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Enzyme-Catalyzed Self-Assembly: A Novel Self-Assembly Methodology and Its Applications

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Abstract

Self-assembly is a potent method for building supramolecular materials for a wide range of applications, including energy harvesting and biomedicine. Enzyme-instructed self-assembly (EISA) is a method for creating supramolecular materials for biomedical purposes that has various advantages. The advantages and unique features of EISA in the preparation of biofunctional supramolecular nanomaterials and hydrogels from peptides are highlighted in this paper. In situ molecular self-assembly can be triggered by EISA. As a result, supramolecular structures can be created in situ using overexpression enzymes in disease locations to improve therapeutic selectivity and efficacy. The precursor may be used in the EISA process, which is a two-component self-assembly procedure. The precursor may aid in the stabilisation of EISA-formed hydrophobic peptide nanostructures. More crucially, the outcome of molecular self-assembly may be determined by the precursor EISA has recently been shown to be able to kinetically control peptide folding and shape, as well as the cellular absorption behaviour of supramolecular nanomaterials. Researchers can produce supramolecular nonmaterial in a more precise way and sometimes under spatiotemporal control using a mix of various methods to initiate

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molecular self-assembly. EISA is a potent and unique technology for making supramolecular biofunctional materials that can't be made any other way.

Introduction

Self-assembly is a simple but effective bottom-up method for making functional nano-materials with ordered structures and new functions. Aside from nanoparticles (NPs), polymers, and other inorganic nano-scale building blocks, several types of biomolecules in nature, including as DNA, proteins, peptides, viruses, enzymes, and others, have shown remarkable potential for self-assembly to produce hierarchical nanomaterials. Self-assembled biological nanomaterials have been widely used for applications in materials science, biomedical engineering, tissue engineering, biosensors, and nanotechnology due to their unique molecular characteristics, tunable functions, and ordered structures.

One of the major obstacles in fabricating functional biological nanomaterials is controlling the self-assembly of proteins to generate desirable shapes. Previous research has suggested that this problem could be solved by adjusting internal molecule–molecule/materials interactions (such as hydrogen bonding, electrostatic interaction, hydrophilic/hydrophobic interaction, and DNA/RNA hybridization) or external stimulations (such as changing the pH, temperature, or ionic strength, or adding organics and enzymes to the system).

Biomolecules' self-assembly mechanisms to diverse nanostructures have been extensively studied, with some reviews on the design, production, and uses of self-assembled bio molecular nanomaterials already published. Yang and co-workers, for example, presented an overview of protein self-assembly to diverse supramolecular

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materials, in which design methodologies for self-assembling proteins were introduced and addressed in detail. Willner et al. compiled a list of biomolecule-based nanostructures and nanomaterials' uses in sensing and nanodevice production. Following our evaluation of these publications, we concluded that we may still provide a review on biomolecule self-assembly to functional nanomaterials from the perspectives of internal interaction processes, external stimulation, and intended functionality.

2. ECSA (Enzyme-Catalyzed Self-Assembly)

- **Definition**

This section introduces and discusses the self-assembly of peptides employing enzymes in both extracellular and intracellular circumstances.

2.1. Peptide extracellular self-assembly driven by enzymes

Phosphatase may hydrolyze the phosphate groups of molecules and cause them to self-assemble to create diverse nanostructures by cleaving the P-O bond [33]. It is extensively found in cells, tissues, and organs. Paclitaxel is a commonly used anticancer medicine that has shown promise in the treatment of lung, breast, colorectal, ovarian, and bladder cancers. Paclitaxel, on the other hand, is a highly hydrophobic medication that must be transformed into a water-active form without compromising its biological activity. To address this issue, Gao et al. created a hydrogel precursor (designated 5a in Figure 1a) that included a self-assembly sequence, an enzyme cutting group, a linker, and a paclitaxel molecule [34]. The precursor was transformed into a hydrogel-forming agent (named 5b) by alkaline phosphatase hydrolysis, which could self-assemble into nanofibers and provide supramolecular hydrogels of paclitaxel derivatives [34]. Without enzymatic

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treatment, no peptide nanofibers were generated (Figure 1b); however, adding enzyme to the peptide solution for 5 minutes triggered the rapid production of peptide nanofibers (Figure 1c). The enzyme-treated peptides generated hydrogels through molecular connecting between the created self-assembled nanofibers after an overnight incubation, as illustrated in Figure 1d. The peptide nanofibers that were created were able to progressively release paclitaxel derivatives into the aqueous medium, achieving the goal of cancer therapy. They also demonstrated the self-assembly of phosphatase-hydrolyzed peptides containing serine phosphate for the first time. Supramolecular hydrogels were discovered to be viable soft biomaterials for cell culture and tissue engineering [35]. Furthermore, Gazit and colleagues showed that the regulated assembly of peptide molecules into uniform nanotubes was mediated by the enzymatic activation of self-immolative dendrimers [36].

