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Vesicles displaying aggregation-induced emission: Fabrication and applications



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Abstract

Vesicles displaying aggregation induced emission are very promising in fields related to biology. In this review, we summarized recent progresses in the creation of such vesicles and their applications. The following contents are included: 1) the general background of AIE vesicles; 2) creation of AIE vesicles with synthetic covalent compounds; 3) creation of AIE vesicles with supramolecular chemistry; 4) the application of AIE vesicles in real-time imaging, visualized drug delivery, cell communication and fission-fusion process, and lightharvesting. Finally, we envision AIE vesicles may have profound impact on medical science, biological science and material science.

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Introduction

Molecular self-assembly is a generic phenomenon in nature and is associated with the spontaneous formation of stable, well-defined nanostructures driven by noncovalent interactions under some certain conditions [1]. The investigation of molecular self-assembly and their potential applications can help us learn from nature better and create many new materials. Study on molecular self-assembly has lasted for more than 100 years and chemists have constructed different patterns ranging from nanometer to millimeter even to larger scales [1-6]. Here we focus on vesicles, which are considered simple but well-organized structures that can mimic the remarkable properties of biological membranes and have been widely employed in pharmacy, food, cosmetics, and other related products [7]. Of the various self-assembled vesicles, the fluorescent ones, are of special interest.

The history of fluorescent vesicles can be dated back to 7 decades ago [8], when people doped traditional fluorescent dyes into them, or designed various probe molecules by attaching a traditional fluorescent group covalently to a self-assembled molecule [9,10]. Endowing sufficient luminescence to vesicles not only allows tracking the circulation of materials stored in the vesicles, but also uncover the physical insight of these fundamental structures and has displayed profound application potentials in a vast number of fields [11]. However, aggregation of the dyes may cause fluorescence quenching, which greatly reduces the luminescent efficiency.

Aggregation-induced emission (AIE) dyes are robust alternatives in creating luminescent vesicles [12–16]. It is now commonly recognized that the self-assembly of molecules containing an AIE moiety could provide excellent luminescence that are suitable for in situ tracking. This not only overcomes the weak fluorescence suffered from traditional fluorescent dyes, but also allows tracking the entire circulation details of the vesicles in the process, providing both fundamental knowledge and practical guidance. Following proper protocols, the bright emission from AIE molecules in aggregation state can light-up an invisible area in a biosystem or a material system, which thus makes it possible to track the status of these systems [17-21]. In this review, we will introduce how AIE technique is combined with vesicles, and what will happen when AIE meets vesicles.

General background of AIE vesicles

Vesicles, sometimes called liposomes, are aggregates with dynamic supramolecular structures consisting of a molecular layer which can encapsulate a volume of solvent [7,22]. They are three-dimensional hollow structures, with spherical shell in which an aqueous chamber is enclosed by a membrane made from amphiphiles, and have found numerous applications in chemistry, biology and materials science. The formation of vesicles depends on a delicate balance between hydrophobic and hydrophilic molecular segments and as well on the packing parameter. Typically, a micelle is self-assembled from several hundred even thousand surfactant unimers in aqueous solution as a result of hydrophobic effect as the concentration of the surfactant solution is greater than the critical micelle concentration (CMC). As the volume of the hydrophobic chain of an amphiphile increases, for instance, changes from single chain to double chain, the curvature of the self-assembly will decrease, so that a double layer may come into formation. The closed structure of double layers will lead to hollow spheres, namely vesicles. The radius of a vesicle could be several micrometers since it might be an onionlike multilayer one. Although the size of vesicles has no relation with the molecular length of the self-assembled

Figure 1

molecules, the thickness of one double-layer of a vesicle is always close to two folds of the extending length of the molecules composed the double layer.

Since the AIE moiety usually has large volume, AIE vesicles can easily come into formation when an AIEgen was incorporated into an amphiphile. The key leading to AIE vesicles is to well balance the volume of the hydrophobic portion and the hydrophilic ones. One can fine tune the hydrophobic/hydrophilic volume ratio both for small and macro molecules to obtain fluorescent vesicles. And the way to obtain molecules that are able to form AIE vesicles mainly involves two main strategies: chemical synthesis and supramolecular pathway.



(a) Schematic illustration of preparation of vesicles with amphiphile 1 [23]. (b) Molecular structures of TPE-BEP and the protonated TPE-BEPH, and schematic illustration of the transformation between TPE-BEP self-assemblies driven by protons [24].

