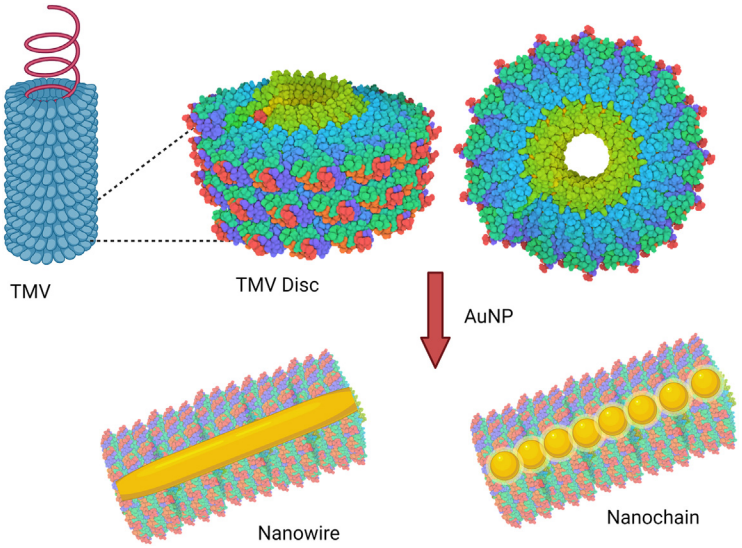

FIGURE 11.3 Tobacco mosaic virus (TMV) -assisted self-assembly. Tobacco mosaic virus capsid subunits have been used as templates to obtain nano-scale arrays made of gold. *Ordered nano-chains have been obtained using gold nanoparticles. Exploiting hollow structure and the self-assembling future of tobacco mosaic virus coat protein, nanoparticles are encapsulated and assembled into nanostructures. AuNP nano-chains are further grown into nanowires (J. Zhang, R. K. Kankala, J. Ma, Y. Zhou, S.-B. Wang, and A.-Z. Chen (2021). Hollow tobacco mosaic virus coat protein assisted self-assembly of one-dimensional nanoarchitectures.* Biomacromolecules *22 (2):540−545. doi:10.1021/acs.biomac.0c01402). Virus structure is drawn with RCSB PDB data (doi:10.2210/pdb2TMV/pdb) (K. Namba, R. Pattanayek, and G. Stubbs (1989). Visualization of protein-nucleic acid interactions in a virus. Refined structure of intact tobacco mosaic virus at 20.9 A resolution by X-ray fiber diffraction.* J. Mol. Biol. *208 (2):307−325. doi:10.1016/0022-2836(89)90391-4).*

manipulated using genetic engineering methods and chemical strategies to provide controlled structured virus-based biotemplates [16−21]. Compared to those produced physically and chemically, capsid-derived nanostructures have high reproducibility due to the controlled self-assembly [22−24]. In approaches using reducible or non-reducible gold substrates to form functionalized nanostructures, cowpea chlorotic mottle virus (CCMV) capsid subunits have been used to fabricate capsids patterned with gold nanoparticles [25]. Nano-arrays with specific geometries have also been obtained using viral capsid subunits. Plant viruses have advantages in the production of nanostructures because they are not pathogenic for animals and can be produced in plants with high efficiency [22−24]. Wild-type and recombinant tobacco mosaic virus capsid subunits have been exploited as templates to obtain nano-scale arrays made of gold, platinum, and palladium nanoparticles (Fig. 11.3) [26, 27, 28]. The surface of the capsids can serve as a nucleator or template for the inorganic materials. Besides these approaches, nanoparticles have been used to nucleate viral capsids. The core of gold particles has been shown to initiate bromine mosaic virus capsid self-assembly to form virus-like particles [29]. Several efforts have been made to synthesize nanomaterials using whole viruses or virus-like particles assembled from capsid subunits as templates for electrochemical reactions used in energy storage and conversion [21,30,31].

With their hollow spherical structure, iron storage protein ferritin can also serve as a cage biotemplate. The iron storage mechanism of 24 subunit ferritin in eukaryotes has inspired the use of natural and mutant forms of this protein to accumulate other inorganic nanoparticles, including gold, silver, and palladium [32,33]. With the genetic engineering approach, fusions of self-assembling protein cage subunits of ferritin with various inorganic binding peptides such as titanium, carbon nanotubes, and silver have been carried out. In this way, subunits form cage structures with their self-assembly properties, while providing a bio-template to produce nanostructures for target inorganic material by integrating selective inorganic binding peptides [34−36].