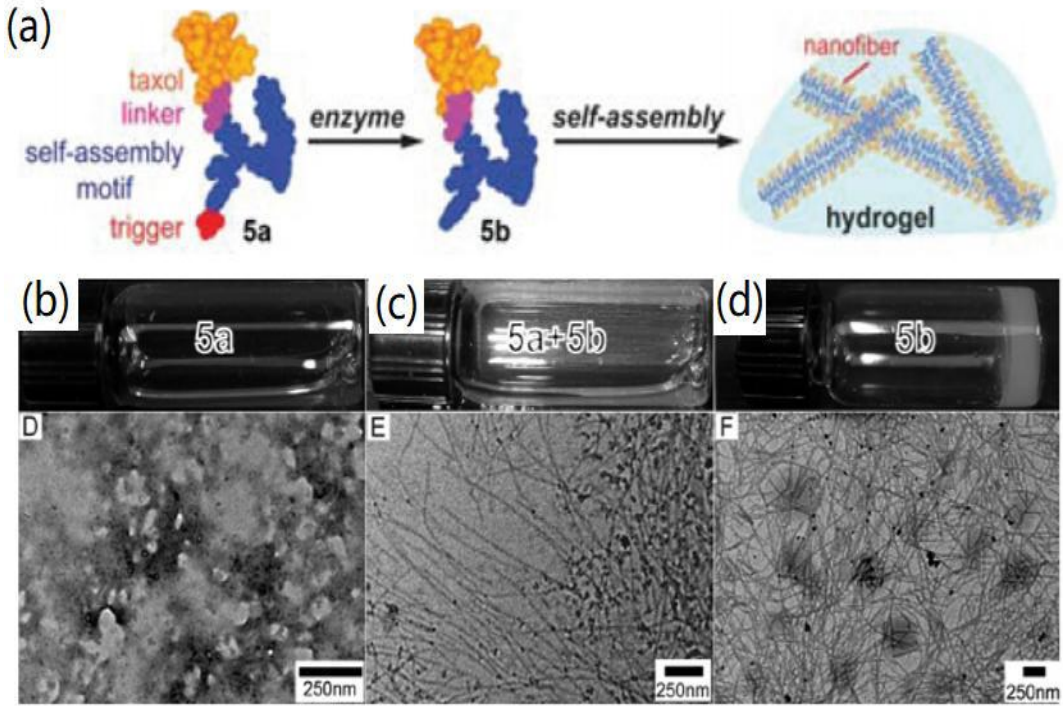

Figure 1: Extracellular peptide self-assembly to produce nanofibers and hydrogels caused by enzyme: (a) self-assembly method, (b) peptide without

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enzyme treatment, (c) mixed peptides, and (d) peptide with enzyme treatment. (Images reproduced with permission from Ref. 34, American Chemical Society, copyright 2009)

Peptide precursors with no self-assembly ability could be induced to form self-assembled nanostructures by breaking chemical bonds with the help of enzymes [37], which could promote the connection of two precursors by forming catalytic bonds to create a suitable hydrogel-forming agent under enzyme catalysis [38]. Toledano et al., for example, employed heat hemolysin to link two peptide derivatives into hydrogel precursors that self-assembled into three-dimensional (3D) nanofiber networks and peptide hydrogels [39]. According to the findings, peptide self-assembly can be initiated by tailoring the conformation and structure of peptide molecules using hydrolase. The first example of employing tyrosinase oxidase to cause the gel-sol phase transition of tiny molecular hydrogels was discovered by Gao and colleagues [40]. Tetra-peptides generated by phosphatase hydrolysis of phosphate in tetra-peptide derivatives can self-assemble into peptide nanofibers and hydrogels. Targeted medicinal molecules could be introduced into the peptide hydrogel first in the peptide hydrogel production process. The loss of - connections between phenol rings causes oxidative tyrosinase to convert tyrosine in tetrapeptides to quinones, culminating in the gel-sol phase transition as a result of the solvation of hydrogels, the matching drug molecules were released. Furthermore, the medication release might be controlled by varying the amount of tyrosinase used. Because tyrosinase activity is increased in malignant melanoma, enzyme-triggered peptide hydrogels with reactive action against tyrosinase could potentially be employed to treat the disease [41].

2.2. Peptide intracellular self-assembly driven by enzymes

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In addition to external enzyme-induced molecular self-assembly, intracellular enzyme-induced molecular self-assembly has also been studied [42–44]. The first stage in the production of peptides is to create non-self-assembled polypeptide precursors outside of cells. After that, polypeptide precursors are delivered into living cells through the cell membrane to create self-assembly construction under the action of enzymes, and after self-assembly, they form self-assembled nanostructures such as nanofibers, impacting cell functions [45–47]. Some peptides that are difficult to get into cells have been combined with other compounds in order to improve their absorption. Because of its high biological activity and stability, D-peptide is a significant molecular platform for biomedical applications. However, because it lacks interaction with endogenous transporters due to its hydrolytic resistance, it is difficult to enter cells [48]. Fortunately, D-peptide may form an ester conjugate with the natural amino acid taurine, which could significantly improve the physiological absorption of tiny D-peptide by mammalian cells [49].