AIE vesicles based on synthetic amphiphiles

AIE vesicles based on synthetic ionic amphiphilic small AIE molecules

As an analogue to phospholipids, synthetic amphiphiles containing AIEgens can self-assemble into AIE vesicles when their hydrophilic/hydrophobic ratio is in the suitable range. Zhang et al. [23] designed an amphiphile 1 (Figure 1a) which consists of a hydrophilic ammonium ion and the hydrophobic tetraphenylethene (TPE) moiety. This amphiphile could spontaneously selfassemble into vesicles (TPE-Vs) with a diameter of \sim 106 nm in aqueous solution. After addition of the crosslinker dithiothreitol (DTT), the -SH groups reacted with the alkenvl groups at the surface of TPE-Vs by thiol-acrylate Michael addition, leading to the crosslinked AIE vesicles (TPE-CVs) (Figure 1a). Combining the advantages of aggregation-induced emission in luminous enhancement and cross-linking in stability, they fabricated TPE-induced cross-linked vesicles with an entrapped acceptor of RhB (TPE-CVs@RhB), which achieved a high efficiency multicolor emission of the visible spectrum, including white, by altering the amount of entrapped acceptor. Besides, Tang et al. [24] elaborately designed and synthesized the AIE amphiphile TPE-BEP, with hydrophilic units of tetraethylene glycol groups and proton-binding sites of pyridine (Figure 1b). The self-assemblies had a spherical structure in neutral conditions with tetraethylene glycol groups located on the outer shell. This structure could transform to nanovesicles in acidic conditions as a result of the charge converse caused by the protonation of the pyridinium group.

AIE vesicles based on synthetic nonionic amphiphilic small AIE molecules

Apart from the ionic groups, the hydrophilic moiety can also be nonionic groups. One of the examples is nonplanar bile acid. The nonplanar steroidal skeleton of bile acids has a convex hydrophobic surface and a concave hydrophilic face full of -OH groups. Li et al. [25] synthesized a series of TPE-bile acid conjugates and explored the synergetic self-assembly of both TPE and bile acid building blocks. It was founded that only compounds with at least two hydroxyl groups in the bile acid unit could self-assemble into vesicular nanostructures in co-solvent systems (water/acetone or water/methanol). They suggested that the hydrophilichydrophobic balance of bile acid units and the hydrogen-bonding probability have critical influence on the morphologies of the self-assemblies. The synergetic combination of the distinct properties of TPE and bile acid units could directly afford uniform fluorescent vesicles with amphiphilic binding pockets in the membrane. Besides, E isomer could self-assemble into monolayer vesicles, while Z isomer could form bilayer vesicular structures. Bi and Zhang et al. [26] present another amphiphilic molecule, which is a conjugate of TPE with β -D-galactose (TPE-Gal). It can facilely selfassemble into pH/ β -D-galactosidase dual responsive vesicles with an average hydrodynamic size of 157 \pm 7.69 nm and a zeta potential of -25 ± 2.3 mV.

AIE vesicles based on synthetic non-amphiphilic AIE molecules

In addition to traditional amphiphilic molecules, some non-amphiphilic molecules were also investigated to fabricate AIE vesicles. Li et al. reported that the oligo (p-phenylenevinylene) (OPV) -based intramolecular charge-transfer (ICT) compound (TCBD)₂-OPV₃ (Figure 2a) could self-assemble into vesicles by injecting its THF solution into well-stirred hexane [27]. However, this is an unstable state and it would undergo a morphology from 0-D hollow nanospheres to 1-D nanotubes. Wang et al. [28] observed the formation of metal-carbonyl (MC) vesicles via the molecular selfassembly of a bithiophene tethered Fp (Fp: $CpFe(CO)_2$) derivative (Figure 2b). The $CpFe(CO)_2$ is hydrophobic and non-surface-active, but it can assemble into MC vesicle (MCsome) in water via water-carbonvl interaction (WCI). The MCsome with a bilayer interdigitated membrane, as confirmed by a number of techniques is highly integrated upon dilution. The spatial segregation of the AIE-active bithiophene domain from the iron-carbonyl units by the butanoyl spacers prevents the fluorescence quenching by iron and renders the photo luminescent MCsome. Jiang and coworkers [29] reported a class of π -conjugated all benzene vesicles based on [8]cycloparaphenylenes ([8] CPPs) and its derivatives, which have eight para-linked benzene rings (Figure 2c). These nonplanar π -conjugated molecular nanocycles can self-assemble into nanoscale crystalline multilayer vesicles in mixed solvent. The core driving forces for the formation of CPP vesicles are crystallization and π - π interaction of nonplanar molecular nanocycles, which is robust enough to maintain the curved structure of the vesicles. And the side group of CPPs influences their close packing in the wall of vesicles.

