REVIEW ARTICLE

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Engineering receptor-mediated transmembrane signaling in artificial and living cells

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Living cells possess a variety of transmembrane signaling systems that receive chemical and physical cues from the environment and transduce this information into an intracellular signal that triggers downstream cellular responses. This Review aims to present recent advances in the design of bioinspired systems that mimic transmembrane signaling in synthetic and living cells. We summarize the building of cell-like membranous structures and the construction of interfacial recognition between chemical or biological components. After introducing two main mechanisms of signal transduction in biology through receptor tyrosine kinase and G-protein coupled receptors, we then highlight the possibility of mimicking transmembrane signaling with transducer integrated systems. We survey the potential for applying supra-molecular materials (e.g., DNA origami, polypeptide structures and polymer scaffolds) to interact with surface receptors on the plasma membrane, providing an avenue for the application of therapeutics.

The plasma membrane not only protects the interior of cell from the outside environment, but also plays an essential role in supporting basic cellular activities such as cell division, replication and cell-cell communication. The hydrophobic nature of the plasma membrane prohibits the direct diffusion of polar molecules (e.g., hormones) across the lipid bilayer. Nevertheless, transmembrane signal transduction is facilitated by receptors on and in the plasma membrane, which receive external stimuli (chemical or physical) and translate them into intracellular responses. In this process, a primary signal selectively binds to the active site of a cell surface receptor on the outer leaflet of cell membrane, leading to the activation of a secondary signal to regulate gene expression and other biochemical reactions.

Cell surface receptors convert specific extracellular signals into intracellular changes, either directly via intrinsic enzymatic activities within the receptor or by activating intracellular messenger molecules. Here we mainly focus on two types of prominent transmembrane protein receptors involved in living cells, i.e., receptor tyrosine kinases (RTKs) and G-protein coupled receptors (GPCRs) (Fig. 1). A RTK requires at least two transmembrane units, in which recognition sites are exposed on the membrane surface and signaling sites are on the interior[1]. Upon the binding of signaling ligands (e.g., growth factor and cytokine) to the recognition sites, two transmembrane units of RTKs are clustered through ligand-induced-dimerization, which triggers the phosphorylation of the intracellular tyrosine residue and activates the tyrosine kinase activity. GPCRs are another important class of cellular signal transduction and are well known for their structures of seven transmembrane helices. The binding of a primary signal to the active site induces conformational changes of receptor and subsequently activates a G protein. GPCRs are the largest family of transmembrane receptors associated with different biological functions such as cell proliferation, and play an essential role in modulating tumor growth and angiogenesis[2].

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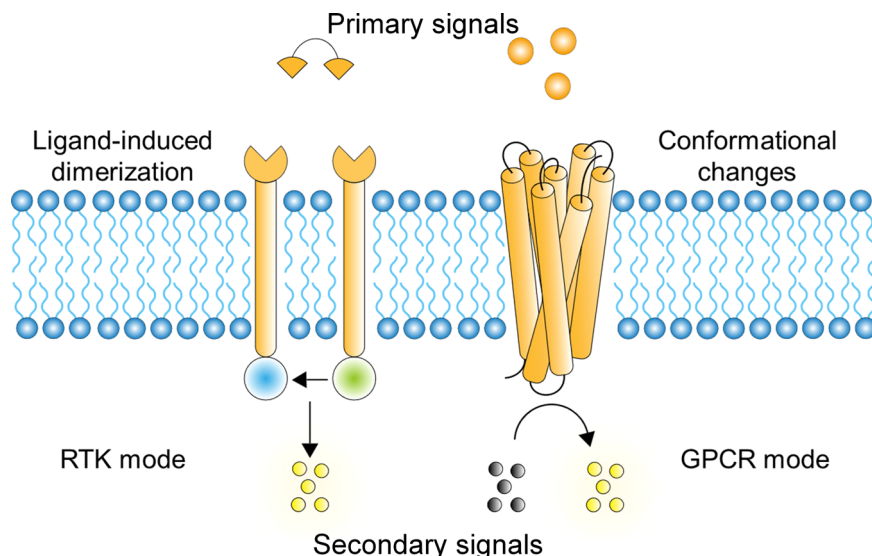
Fig. 1 Schematic illustration of transmembrane signaling.