Heat shock protein is another type of protein that can self-assemble symmetrically and naturally forms a cage structure. It has been reported that the cage structures formed by heat shock proteins can drive nanoparticle array self-assembly, such as quantum dot arrays [37].

11.3.3 Microorganism as biotemplates

In addition to using various peptide and protein structures in the biotemplate-based production of nanostructures, the use of organisms themselves covers a wide range of research topics. These include microorganisms, algae, plants, insects, etc. As mentioned above, nanostructures can be formed using viruses or virus-like particles as biotemplates. Different from these acellular structures, some examples of microscopic cellular structures are discussed below.

Studies have shown that bacterium and yeast cells function as biotemplates to form functional nanostructures. Bacteria and yeast cells can adsorb and reduce metal ions in or on the surface of their cell walls. Electrochemically active bacterium *Shewanella oneidensis* has been utilized to biosynthesize metal nanoparticles, i.e., palladium and gold nanoparticles, placed on the bacterium's surface [38,39]. In addition, *Bacillus subtilis* has been used as soft templates to produce multiphasic hollow rods consisting of Sn-based nanostructures [40]. Silver nanoparticles with spheres and flake morphology have been synthesized using *Spirulina* as a template. These silver nanoparticles assembled orderly along with the cellular structure of *Spirulina* and achieved tunable and ordered 3D assembly of nanoparticles using microalgal cell structure [41].

11.4 Scaffold forming self-assembled nanostructures

In medical research, tissue engineering requires superior scaffolds to repair damaged tissues and organs and improve their properties. The formation of controllable and modulated nanostructures, which are formed by self-assembly of specific biomolecules for the development of desired scaffolds, has been the subject of many studies in recent years. In tissue engineering, scaffold-based designs promote cell viability, integration into surrounding tissue and encourage host response. For tissue regeneration to be successful, first of all, the designed scaffolds must be capable of mimicking the ECM, the natural three-dimensional environment of the cells in the tissue [42]. An essential approach in the design of scaffolds is the formation of nanostructures by self-assembly, similar to the formation process of superior materials in nature, which are formed in hierarchical order [43]. Self-assembled proteins and peptides are of interest in regenerative medicine with their potentials such as providing the natural microenvironment, biodegradation, biocompatibility, non-toxicity [44–49]. The properties of peptides and proteins, such as structural and functionality, including nano-level organization at the target surface, can be tuned according to amino acid sequences they have with molecular engineering and rational design approaches [50–52]. The self-assembly process of peptide building blocks in a nanofibrous network can be controlled by stimuli such as ionic strength, temperature, pH, and light, which can be modulated according to the design [53–55].

11.4.1 β-sheet, β-hairpins, α-helix, coiled coils

In nature, various motifs, including α-helix, coiled coils, β-sheet, hairpins, and turns, are found in proteins. Natural self-assembling peptides use these conformational units to form ordered scaffold structures. α-helical coiled-coils forming self-assembling fibers have been obtained using two complementary peptide chains with 28 residues containing a seven amino acid repeat. Engineering peptide sequences by altering three amino acids in the repeating unit to alanine led to enhanced hydrophobic interactions between fibrils. When glutamine is preferred instead of alanine, the propensity to hydrogen bond formation occurs [56,57]. This approach is one of the significant efforts to engineer scaffolds to control the functions or properties at the nano-level.

Yeast protein Zuotin was reported to have a repetitive peptide sequence with the β-sheet structure that formed nanofibers. The repetitive sequence was named EAK16 (AEAEAKAKAEAEAKAK). Based on this, different peptides such as RADA16 (RARADADAARAARADADA), which consists of a hydrophobic and hydrophilic amino acid sequence, have been developed to form nanofibrous self-assembly scaffolds [58–60]. RADA16 and its derivatives create scaffolds that provide three-dimensional structure and have the ability to promote regeneration of damaged bone, cartilage, intervertebral disk, axonal, and skin [61–63]. MAX1 and MAX8 peptides form b-hairpin structures consisting of two b-strands. Both peptides are composed of 20 amino acids; the difference between them is that the lysine residue in the amino acid sequence of the MAX1 peptide has been altered with the glutamic acid at MAX8 [64]. β-hairpin peptides, which are ion- and pH-responsive, have been shown to support the viability of the cell types, including MSCs, fibroblasts, and osteoblast cells [65–67].