AIE vesicles based on synthetic polymeric AIE molecules

The synthetic AIE polymers that could form AIE polymer vesicles (AIE polymersomes) usually have similar amphiphilicity to that of AIE small-molecule amphiphiles, but show much higher molecular weights. For example, most vesicles self-assembled from small molecules disassemble if the electrical charge of the component molecules increases [30-33], whereas polymeric vesicles often exhibit "breathing" behavior, namely, the size of the same vesicle increases upon increasing the electrical charge but contracts upon discharging [34,35]. Therefore, AIE polymersomes have many superior properties over small molecule AIE





Chemical structure of the molecules that could self-assemble into vesicles (TCBD)2OPV3 (**a**), bithiophene tethered Fp (Fp: CpFe(CO)2) derivative (**b**) [8],cycloparaphenylenes ([8]CPPs) and its derivatives(**c**), PEG-POSS-(TPE)7(**d**) (PEG44-P (AIE)n) (**e**), PEG-b-P (DEAEMA-co-TPEMA) (**f**), P (TPE-alanine) (**h**) and trans-PEG550-TPE-Chol and cis- PEG550-TPE-Chol(i). (**g**) Oligonucleotides Strands A and B modified with three phosphodiester-linked E-TPE unit at their 3'-ends and their hybridization.

vesicles, such as higher toughness and better stability and have been widely investigated [36,37].

As a hydrophobic molecule, the AIE moiety is normally incorporated in the hydrophobic block of AIE amphiphilic polymers. The AIEgens can be as the main-chain or side-chain and the as synthesized polymers can be either block copolymers or alternating copolymers. Wu's group [38,39] developed tadpole-shaped AIE amphiphilic polymers PEG-POSS-(TPE)₇ by attaching TPE groups to the multi-terminals of POSS in the prepolymers PEG-POSS via Schiff base bonds (Figure 2d).

In these polymers, poly (ethylene glycol) chain serves as the hydrophilic moiety, and rigid cage-shaped POSS functionalized with TPE units as the hydrophobic moiety. Depending on the ratio of hydrophilic moiety. PEG-POSS-(TPE)7 could self-assemble into polymersomes or polymer micelles by nanoprecipitation method in THF/water co-solvent system. PEG₃₅₀-POSS-(TPE)₇, with the short PEG chain (Mn = 350), self-assembled into polymersomes with diameter of 83 nm [39]. Further increasing the PEG molecular weight to Mn = 750, polymersomes with large diameter of 350 nm could be formed [38]. Abdelmonhsen and coworkers [40,41] synthesized a range of well-defined amphiphilic poly(ethylene glycol) (PEG)-PTMC(TPEDC) copolymers (PEG₄₄-P (AIE)_n), where n = 5,8,14, or 22) to explore the effect of increasing steric bulk upon molecular self-assembly in order to achieve functionallydense, morphologically discrete AIE polymersomes (Figure 2e). They investigated the effect of molecular composition upon molecular self-assembly using a dropwise solvent switch process from THF to water (at 50 vol %) followed by dialysis purification. PEG₄₄-P (AIE)_{5/8/14} were compatible with this process, assembling into nanovesicles of around 300-500 nm in size with low polydispersity (PDI ≤ 0.1) while PEG₄₄-P (AIE)₂₂ vielded micelles/polymer nanoaggregates.

Zhang et al. [42] synthesized amphiphilic block copolymer PEG-b-P (DEAEMA-co-TPEMA) in which the hydrophobic block was a copolymer made of DEAEMA and tetraphenylethene functionalized methacrylate (TPEMA) with unspecified sequence arrangement (probably random because of the monomer similarity between DEAEMA and TPEMA) (Figure 2f). TPEMA was used because it presents both a hydrophobic feature and fluorescence. They studied the vesicle formation by nanoprecipitation with the presence of a nonselective cosolvent (THF or dioxane) and the morphological transformation of the vesicles upon CO₂/Ar stimulation using several techniques especially cryo-electron microscopy (cryo-EM). And a reversible CO₂/Ar-driven vesicle-micelle transition was clearly identified. The dynamics of molecular self-assembly was achieved by the reduction of the interfacial tension between the hydrophobic block and aqueous solution, which was realized either by adding nonselective co-solvent or by introducing hydrophilic units in the hydrophobic block along with protonation of DEAEMA upon CO₂ bubbling.