In this Review, we discuss ongoing research spearheading the effort to prepare membranous structures as cell mimics and different strategies to realize interfacial recognition at the interface of lipid membranes. We then summarize recent progress in the design of artificial receptors built in synthetic membranes to mimic biological signaling across lipid bilayers. Lastly, we showcase the vast possibility to develop potential therapeutic drugs from supramolecular systems (e.g., polypeptides, polymers, and DNA structures) that serve as agonists or antagonists to instruct downstream cellular responses.

Construction of cell membrane mimics

According to the fluid mosaic model, cell membranes are organized bilayer structures composed of lipids, proteins and carbohydrates. Subcellular organelles such as the nucleus, Golgi complex, and lysosomes, are also enclosed by lipid membranes. To understand the physicochemical properties of cell membrane, bottom-up approaches have been developed to build liposomes or lipid vesicles as the simplest model of cells[3]. Typically, unilamellar vesicles are named according to their size as GUVs (giant unilamellar vesicles, >1000 nm), LUVs (large unilamellar vesicles, 100~1000 nm) or SUVs (small unilamellar vesicles, ~50 nm). LUVs are facilely prepared with the thin-film hydration followed by extrusion method, in which a dry lipid film is hydrated and extruded mechanically through a polycarbonate membrane with designate pore size. SUVs with smaller sizes are simply prepared with sonication-based method, which does not produce uniform liposomes with good reproducibility. GUVs can be achieved with direct hydration of a phospholipid film, which works only with certain lipid compositions and salt conditions[4,5]. To address this challenge, hydrogel-assisted hydration method has recently been developed to prepare GUVs, in which phospholipid films are placed on top of a dried polymeric hydrogel surface and swollen in aqueous solution[6]. Another widely used method to prepare GUVs is electroformation, where an alternating electrical field is applied across a solution-filled chamber to facilitate bilayer separation and bending of the lipid film by electro-osmotic effects[7]. However, the encapsulation of biomolecules in these liposomes is still inefficient. To tackle this challenge, water-in-oil emulsion droplets are exploited as soft templates to prepare bilayer vesicles by transferring lipid-stabilized emulsion droplets through an oil/water interface or by forming double emulsion droplets with an oil shell followed by extracting the oil[8–10]. Recently,

microfluidic devices have been developed to produce monodisperse giant vesicles via microfluidic jetting or emulsion-based methods[11–14].

In addition, rudimentary forms of membranous structures have been explored in colloidosomes[15–17], dendrimersomes[18,19], polymersomes[20,21], layer-by-layer capsules[22,23], and proteinosomes[24–27]. The building blocks of these membranous protocells include organic or inorganic particles, dendrimers, polymers, surfactants, polyelectrolytes and proteins. These membrane-bound compartments offer new opportunities to mimic cell-like behaviors such as growth[28], division and fission[29–32], fusion[33,34], signaling[35–37], and motility[38,39]. Chemical communication between these membranous compartments is described in a recent Review[40]. Here we mainly focus on transmembrane signaling across phospholipid membranes.

Biomimetic interfacial recognition on phospholipid membranes

Recognition and binding of an extracellular signal by a cell surface receptor is the first step of transmembrane signaling[41,42]. Understanding the ligand-receptor interactions on cell surface is vital to reveal the molecular basis of cell signaling or cellular responses to external stimuli. Here we review the recent effort devoted to exploring biological recognition on cell-mimicking membranes, which avoids the difficulty in the direct inspection of cellular properties at the molecular scale. Non-covalent interactions accounted for interfacial recognition on the surface of lipid membrane include hydrogen bonding[43–46], host-guest interaction[47–49], DNA hybridization[50–52], metal-ligand coordination[53] and biological interactions[54] (Fig. 2).