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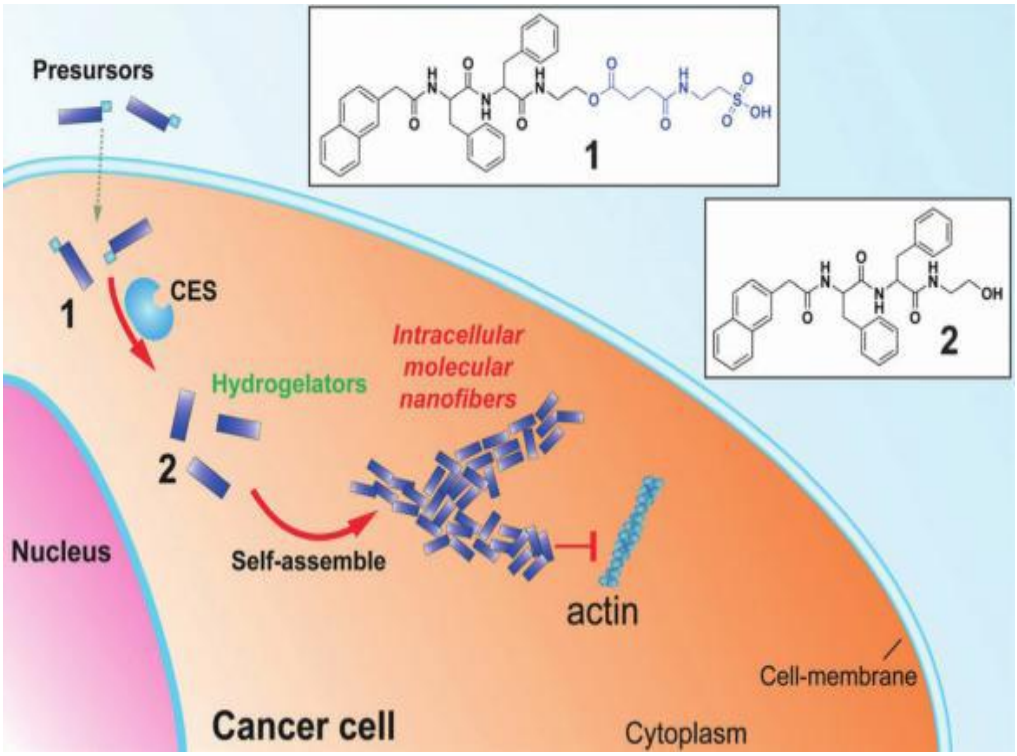

Figure 2: Intracellular synthesis of peptide nanofibers generated by enzymes for the death of cancer cells. For intracellular self-assembly, the CES mediated the conformation transition of peptide precursors to hydrogelators. (Image reprinted with permission from Ref. 50, Wiley VCH, copyright 2015)

Xu and co-workers conducted the first investigation on the combination of intracellular enzyme-induced self-assembly and cisplatin for the treatment of drug-resistant ovarian cancer [50] to address the problem of anti-tumor drug resistance. Figure 2 shows how they used two peptide precursors with mirrored structures (L-1 and D-1) to confirm their hypothesis, in which they used carboxylesterase (CES) to convert the precursors into self-assembling L-2 and D-2 peptides. The nanofibers formed after the self-assembly of both L-2 and D-2 in one system for the creation of peptide nanofibers could interact with actin to suppress cancer cell proliferation. Furthermore, co-culture of cancer cells and normal cells demonstrated that the self-

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assembly mechanism is specific to cancer cells due to overexpression of carboxylesterase in cancer cells. By combining non-cytotoxic components with cisplatin, the enzyme-induced peptide nanomaterials were able to limit tumour cell development while also having unintended effects on normal cells.

- Why does an enzyme cause a reaction?

2-1. Nanostructures and self-assembly control

The control of self-assembly by enzymes and the production of matching peptide nanostructures will be discussed in this section.

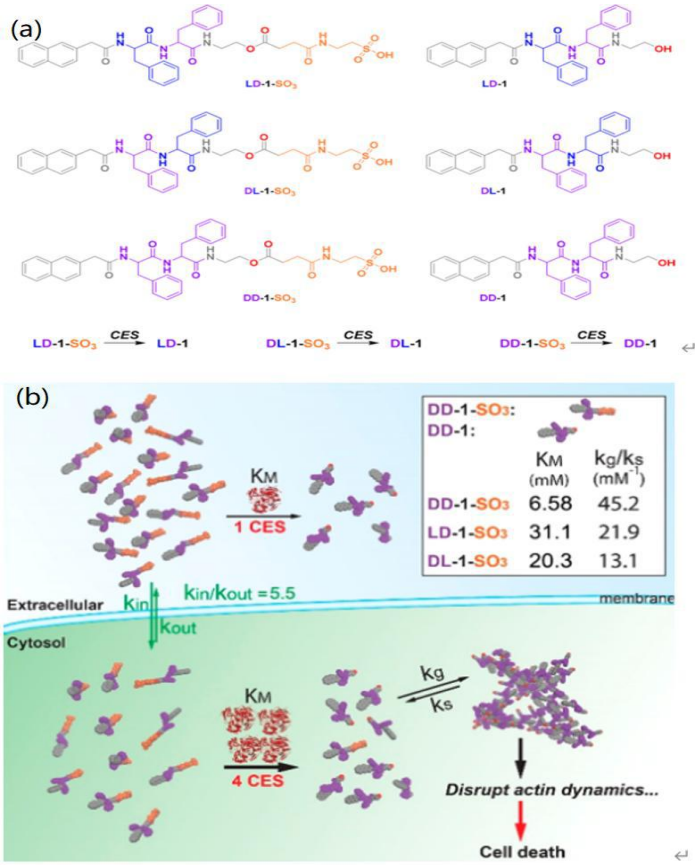

Figure 3: Enzyme-induced peptide self-assembly kinetic control: (a) chemical structures of peptide precursors before and after enzyme catalysis, and (b) kinetics in the formation of various nanostructures. (Images reprinted with permission from Ref. 53, American Chemical Society copyright 2018)