Apart from these classical vesicles, Zuber and Häner et al. demonstrated that the DNA hybrids possessing tetraphenylethylene sticky ends at both sides selfassemble into two different types of vesicular architectures in aqueous medium [43,44]. The chemically modified oligonucleotides Strands A and B were prepared via solid-phase synthesis and modified at their 3'ends with three phosphodiester-linked E-TPE units. Due to the complementarity of DNA single strands A and B, they hybridize and form the DNA duplex A-B, which contains TPE overhangs (sticky ends) on both sides and either self-assembles into vesicles with an extended alignment of the DNA duplexes (type I) or in a compact arrangement (type II). Vesicles of type I appear as prolate ellipsoids with a diameter of 50-100 nm. Type II vesicles, on the other hand, exhibit a thicker membrane, which is compact (columnar) manner. Li et al. [45] reported a stereoisomer-directed self-assemblies, nanoporous vesicle with aggregationinduced emission (AIE) properties. They synthesized amphiphilic polymer PEG550-TPE-Chol the (Figure 2h), in which the hydrophobic part is composed of a tetraphenylethene (TPE) group and a cholesterol moiety and the hydrophilic block is a poly (ethylene glycol) (PEG, $M_n = 550$ Da). This molecule has two stereoisomers, trans-PEG550-TPE-Chol and cis-PEG550-TPE-Chol. And they showed distinct selfassembly behavior in water: trans-PEG550-TPE-Chol self-assembles into classical vesicles, while cis- PEG550-TPE-Chol self-assembled into cylindrical micelles. Interestingly, trans/cis mixture of PEG550-TPE-Chol (trans/cis = 60/40), either naturally synthesized without isomers separation during the synthesis or intentionally mixed, construct perforated vesicles with nanopores.

Beside the block copolymers, main-chain AIE amphiphilic alternating copolymers have also been prepared by click reaction from two bi-functional monomers: TPEtype diazide and alanine-containing divne [46]. These polymers, P (TPE-alanine), are also amphiphilic, where the amide groups on the side chain and triazole segments on the main chain act as hydrophilic part, and the TPE in the main chain and the ester groups in the side chain as hydrophobic part (Figure 2g). Notably, unlike the conventional AIE amphiphilic block copolymer containing TPE side chains, which has almost no fluorescence in diluted solution, the P (TPE-alanine) exhibited weak fluorescence emission at 463 nm in solution. This is because the intramolecular rotation of TPE moieties would be already restricted to some extent as they were in the polymer backbone. Using nanoprecipitation method, P (TPE-alanine) self-assembled into polymersomes with strong aggregation-induced emission in THF/H2O mixture, at water fraction of 50%.

Supramolecular AIE vesicles

Despite these achievements, synthetic amphiphiles can suffer from tedious synthesis and low response speed, due to the irreversible nature of covalent bonds. Inspired by nature and toward the goal of constructing smart self-assemblies, the concept of the supraamphiphile is proposed. Supra-amphiphiles [6,47] can be constructed by two or more molecular/macromolecular building blocks via noncovalent interactions, such as electrostatic interaction, host-guest interaction, π - π





(a) Illustration of molecular self-assembly of WC4P-20 [49]. (b) Molecular structures of TPA-1 and illustration of the molecular self-assembly of TPA-1/Zn²⁺ fluorescent vesicle which is capable of drug loading and displays two-photon excited emission [16]. (c) The self-assembling system of TPE-BPA with different cation surfactants and the metal-ions-facilitated functionalization of the fluorescent vesicles [13,14,51,52].

interaction, etc. The noncovalent nature of supraamphiphiles may simplify the procedures for chemical synthesis. And incorporation of functional moieties can be easily achieved. Besides, supra-amphiphiles with various topologies can be formed and both low and high molecular weight supra-amphiphiles can be fabricated. The strategy of constructing AIE supra-amphiphiles provides another interesting way toward AIE vesicles that does not need direct synthesis of various amphiphilic molecules with different hydrophobic/hydrophilic ratios, which is sometimes tedious and complicated [7].