11.4.2 Peptide amphiphiles, peptides with aromatic moieties and elastin-like peptides

Peptide amphiphiles, consisting of a polymer-bound to a peptide, carry a hydrophobic aliphatic tail and a hydrophilic peptide sequence that provides excellent stability to the self-assembled structure. The peptide sequence is attached to

the tail by an amide bond. Hydrophobic interactions of the alkyl chains primarily drive self-assembly. Peptide amphiphiles that respond to pH or ionic strength self-assemble into various supramolecular structures following triggering by these factors. These structures include fibers, nanofibers, ribbons, and nanoribbons [68–70]. Peptide amphiphiles vary in length and amino acid content in the tail, resulting in changing self-assembly conditions. Peptide amphiphiles are diverse, as the alkyl chain lengths and amino acid content in the tail may vary, and the conditions for self-assembly vary accordingly.

The aromatic moieties such as fluorene and naphthalene can be attached to peptides to form the hybrid polymeric constituents. Aromatic side chains promote molecular self-assembly through $\pi-\pi$ stacking. 9-fluorenylmethoxycarbonyl (Fmoc) aromatic residue-protected peptides can self-assemble into nanofibrils through $\pi-\pi$ stacking of the Fmoc. Short peptides modified with the Fmoc group exhibits superior self-assembly features [70,71]. Although diphenylalanine forms well-ordered and tubular nanofibers in organic solvents, it can not build supramolecular structures under biological conditions. On the other hand, it has been shown that adding the Fmoc-group to diphenylalanine can spontaneously form supramolecular structures using a pH response method [72].

Peptides/proteins inspired by naturally occurring proteins such as silk, collagen, elastin are important alternatives for building scaffolds [73,74]. Elastin-like proteins (ELPs) are elastin protein-based peptides composed of VPGXG repeats. While these peptides, which have self-assembly properties, are liquid at room temperature, they quickly self-assemble when the temperature is shifted to 36 degrees and above. Elastin-like peptide-based scaffolds have been exploited for studies on cartilage and vascular tissue engineering [75–79].

11.5 Protein-based self-assembled nanostructures as nano-carriers

Drug delivery systems are engineered platforms for targeted and controlled delivery of therapeutic agents. The recent progress in nanobiotechnology has established nanoparticle-based drug delivery systems as promising tools, where the nanoscale formulations potentiate an increase in delivery efficiency [80].

Programmable self-assembled bio-nanostructures, especially protein nanoparticles, have recently revolutionized the nanomedicine era. Proteins are one of the most common biomacromolecules found in the body and are involved in most biological functions.

Their particle size, morphology, surface charge, drug loading, drug entrapment, and in vitro drug release are some parameters that account for characterizing protein nanoparticles as potential nanocarriers [81]. In addition, several other factors make them ideal as drug delivery platforms. Proteins are endogenous to the cell, which makes protein-based nanocarriers exhibit excellent biocompatibility and biodegradability. Amino acid residue, the basic compositional unit of protein, can have various functional groups such as -NH2, -COOH, -SH [81]. These functional groups can be modified by using a growing variety of bioconjugation techniques, enabling several surface modifications. Therefore, these protein nanoparticles can be fabricated to carry and deliver cargoes such as imaging agents, analyte-processing enzymes, small molecules, ions, and nucleic acids [82].

Protein nanostructures for drug delivery have been synthesized by using proteins such as albumin, ferritin, transferrin, etc. Albumin is one of the most common proteins found in the body and accounts for almost 60% of blood serum [83]. It is known for binding and transporting metal ions, small molecules, and fatty acids around the body; owing to these properties, several albumin-based nanoplatforms have been developed for drug delivery, especially for cancer theranostics [83]. Albumin-based nanoplatforms have been actively involved in photothermal therapy, photodynamic therapy, and sonodynamic therapy of various cancer types. Several synthetic dyes such as IR825, IR780 have been conjugated with Human serum albumin (HSA) via hydrophobic interactions to form HSA nanoparticles [84]. These nanoparticles display fluorescence imaging accompanied by tumor suppression at different wavelengths allowing for effective imaging-guided combination therapy. In addition to small synthetic molecules, metal ions can also be loaded into HSA nanoparticles. In a study carried out by Yang et al., HSA was utilized as scaffolds for synthesizing Ag_2S nanodots in situ with NIR-II fluorescent imaging. The intravenous injection of these nanodots with subsequent photothermal therapy resulted in the complete eradication of the subcutaneous tumor [85].