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3.1. Control of self-assembly

Both kinetics and dynamics can be used to influence the self-assembly of peptide molecules, resulting in reasonably stable components. Ulijn et al. studied the change in the free energy of the amide hydrolysis process to evaluate the self-assembly of aromatic short peptide derivatives catalysed by nonspecific endoprotease [51]. The production of amide was shown to be ineffective in mediating the thermodynamic reaction, but the decrease in free energy was very minor. The produced free energies were followed as Gself-assembly-Gamide hydrolysis 0 for the self-assembly of aromatic peptide derivatives in the process of forming self-assembled nanostructures. As a result, the entire process favours the production of amide structures, and this sort of reversible system was carried out under thermodynamic control. Furthermore, because the mechanism was totally reversible, self-tuning could be done while the self-assembled structure was being formed, and the self-assembly components could be chosen to build stable self-assembled nanostructures. They looked into the sequence-structure correlations in the creation of aromatic dipeptide hydrogels in another study and discovered that the thermodynamics governed the enzyme-induced self-assembly of peptides [52]. Li et al. investigated the kinetics of intracellular enzymatic self-assembly as well [53]. For exploring the self-assembly controlled by kinetics, three stereoisomers of dipeptide precursors (LD-1-SO3, DL-1-SO3, and DD-1-SO3) were developed and synthesised. These precursors produced equivalent hydrogel agents after being hydrolyzed by carboxylesterase (CES) (Figure 3a). The morphology of the self-assembled peptide nanofibers differed due to the stereochemistry of the produced hydrogel agents. The lowest and strongest inhibitory actions on cancer cells were found in the precursors of DL-1-SO3 and DD-1-SO3,

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which were inversely proportional to their response rates on the creation of hydrogels in PBS buffer.

They chose three key processes to reflect the interactions between peptide drugs and cancer cells to better understand the enzyme-instructed self-assembly of peptide molecules, including the exchange of enzymatic self-assembled molecules inside and outside the cell, the chemical mechanism of supramolecular assembly through carboxylesterase, and the interaction between self-assembled nanostructures and cancer cells. As shown in Figure 3b, three kinetic parameters were investigated: the molecular transport coefficients of in and out cells (Kin/Kout), the Michaelis constant (KM), and the hydrogelation rate constant (Kg/Ks). The findings showed that the stereochemistry of precursors influenced the form of final nanostructures, and that the cytotoxicity of intracellular enzymatic self-assembly to cancer cells was mostly dictated by peptide molecules' intrinsic properties. This research demonstrated that using the stereochemistry of precursors, it is possible to maximise intracellular enzyme-induced self-assembly of peptides while diminishing the extracellular hydrolysis of molecules.

2.1b Self-assembled nanostructures (Conformation)

Peptides with chosen sequences could be catalysed under enzymes to produce diverse self-assembled nanostructures such as nanofibers, nanotubes, vesicles, networks, and hydrogels under the control of kinetics and dynamics. We'd like to provide you a quick overview of these self-assembled nanomaterials. For the first time, the Stupp group used enzyme response nanostructures to study the development of amphiphilic peptide nanofibers [54], in which a pair of reversible enzymes were used to stimulate the assembly and disassembly of peptide amphiphilic (PA) nanostructures (Figure

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4a). The PA they employed in their investigation has a common substrate sequence that is unique to protein kinase A. (PKA). The PA molecules were phosphorylated after being treated with PKA, resulting in the breakdown of PA nanofibers with a high aspect ratio. As illustrated in Figure 4b, filamentous nanostructures were rebuilt by removing phosphate groups after adding alkaline phosphatase (AP) to the deconstructed peptide solution. The developed peptide's intriguing features could be used to make enzymatic biosensors with great sensitivity and selectivity. Furthermore, the generated peptide nanofibers could be employed to deliver specific drugs. PKA is a biomarker for extracellular malignancies that is mostly found in the surroundings of cancer cell lines. As a result, anticancer medications might be included into PA, allowing them to be released in the presence of cancer cells.