AIE vesicles directed by host-guest chemistry

It is well known that host molecules, such as cyclodextrins, cucurbit [n] urils, and calixarenes, are able to form inclusion complexes with particular guest molecules, which is regarded as a molecule recognition process. Hu and coworkers explored the fabrication of multilayer vesicles based on the noncovalent supramolecular assembly between a water-soluble pillar [5]arene (WP5) and a bola-type tetraphenylethylene-functionalized dialkyl ammonium derivative (TPEDA) [48]. ¹H NMR spectroscopic studies and isothermal titration calorimetry (ITC) were conducted to investigate the host-guest binding ability between WP5 and TPEDA. Sessler et al. successfully constructed multilamellar AIE vesicles with supra-amphiphile WC4P-20 (Figure 3a) [49]. Under neutral or basic conditions, the complexation of TPE-containing pyridine bis-N-oxide (20, guest molecule) and a water-soluble calix [4]pyrrole with aryl peripherv functionalized by four COO- groups (WC4P, host molecule) could form neutral supramolecular complex WC4P-20. The host-guest interaction with a combination of hydrophobic interactions and hydrogen bonds stabilized the complex with the guest binding deeply embedded into the aromatic cavity of calix [4] pyrrole receptor. The supra-molecular complex WC4P-20 is a bola-type supra-amphiphile which is suitable for vesicle formation. Multilamellar AIE vesicles with average diameter of 148 nm were formed when 2 equiv. of WC4P was added to the solution of the guest molecule 20, which exhibited strong blue fluorescence originated from the restricted rotation of the phenyl rings of TPE.

AIE vesicles based on coordination interactions

Usually, the AIEgens can hardly spontaneously selfassemble into vesicles in solution due to their poor packing ability resulted from the non-planar geometry of the AIEgens. Triarylamine (TPA) and its derivatives are such AIEgens. However, Yan's group [16] successfully obtained metallo-organic AIE vesicles with triarylamine carboxylate (TPA-1) upon coordination with Zn^{2+} ions or other divalent transition metal ions (Figure 3b). This is because one Zn^{2+} coordinate with two TPA-1, which drastically enhanced its hydrophobic effect. As a result, the rigid Zn (TPA-1)₂ supramolecule self-assemble into bilayers, which finally enclose into vesicles. Since the TPA-1 molecules were firmly confined in the vesicle membrane, the obtained vesicles displayed strong green fluorescence. Interestingly, this dense packing of TPA-1 in the vesicle membrane also allows absorption of two photons at one time, exhibiting two-photon emission.

AIE vesicles based on electrostatic interactions

Electrostatic interaction could also be employed to fabricate supramoleclar building blocks for the molecular self-assembly of AIE vesicles [13,14,50-52]. Yan and co-workers [50,51] developed a TPE derivative carrying four water soluble carboxylate heads (TPE-BPA, Figure 3c). TPE-BPA was highly soluble in water with negligible emission. Upon addition of cationic hydrocarbon chain myristoylcholine chloride (MChCl), TPE-BPA@8MChCl supra-amphiphile could selfassemble into fluorescent vesicles (Figure 3c) with diameter of 110 nm [51]. With the same strategy, they successfully created another example of supramolecular complex by changing the cationic hydrocarbon chain from MChCl to hexadecyl trimethyl ammonium bromide (CTAB). A neutral supramolecular complex TPE-BPA@8CTAB was obtained at the CTAB:TPE-BPA molar ratio of 8:1, which simultaneously self-assemble into fluorescent vesicles [50]. On account of the chelating point provided by dicarboxylate pyridine heads of TPE-BPA, metal ions could be introduced via coordination interactions to enable the system multiple functions. Tang et al. reported that upon the introduction of Fe²⁺ to the TPE-BPA@8CTAB, the vesicles underwent a fusion process upon oxidation of Fe^{2+} to Fe^{3+} , while a fission process further proceeded when Fe^{3+} was reduced to Fe^{2+} [13]. Similarly, Zn^{2+} can also be introduced into the system to fabricate vesicles with triggered fission behavior [14]. Besides, Gd³⁺ can be coordinated onto the surface of fluorescent vesicles fabricated by TPE-BPA and double-tail surfactant didodecyldimethylammonium bromide (DDAB) [52]. The Gd^{3+} performed as a magnetic resonance imaging (MRI) component, as well as positive charge suppliers which are usually highly toxic to cells due to the charge-causing breakdown of the membrane of the organelle (Figure 3c).