FDA has approved many albumin-based nano-drugs for clinical therapy against cancer. These include Abraxane, which is a conjugation of HSA and paclitaxel via hydrophobic interactions [86]. Albumin-bound rapamycin and perifosine have also been approved as therapeutic agents against myeloma [87]. Traversing BBB remains one of the most critical challenges while combating orthotopic glioma. Lin et al. engineered a Bovine serum albumin (BSA)-based nano-platform decorated with cell-penetrating peptide -LMWP on the surface and loaded with paclitaxel and fenretinide [88]. This albumin-based nano-drug was able to penetrate the BBB and target glioma with increased efficiency.

Ferritin is a widely distributed protein, famously known for its role in iron storage. The core-shell structure of ferritin with enhanced stability, high biocompatibility, and biosafety makes it a promising nanocarrier for drug delivery. Ferritin exhibits a unique pH dependant disassembly-reassembly property exploited to encapsulate different organic and inorganic molecules [89]. Doxorubicin (DOX) is a widely used drug in chemotherapy and can be loaded easily into the ferritin cavity. Ferritin can cross the BBB, which makes ferritin encapsulated DOX an effective chemotherapy agent against glioblastoma [90]. Furthermore, combination therapy can also be achieved by surface modification of ferritin Core-shell (with Bi_2S_3) and loading the core with DOX. Zhang, et al. demonstrated such a system for CT imaging-guided chemo/radiotherapy. Ferritin nanocages have also been modified for detecting viral proteins [91]. This is achieved by engineering the nanocages to display nanobodies that can bind to viral antigens to create a fenobody. This approach has successfully detected H5N1 virus and Newcastle disease virus (NDV) with high sensitivity.

In addition to these BSA, HSA, and ferritin protein-based nanocages, virus-derived nanocages have also been explored as drug delivery agents. Viral nanoparticles (VNPs) are nanomaterials that are generated spontaneously by viruses. VLPs (Virus like particles) are VNPs that lack viral genomic content [92]. Due to their large sizes and amenability towards surface modification, VLPs are being explored rapidly for a vast array of applications in nanomedicine. VLPs can be genetically or chemically conjugated to display ligands for targeted drug delivery and can be exploited to encapsulate a range of cargo molecules. Several VLP based protein nanoparticles have been reported for targeted delivery of chemotherapy drugs, vaccines, antimicrobial medications, gene therapies, and theranostics. These include the bacteriophage VLP Ms2, Red clover necrotic mosaic virus VLP, bacteriophage P22 VLP, multiple plant VLPs, and mammalian VLPs.

Different strategies can be applied for loading VLPs with cargo molecules. The self-assembly and disassembly of VLPs can be regulated by exogenous factors such as pH and salt concentrations; this can be exploited for infusing cargo molecules within VLPs. Genetic engineering strategies for conjugating scaffolding proteins have also been reported for encapsulating drugs inside P22 Virus. Furthermore, bioconjugation, adsorption, polymerization chemistries have been applied to modify VLPs, making them more amenable for carrying drug molecules to the desired location.

In addition to delivering drug molecules, VLPs have been exploited for vaccine development. Naskalska et al. engineered an HCoV-NL63 VLPs system to develop a vaccine against SARS-CoV-2. VLPs derived from the baculovirus system showed effective delivery of cargo to the cells expressing the ACE2 protein [93]. However, engineering VLPs as cargo vehicles for drug delivery is a cumbersome multistep process. Overcoming this, genetically encoded nano compartments such as encapsulins have attracted attention recently. Encapsulins are bacterial organelles that are easily engineered for loading cargo molecules. The ease of production, modular composition, self-assembly, and biodegradability of encapsulins make them promising candidates for drug delivery systems. Van der Steen et al. reported a redesigned encapsulation-based drug delivery system for breast cancer therapy. In this study an encapsuliun from Thermo- toga Maritima was engineered to display Designed Ankyrin repeat protein (DARPin) on its outer surface, which has an affinity towards human epidermal growth factor receptor 2 (HER2), present on breast cancer cells. In addition, the encapsulin was loaded with cytotoxic protein miniSOG. The cytotoxic load was released in breast cancer cells upon binding to HER2-positive breast cancer cells, which triggered apoptosis [94].