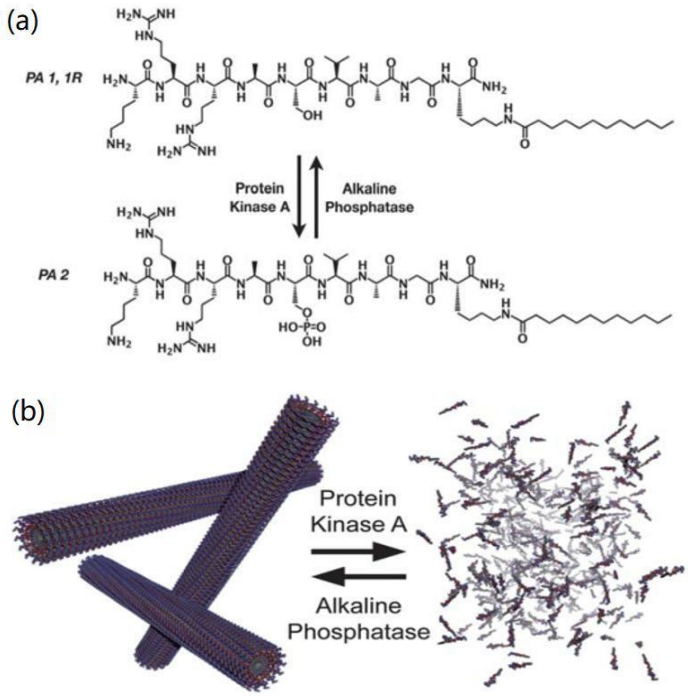

Figure 4: Enzyme-induced peptide assembly and disassembly: (a) peptide sequences after reacting with PKA and AP enzymes, (b) peptide nanofiber disassembly and assembly method. (Images reprinted with permission from Ref. 54, Wiley VCH, copyright 2015)

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Aromatic dipeptide nanotubes are a type of organic nanostructure that is one of a kind. Peptide nanotubes with high water solubility and biocompatibility could be formed under mild conditions using inexpensive starting materials, and the formed nanotubes had good chemical and thermal stability as well as high mechanical strength, making them widely used in biological and nanotechnological fields [55–57]. Adler-Abramovich et al. proposed using a self-immolative dendritic structure as a platform for controllable assembly of peptide nanotubes to improve control over the assembly process in the preparation of self-assembly of peptide nanotubes [36]. As shown in Figure 5a, the penicillin G amidase (PGA) enzyme catalysed the disassembly of a dendritic macromolecule 1 (AB3) to generate an amine intermediate (1a), which was further deconstructed through triple elimination to release three drug units. Based on this technique, a new self-immolative dendritic system for the synthesis of peptide nanotubes was developed using diphenylalanine (FF) and a PGA-specific trigger (Figure 5b). The advantage of this technique was especially substantial when the amount of specific activating enzyme in malignant tissue was low [58]. The developed AB3 dendritic structure also served as an efficient carrier for the synthesis of FF nanotubes under regulated conditions. When the peptide was bound, it prevented any tissue structure from forming. The dendritic peptide decomposed into three FF groups after enzyme activation, allowing it to be released swiftly when the trigger was broken. Furthermore, the method allowed for the release of terminal groups via a variety of triggers, and the self-assembly of terminal groups resulted in the formation of peptide nanotubes.

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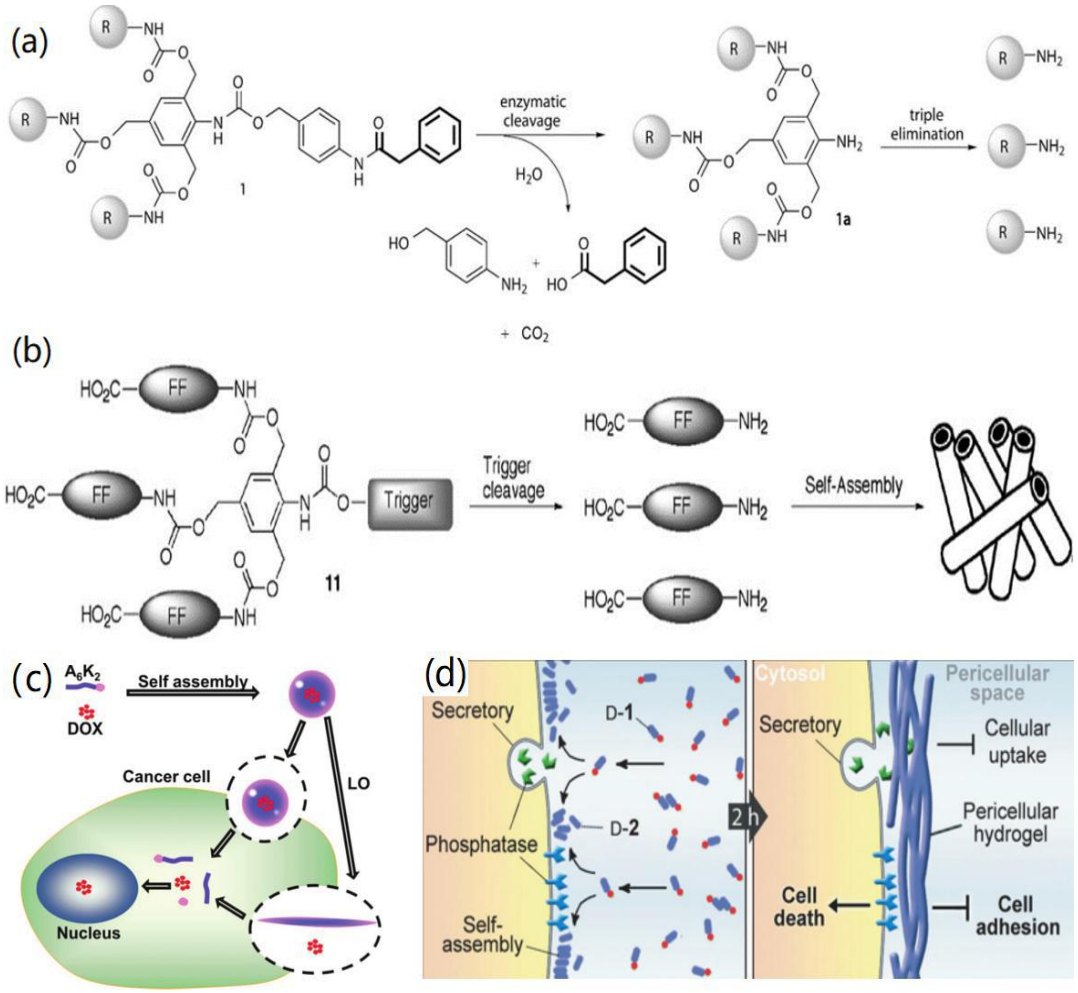