Applications of AIE vesicles Cell models

Vesicles have long been considered as ideal model systems of biological membrane for fundamental studies of membrane biophysics. Endowing vesicles would no doubt provides "visible" information at molecular scale. Yan et al. [50] reported that TPE-BPA@8CTAB vesicles could divide into many smaller ones upon addition of Zn^{2+} , accompanied by the reduction of fluorescence, suggesting a looser molecular packing in the charged vesicles. The Zn^{2+} triggered vesicle fission is attributed to the increased surface charge, as indicated by zeta potential test. This model system, taking the advantage of the coordinating aggregation induced emission (AIE) molecule, for the first time reveals that electrical charge not only promotes the membrane division of cancer cells, but also leads to looser molecular packing in the cancer cells which facilitates much quicker mass exchange through the membrane (Figure 3c). Recently, they [13] developed another Fe@TPE-BPA@8CTAB exosomemimetic vesicles with fusion and fission behaviors

Figure 4

modulated by redox treatments. When Fe^{2+} was oxidized to Fe^{3+} , positive charges were removed from vesicle because the hydrolysis of Fe^{3+} ions decreased their coordinated capacity. Consequently, vesicles tended to fuse together and formed large-sized vesicles to lower the intension free energy. Benefiting from the AIE features of the vesicle building blocks, the molecular packing states in vesicular transformation were monitored by fluorescence emission changes (Figure 4).



(a) Real-time scattering intensity change and (b) size distribution of Fe^{2+} @vesicles exposed to O_2 . (c) TEM images of fusion behaviors of Fe^{2+} @vesicles upon oxidation. (d) Real-time scattering intensity change and (e) size distribution of Fe^{3+} @vesicles with VC. (f) TEM images of fission process of Fe^{3+} @vesicles upon reduction. (g) Schematic illustration of possible mechanism of reversible and controllable fusion and fission behaviors [13].

Bioimaging

Biological imaging is an important tool that could provide critical information for understanding various physiological and pathological processes that are very useful for a number of biological applications such as cancer detection and treatment, stem cell transplantation, immunogenicity and tissue engineering. Chen et al. [53] firstly reported the molecular selfassembly and applications of glycopolypeptide-TPE bioconjugate for bioimaging and tracing of live cells. Amrita and co-workers [54] synthesized a series of ethylene glycol modified water-soluble tetrameric TPEamphiphiles with pyridinium polar heads for protein and DNA binding assay, wash-free bacterial imaging, and staining agents for nucleic acids. Li et al. [55] developed

Figure 5

a cation—anion interaction-directed functional vesicles using imidazolium salts with multiple imidazolium moieties and alkyl carboxylate counter-anions. The vesicles display strong fluorescence owing to the presence of TPE moiety in the TPEI-C8 cation. This fluorescent vesicle was able to penetrate the cell membranes without obvious toxicity and target to the nucleus with a bright blue emission. In contrast, only a very weak blue emission could be observed for the imidazolium salt TPEI-Br with bromide as the counteranion during the cell imaging process, indicating that the octanoate anion and the corresponding molecular self-assembled structures might play key roles in the penetration of the cell membranes for these imidazolium salts. Wu et al. [38] fabricated a pH-responsive and



(a) Schematic illustration of the response process of PTPE-b-PAD-b-PEO with CO_2 and N_2 [56]. (b) Schematic illustration of the mechanism for cell imaging [56].

AIE characteristic vesicles via the introduction of Schiff based bonds for long-term live cell imaging and biomedical applications. Wang et al. [56] designed and synthesized a novel "breathable" block polymer supramolecular assembly probe consisting of a hydrophilic block, an amidine-containing CO2-responsive block, and an aggregation induced emission (AIE) luminescence block to detect CO₂ metabolized by cancer cells (Figure 5a). This triblock copolymer could be selfassembled into "breathable" aqueous solution vesicles. In the presence of CO_2 , the amidine containing CO_2 responsive block (PAD block) of the vesicle "inhales" an amount of CO₂, which causes the volume of the vesicle to expand. The expansion of the vesicle induces the aggregation of the AIE luminescence block (PTPE block), which resulted in the fluorescence intensity enhancement. The supramolecular vesicles "exhale" CO₂, and the volume and AIE phenomenon of the vesicles decrease when N₂ is passed into the solution. On the basis of this reversible change of fluorescence intensity, HeLa cervical cancer cells, CNE1 nasopharynx cancer cells, 5-8 F nasopharynx cancer cells, 16HBE human bronchial epithelial cells, and GES-1 human gastric mucosa epithelial cells have all been successfully detected and identified (Figure 5b).