Self-assembling peptides are comprised of monomers of natural or synthetic amino acids, which assemble to form nanostructures. Peptides can be self-assembled into nanostructures by solid-phase peptide synthesis, protein engineering, or ring-opening polymerization. Solid-phase peptide synthesis allows for fabrications of short peptides at molecular levels. Protein engineering techniques are employed to fabricate peptide sequences with longer sequences, and ring-opening polymerization has been applied to large-scale polypeptides production [95]. These self-assembled peptides harness distinctive biochemical and physicochemical properties, which allows for various functional possibilities. Naturally occurring protein's secondary structures such as α-helices and β-sheets are utilized for driving the self-assembly processes. Based on the design and assembly conditions, these structures can be assembled into nanotubes, nanofibres, or nanovesicles. Furthermore, previously described fabrication techniques can enhance peptide functionality by introducing different moieties to the peptide structure.

Owing to their intrinsic physical and biological properties, high stability, and multi-functionality, self-assembled peptides have been extensively explored as drug delivery platforms [95].

Self-assembled peptide-based nanostructures have been reported as delivery agents for anti-cancer drugs. Amphiphilic self-assembled peptides can form nano-vesicles encapsulating hydrophobic drug molecules in the core. Additional surface modifications can be done on the hydrophilic exterior for enhancing specificity. Self-assembled peptides in the shape of nanotubes have shown promising results when conjugated with anti-cancer molecules such as doxorubicin, curcumin, flurocel. These anti-cancer drugs conjugated nanotubes display exceptional biocompatibility and biodegradability, making them highly favorable for cancer therapy. Self-assembled peptides as Nano-fibers can

form peptide hydrogels. These injectable hydrogels allow for a controlled release of drug molecules at the target site. In addition to being used as delivery vehicles for anti-cancer drugs, self-assembled peptides have also been investigated for gene-drug delivery [95].

Cationic peptides based nanostructure display high loading capacity for nucleic acids (DNA, RNA) and have been extensively studied as gene-drug nanocarriers [96]. Panda et al. reported a cationic dipeptide nanoparticle-based delivery system that successfully delivered DNA to hepatocellular carcinoma (HuH 7) cells [97].

Peptide self-assembled nanotubes can be transformed into nanovesicles while being internalized during cellular endocytosis [98]. Therefore conjugating genes to these SNPs allows effective delivery of therapeutic genes to target cells without exerting any significant cytotoxicity.

11.6 Bioinspired-bioderived materials: modified microbial nanowires, modified biofilms

Microorganisms have evolved different extracellular structures to survive in the natural environment and achieve sophisticated tasks for collecting resources. Besides, bacterial colonies in nature are capable of re-organizing their extracellular components so that unnatural conditions become habitable for an optimized trait of energy consumption and material formation [99]. In the literature, scientists visited these microbial structures widely. They realized that microbial wire-like formations and biofilms could be used as a chassis to create enhanced functionalities that could address many of the challenges we face in today's world. Traditionally, biological materials are extracted from nature and used as their solely available form. With the power of biological engineering and synthetic biology, fascinating biomaterial properties obtained and the repertoire of modified biomaterials are growing daily. In this part of the chapter, we will investigate biologically inspired materials or materials derived from biological systems, focusing on intelligent design and modifications from the perspective of microbial nanowires and modified biofilms.

Electrically active microorganisms discovered in nature can reduce surrounding metal sources by using respiration products as electron donors and metals as electron acceptors [100]. This chemical manipulation ability results in the collection of ionized metals for use in metabolism and energy production. In order to achieve an optimized path to cytoplasmic electron generation to the target, those organisms also evolved conductive extracellular structures. *Geobacter sulfurreducens* and *Shewanella oneidensis* are two of the well-known electrically active bacteria that show natural examples of these conductive structures. These structures are named in the literature as "microbial nanowires," and with the emergence of nanotechnology, they gained massive attention from researchers around the globe. Also, with the latter effort, it is discovered that many of the organisms from soil samples and microbiomes have acquired the ability of electron transfer to the extracellular space. The main reason for these structures' importance is their excellent conductivity and possible incorporation with non-biological systems.