Figure 5: Nanostructures formed by enzyme-induced self-assembly: (a,b) peptide nanotubes: (a) dendritic system after enzymatic cleavage for the synthesis of FF nanotubes, (b) FF-based dendritic system after enzymatic cleavage for the formation of FF nanotubes (Images reprinted with permission from Ref. 36, Wiley VCH, copyright 2007.) C) enzyme-induced peptide vesicle disassembly for drug delivery Reprinted with permission from Ref. 62, Royal Society of Chemistry, copyright 2019. (d) The creation of a peptide nano-network to stop cancer cells from growing. Reprinted with permission from Ref. 63, Wiley VCH, copyright 2014)

Drug distribution and stimulus response materials are both significant roles for peptide vesicles [59–61]. For example, an amphiphilic peptide A6K2 with self-assembly capabilities has been engineered to create peptide vesicles for drug administration of the fat-soluble anti-cancer medication doxorubicin (DOX) [62]. Because most tumour cells' out membranes are negatively charged, the proposed positively charged peptide might connect with the cell membrane by electrostatic contact, allowing DOX-coated peptide vesicles to be transported into tumour cells via

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endocytosis, as shown in Figure 5c. The plasma amine oxidase (PAO) and lysine oxidase (LO) enzymes were shown to be able to oxidise two charged lysine residues in the proposed peptide molecule, causing self-assembled peptide vesicles to degrade and release DOX, and the vesicles to disassemble into nanofibers. The drug loading and release investigations revealed that the produced peptide vesicles were suitable for long-term slow drug release and might be used as high-performance nanocarriers for treating diseases that require long-term treatment. In addition to causing cancer cell apoptosis through enzymatic peptide self-assembly, Kuang et al. discovered that small D-peptide derivatives in the surrounding space could be phosphorylated by phosphatase on the cell surface, triggering peptide self-assembly to form nanoscale networks on the cell surface, as shown in Figure 5d [63]. The generated hydrogels and nano-networks were selectively created on the surface of cancer cells due to over-expression of phosphatase around cancer cells. Furthermore, the nano-networks developed stopped cancer cells from exchanging chemicals, slowing cancer cell proliferation and finally causing cancer cell death. Criado-Gonzalez and colleagues discovered that an enzyme could catalyse the activity of a tripeptide to produce chemical hydrogels through self-assembly, resulting in the production of a supramolecular nano-network structure inside the covalent host material [64]. Aside from the self-assembled nanostructures mentioned above, peptide can also be directed to form 3D hydrogels by the activation of enzymes, and the relevant findings can be found in a recent review by us [13].

2-2. Tuning Noncovalent Interactions in Enzymatic Reactions

- ✓ Bond Formation (for example, lipase, microbial transglutaminase (MTGase), and thermolysin)

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- ✓ Bond Cleavage (e.g., -lactamase, esterase, -chymotrypsin, thrombin, or chymotrypsin) catalyse bond cleavage
- ✓ Oxidation (oxidation of the substrate) (e.g., glucose oxidase, peroxidase, and tyrosinase)
- ✓ Table Enzymes as a Catalyst

2-3 Control of Spatiotemporal

3. Applications in biomedicine

The biomedical applications of enzyme-instructed peptide self-assembly for cancer diagnostics, cancer therapies, bioelectronic devices, and biosensors are presented in this section.

3-2. Diagnosis and treatment of cancer

Chemotherapy still faces a huge problem in achieving specific suppression of cancer cells. In supramolecular chemistry and chemical biology, a new approach based on enzyme-instructed peptide self-assembly has recently been employed, particularly in the creation of a multi-step cancer treatment. Enzyme-instructed peptide self-assembly consists of two processes: enzymatic reaction and self-assembly, which can accomplish selective cancer cell targeting. This mechanism uses local molecular self-assembly to create a mix of enzyme catalysis and molecular self-assembly, interrupting many biological functions [63]. Based on this, Zhou and colleagues created two tetrapeptides with one or two phosphate tyrosine residues that are inhibited by naphthyl at the N-terminus [21]. After enzymatic dephosphorylation, tetra-peptides self-assemble into molecules. When comparing the phosphorylated D-tetrapeptide to the unphosphorylated D-tetrapeptide, they discovered that the phosphorylated D-tetrapeptide had a great inhibitory effect on cancer cells.