Drug delivery systems

To date, targeted drug delivery to tumor cells with minimized side effects and real-time in situ monitoring of drug efficacy is highly desirable for personalized medicine. Fluorescent vesicles functionalized with targeted drugs based on AIE dyes have great potential in this area due to their fluorescence properties. AIE vesicles can be used as theranostics reagents which are able to encapsulate both hydrophobic and hydrophilic drugs. Such vesicles thus become ideal theranostics reagents that display both imaging and therapeutic capabilities. Many AIE vesicles used for drug delivery systems (DDS) have been reported [26,36,39,57–59]. Yan et al. construct an AIE vesicle from the ionic supramolecular amphiphile formed with TPA-BPA and MChCl [51]. As the MChCl is the substrate of cholinesterases (AChE or BChE), the vesicles dissemble in the presence of cholinesterases, which is the signal of Alzheimer's disease. In this case, the fluorescent intensity decrease is correlated to the level of enzymes. The resulting fluorescent vesicles are thus capable to recognize the site of Alzheimer's disease. If the enzyme inhibitor was preloaded into the vesicles, the enzyme triggered release of the inhibitor could be used for the therapy of Alzheimer's disease. Other self-assembled vesicles were laterly developed. The anticancer drug 5-fluorouracil (5-Fu) was loaded to $2\text{TPA-1}@2n^{2+}$ vesicles [16] with loading capacity up to 53.4% and a gradual release of the drug is possible within 3 h. The vesicle itself did not display cytotoxicity while the free 5-Fu displayed weaker cytotoxicity. After loading 5-Fu into the vesicles,

the cell viability of HeLa cells was reduced considerably, indicating the encapsulation of 5-Fu will promote the drug efficiency. In the meanwhile, the cells were lighten-up under the mode of two-photo imaging. In order to improve the therapeutic efficiency, the selfassembled AIE vesicles were further silicate to avoid dilution triggered disassembly of the vesicles before they arrive at the target places in biosystems. Upon depositing folic acid modified silica shell on the surface of the TPE-BPA@8CTAB vesicles, the obtained hybrid siliceous fluorescent vesicles (HSFVs) display low cytotoxicity, significant fluorescence, and targeted drug delivery toward cancer cells built-in template [60].

Light harvesting system

Fluorescence resonance energy transfer (FRET) is a fundamental step occurring in natural photosynthetic systems for light-harvesting. Design and creation of noncovalent artificial FRET systems is particularly favorable in mimicking the light-harvesting assemblies in a supramolecular manner. By means of the AIE effect, a variety of AIE vesicles have been adopted into FRET systems. The membrane of AIE vesicles is an ideal place to take place FRET, since the dimension of these vesicle membrane is in the range of 2-5 nm, which is a reasonable distance for effective FRET. High efficiency FRET was reported by Li et al. using the AIE vesicles self-assembled from TPE-bile acid conjugates [25]. Because the vesicle membrane has both hydrophilic pockets and hydrophobic domains, FRET always use the hydrophilic thioflavin T (ThT) or the hydrophobic fluorescent protein chromophore analog (GFP) as acceptors. Wu et al. demonstrate a facile approach to constructing FRET systems from a pH-responsive AIE fluorescent vesicles assembled by a PEG-POSS-(TPE)7 polymer [42]. The narrow wall thickness provides an ideal confined space for creating FRET systems between TPE donors and encapsulated FITC or DOX acceptors. Wang and co-workers [48] reported a novel artificial light harvesting system with efficient FRET process that occurred from the donor (WP5⊃ TPEDA assembly) to the acceptor (ESY). The vesicles were based on the noncovalent supramolecular assembly between a water-soluble pillar [5]arene (WP5) and a bola-type tetraphenylethylene-functionalized dialkyl ammonium derivative (TPEDA) with non-covalently encapsulation of the hydrophobic fluorescent dye ESY(Figure 6a). Moreover, when a second hydrophobic fluorescent dye NiR was further entrapped into the WP5 \supset TPEDA assembly, a light-harvesting system with two-step sequential energy transfer could be achieved from WP5 \supset TPEDA to ESY and then to NiR. By tuning the donor/acceptor ratio, bright white light emission can be successfully achieved with a CIE coordinate of (0.33, 0.33). To better mimic natural photosynthesis and make full use of the harvested energy, the WP5 \supset TPEDA-ESY-NiR system can be utilized as a





(a) Illustration of the molecular self-assembly of pillar [5] arene-based aqueous light-harvesting system with two-step sequential energy transfer. (b) A plausible mechanism for the dehalogenation reaction using WP5 \supset TPEDA-ESY-NiR assembly as a nanoreactor in aqueous medium [48].

nanoreactor: photocatalyzed dehalogenation of abromoacetophenone was realized with 96% yield in aqueous medium (Figure 6b).