In *Geobacter* species, PilA and OmcS are two proteins on focus claimed to transport cytoplasmic electron generation to the outside environment, just like the electric wires transporting electricity from the main supply [101]. As a difference, since being genetically encoded and susceptible to modifications, these proteins are used in the literature as protein engineering targets. In Ueki et al. [102] study, *G. sulfurreducens* PilA was modified with various surface exposing peptides to achieve metal or antibody binding to genetically produced microbial nanowires [102]. This approach shows the potential of microbial wire engineering so that surface decoration could lead to sophisticated functionalities that classical manufacturing methods could not obtain.

Biofilms are generally classified as biological structures secreted and assembled outside the cell by microorganisms for various purposes. These include the protection from hazardous chemicals, separating the shared content among colonies, and attachment to the colonized environment. In general, proteins, carbohydrates, and lipids are considered the main components of biofilms. Due to that, these structures are also considered polymeric structures. Proteins are the main focus of modifications and engineering among these molecules since they are genetically encoded and easily manipulated. Compared to the other bacterial systems, *Escherichia coli* biofilms have been used as a model for engineered biofilm studies. There are many advantages of using *E. coli* biofilm proteins with the studies aiming to generate enhanced biomaterial properties. In a very well-known perspective, those are advantageous to characterize as single monomers, stacked in long-thin structures and free-ends on protein sites susceptible for fusion and functionalization [103]. Literature has many examples of engineered biofilms that are developed with the synthetic biology approach. Functional amyloid curli fibers are bacterial amyloid protein that forms an important protein component of the biofilm extracellular biofilm matrix. Bacterial curli amyloid nanofibers, composed of major CsgA and minor CsgB subunit proteins, are the subject of many studies involving genetic manipulations for bio-inspired material production. These

studies include recombinant production and controlled secretion of CsgA and CsgB, investigating the morphological and mechanical properties of CsgA and CsgB to provide amyloid nanofiber assemblies with different mechanical properties and characterization of their interactions with various solid surfaces. Conductive peptide motifs were integrated into the curli subunits to form conductive protein nanofibers. In addition, controlled assembly and patterning of biofilm amyloids have been fulfilled using genetic logic gates to create an organized living material system with superior features [99,104–108]

Nguyen et al. [107] study, *E. coli* major biofilm protein CsgA engineered to have a modification site in which any desired protein could be displayed on the outer side of the cells [107]. This approach has led to many applications including biocatalysis and bioremediation. On a different approach, a study has shown that modified *E. coli* biofilm proteins can also be used to build patterned biofilm structures [99]. In a recent study, scientists build a 3D bioprinting ink from living materials by inspiring fibrin structure [109]. By fusing N- and C-terminal domains of fibrin protein, which is responsible for blood clotting, a versatile biomaterial was obtained. This biomaterial solidified within seconds and could be used as a 3D printing matrix. As an alternative to *E. coli*, *Bacillus subtilis* biofilm protein TasA is also used in the literature for various studies. In the Zhang et al. [110] study, TasA protein was fused with mussel foot protein (mefp5) to obtain a living biomaterial-based strong glue [110]. In a recent Sahin-Kehribar et al. study, *Campylobacter jejuni* glycosylation pathway and glycosylation motif fused TasA to obtain increased adhesive properties for TasA biofilm proteins [111].

11.7 Conclusion

Taking whole branches of peptide- and protein-based nanomaterial usage into consideration, it could be concluded that the superiority of these molecules on material perspective comes from their modular nature and the possible combination of biological susceptibility to natural systems. In the future, peptide-based nanostructures are envisioned to be involved in almost every field of our daily lives from medicine to electronic devices [112].

Biomaterials built by microbial nanowires and biofilm proteins modified with rational biological design have a vast potential for future applications. Having the power of genetic production and being self-assembling structures, natural proteins possessing polymerization traits for material generation will be the focus of biological design for the next stage of molecular engineering.

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