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Furthermore, when monophosphorylated D-tetrapeptide and bisphosphorylated D-tetrapeptide were compared, the monophosphorylated D-tetrapeptide had a superior effect. As seen in Figure 6, cancer cells with higher levels of expression are more likely to be suppressed by precursors, according to the findings. This concept can be used to other enzymes, self-assembly molecules, or systems to investigate supramolecular assembly in the cellular environment [65], demonstrating a potentially highly successful cancer therapeutic method.

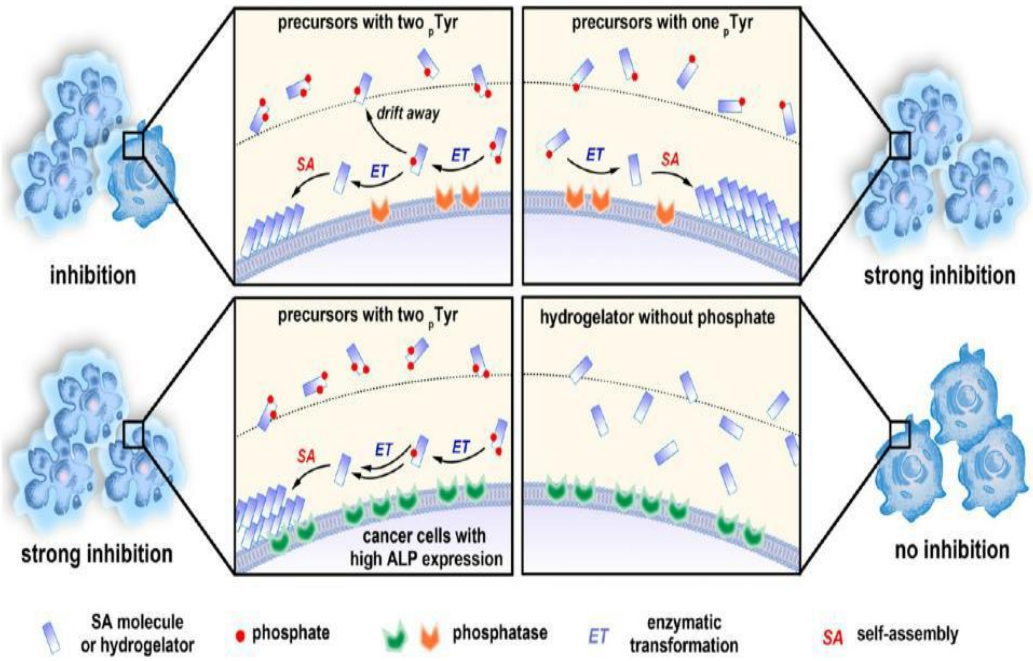

Figure 6: Peptide self-assembly guided by enzymes for the destruction of cancer cells. (Image reprinted with permission from Ref. 21, American Chemical Society, copyright 2016)

In stem cells and some cancer cells, the enzyme alkaline phosphatase (AP) is over expressed. It can convert ATP to adenosine in the body, resulting in illnesses including cancer. The method of blocking AP activity was commonly utilised in past study methods to organise the occurrence of this process, but the efficiency was not particularly satisfactory. Enzyme-guided peptide self-assembly has been demonstrated to effectively destroy cancer cells that over express AP [66, 67].

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Peptide assemblies were produced preferentially in cancer cells and within cells, triggering cancer cell death through external cell death receptor activation or intracellular cellular stress. Feng et al., for example, found that AP guiding successfully inhibited the peptide self-assembly of osteosarcoma tumours in vivo [68]. In animal studies, it was discovered that AP created peptide assemblies via a dephosphorylation process triggered by precursors. This method suppressed tumour growth in an in-vivo osteosarcoma mouse model while causing no harm to other bodily tissues, making it ideal for producing enzyme-guided peptide assembly as functional nanomaterials for in vivo cancer therapy. Self-assembled peptide nanostructures can be used as drug carriers to carry anti-tumour drugs to kill cancer cells in addition to directly destroying cancer cells. Small molecules can self-assemble to produce molecular hydrogels through noncovalent interactions, making them useful for drug delivery and tissue engineering [69]. Small molecules that can respond to environmental stimuli have a lot of potential, especially in medicine administration. Gao et colleagues. The production of a tiny molecular hydrogel of Ac-YYYY-OMe and postulated that tyrosinase oxidase may be responsible for the gel-sol phase shift [40]. As a comparison, three structural compounds were synthesised utilising phenylalanine (F) instead of tyrosine (Y). The drug molecules were added to the structure during the process of creating supramolecular hydrogels, and the encapsulated pharmaceuticals were released by varied amounts of tyrosinase to achieve cancer therapy in this method.