Other applications

In addition to the aforementioned applications, AIE vesicles may also generate other useful functions. For instance, Abdelmohsen and coworkers [40] presented AIE polymersomes coated with a gold hemisphere that show increased autonomous propulsion via an AIEmediated enhanced photothermal effect and that are capable of ROS production when irradiated using NIR. Combining the properties of both AIE and Au, the advantages of both classes of material are captured whilst creating a therapeutic nanotechnology with increased efficacy and enhanced cytotoxic response upon targeted NIR irradiation. Such functional modalities do not simply act concurrently but also in unison-whereby the AIE capacity transduces TP-NIR irradiation and, through highly stable fluorescence, photothermally activates the Au layer to provide enhanced motile behavior to increase the therapeutic effect. Jiang et al. [29] demonstrated that the π -conjugated nanocycle-based vesicles assembled by Ref. [8]cycloparaphenylenes ([8]CPPs) molecules show a remarkable ability to enter cells in an energy- or temperature-independent manner and kill cancer cells. When the side groups of the CPP molecule were changed, the CPP vesicles showed a large difference in the cytotoxicity, and two CPP vesicles could effectively kill cancer cells as well as first-class antitumor agents. Besides, luminescence-tunable vesicles (LTVs) based on AIEgens were also widely investigated, which have potential application in optical sensors and lighting devices. Especially, white emission becomes possible by altering the amount of entrapped acceptor simply. Furthermore, the condensed and ordered packing of the AIEgens would enhance the efficiency of light absorption and energy conversion. An interesting example is the metal carbonyl AIE vesicle reported by Wang et al. which they referred as MCsome [28]. Except for the aggregation-induced emission, this vesicle also exhibit aggregation-enhanced IR absorption (AEIRA) owing to the molecular self-assembly of a bithiophene tethered-Fp acyl derivative (Fp: $CpFe(CO)_2$). Because the refractive index of $CpFe(CO)_2$ is very high, MCsome creates an enhanced optical field upon infrared (IR) irradiation, resulting in 100-fold enhancement in IR absorption for the carbonyl groups, which immediately generates laser manipulability without using additives.

Summary and outlooks

In this review, we summarized the recent developments of the chemical structures of the molecules that constitute the AIE vesicles and their applications. The nonplanar configuration avoids fluorescence quenching in the aggregate stage, yielding AIEgens-based supramolecular vesicles with high luminescence efficiency. Simultaneously, the nonplanar configuration also prevents AIEgens from packing together, considerably deconstruction of highly terring the ordered supramolecular architectures. Much effort has been made to ensure the AIEgens with sufficient aggregation ability. For example, AIEgens can be decorated with moieties that possess a strong tendency toward aggregation or AIEgens can be incorporated into the fabricated supramolecular structures. These strategies have prompted the emergence of a large number of AIEgensbased molecules that can assemble into vesicles, including amphiphilic AIE small molecules, block polymers, and non-amphiphilic molecules capable of the ability to co-assemble into vesicles with other components. Compared to random aggregation, the ordered molecular packing in vesicles allows restricting the conformation of the AIEgens more efficiently, which thus enhances the emission efficiency and emission lifetime. Furthermore, the ordered molecular packing in vesicles also makes it easier to couple the aggregationinduced emission with other emission through a FRET process, generating color tunable materials for various applications. Another important feature of the AIE vesicles is the dense packing of the AIEgens, which enhances the light-capturing ability. Two-photon absorption becomes possible without resorting to specific molecular design. Finally, the encapsulation ability and AIE characteristics of the AIE vesicles makes them promising carriers not only for encapsulation and delivery of active substances, but also the innovative approaches for in vivo study of drug release and drug distribution.

Further investigation of AIE-vesicles is expected to bring forth more surprising results, such as novel AIEgens and innovative applications. The examples covered in this review mainly involve short-wavelength AIEgens, such as TPE and its derivates, which restrict in vivo applications. Developing AIE-vesicles based on red or FR/NIR-emissive AIEgens is highly desirable because their deep penetration and low auto fluorescence can considerably widen the scope of preclinical research and clinical applications. In addition to highly fluorescent emissions, AIE vesicles possess the amazing capacity of photodynamic, photoacoustic, and photothermal therapeutic efficiencies are also desirable, which can accelerate the development of advanced theranostic platforms with an extremely simple and innovative strategy. In addition, manipulating and controlling the size distribution and morphologies of AIEgens-based vesicles has become imperative. It can be envisioned that with the development in molecular and supramolecular design, AIE vesicles would bring up profound impacts on biological science, medical science, and material sciences. We hope that this review can trigger more interest and garner more ideas from researchers and further advance the development of supramolecular chemistry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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