3-3. Bioelectronic devices and biosensors

Some organic molecules have a stacking structure that allows them to self-assemble into nanoscale wires, which can be employed in optical and bioelectronic devices

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[70–72]. Although some electronic materials have been created using peptide self-assembly [73], the electrical conductivity of peptide-based nanomaterials has not been directly tested. Other methods of measuring charge transport, such as spectroscopy, invariably result in mistakes in the measurement of electrical conductivity. The enzyme-triggered peptide self-assembly was discovered to be straightforward to manage and can better translate unassembled premise into self-assembled construction modules. Changing its chemical composition or the qualities of self-assembled components during the self-assembly process might not only modify the morphology of its nanostructure, but also affect its electrical conductivity [74]. Xu et al. went on to investigate the development of a -peptide nanotube network by enzyme-triggered self-assembly initiated by aromatic peptide amphiphiles, which resulted in considerable charge transfer [75]. At ambient temperature, the team observed the lowest thin layer resistance of macromolecular peptides capable of 0.1 MΩ/sq in air and 500 MΩ/sq in vacuum. Biosensors, intelligent biomaterials, and certain biological photovoltaic devices are projected to be made from the nanomaterials created.

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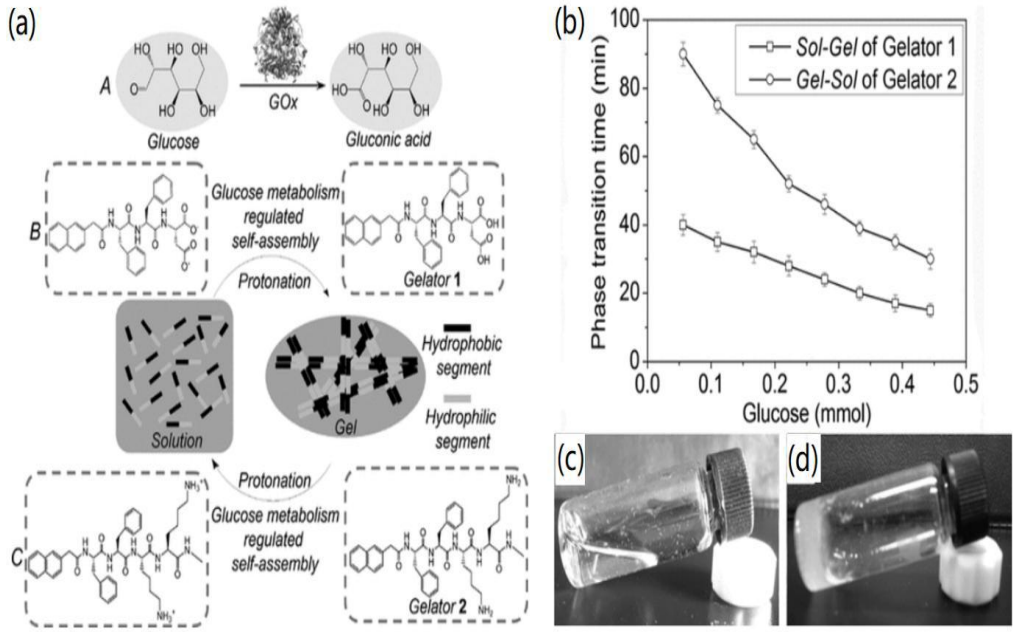

Figure 7: Peptide nanomaterials with enzyme-instructed phase transitions for biosensor applications: (a) Peptide design and glucose metabolism phase transition mechanism. (b) Phase transition time vs. glucose concentration, (c) gelator 1 after addition of GOx and fructose, and (d) gelator 2 after addition of GOx and fructose. (Images reproduced with permission from Ref. 76, Wiley VCH, copyright 2012)

Enzyme-induced peptide nanoparticles can also be utilised to make biosensors, in addition to their uses in electronic nanomaterials. Zhang and colleagues, for example, demonstrated glucose metabolism-induced peptide self-assembly for colorimetric glucose detection [76]. Glucose oxidase (GOx) mediated glucose metabolism and facilitated the self-assembly of peptide-based building components, as seen in Figure 7a. The glucose metabolism systems were formed when glucose and GOx were introduced to the peptide-based gelator 1 and gelator 2 systems, and the metabolic products prompted the development and disintegration of hydrogels (Figure 7b). As a result, the phase transition of gelators 1 (sol-gel) and 2 (gel-sol) might be employed as a colorimetric glucose sensor indicator. The addition of GOx and fructose to gelators 1 and 2 did not produce phase change within 24 hours, as seen in Figure 7c

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and 7d. Ulijn et al. used thermolysin to create the production of peptide hydrogels via enzyme-triggered reverse hydrolysis [39]. They discovered that enzyme-triggered peptide gelation might be used to measure protease activity during their research procedure. In a separate investigation, Bremmmer and colleagues showed that enzyme-induced peptide gel formation may be used to induce fake blood clots in human blood plasma [77].

4. Summary and Outlook

Self-assembly is a potent method for building supramolecular materials for a wide range of applications, including energy harvesting and biomedicine. Enzyme-instructed self-assembly (EISA) is a method for creating supramolecular materials for biomedical purposes that has various advantages. The precursor may be used in the EISA process, which is a two-component self-assembly procedure. The precursor may aid in the stabilisation of EISA-formed hydrophobic peptide nanostructures. More crucially, the outcome of molecular self-assembly may be determined by the precursor. EISA has recently been shown to be able to kinetically control peptide folding and shape, as well as the cellular absorption behaviour of supramolecular nanomaterials.

Acknowledgement

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