Hydrogen bonding is responsible for the stabilization of many biological structures including protein secondary structures (e.g., α-helices and β-sheets) and DNA double helices. Hydrogen bonds also play a central role in the biological recognition involving carbohydrates and membrane proteins. It is worthwhile to note that water molecules will compete with the hydrogen bonds between biomolecules since water serves as hydrogen donor and acceptor. To address the role of hydrogen bonding on the surface of vesicles, multivalent H-bond pairs such as melamine/thymine and cyanurate/melamine have been designed. For example, lipid vesicles composed of cyanuric acid/melamine[43,44] or 2-ureido-4[1H]-pyrimidinone[46] at the membrane surface undergo selective adhesion and fusion driven by multivalent hydrogen bonding.
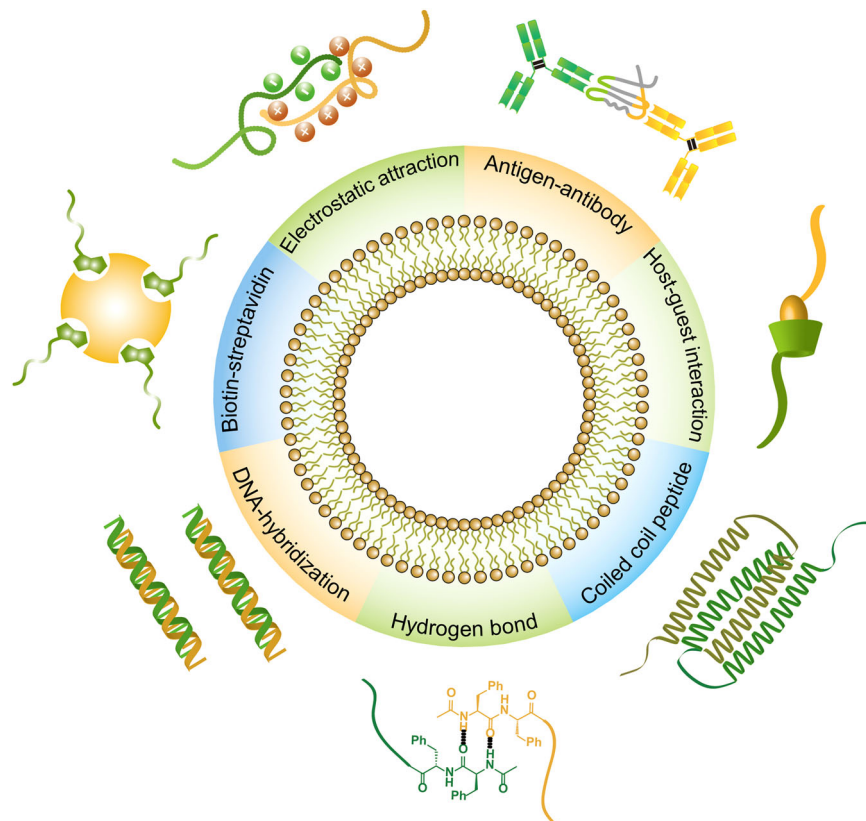
Fig. 2 Supramolecular interfacial recognition on lipid membranes. The main intermolecular forces include electrostatic attraction, antigen-antibody affinity, host-guest interaction, coiled-coil peptide structures, hydrogen bonding, DNA hybridization and biotin-streptavidin recognition.

This suggests that low-dielectric hydrogen bonding can translate effectively to the lipid−water interface.

Host–guest chemistry is an intriguing concept that describes the formation of structural complexes by two or more molecules through non-covalent forces. The displaying of macrocycle hosts (e.g., crown ether, cyclodextrin and cucurbit[n]uril) on the surface of the lipid vesicles allows for specific ligand recognition via host-guest interactions. Ravoo et al.[47,48] developed supramolecular vesicles displaying cyclodextrins on the membrane surface, which aggregated and adhered to each other in the presence of azobenzene-bearing linkers. The aggregated vesicles reversibly dissociated by transforming *trans*-azobenzene to *cis*-form upon ultraviolet (UV) light irradiation, which weakened the host-guest interaction between cyclodextrin and azobenzene. Moreover, phospholipid vesicles can display bioactive maltose and lactose on the surface by using a sugar-adamantane conjugate as a guest[49]. The maltose-decorated liposomes agglutinate in the presence of lectin concanavalin A, whereas the lactose-decorated liposomes agglutinate with the addition of peanut agglutinin.

Hybridization of complementary nucleic acids is a well-established tool to engineer the surface of phospholipid vesicles, in which the strength of interfacial recognition depends on a variety of factors including temperature, DNA sequence, and the concentration of inorganic salts. Although nucleic acids are not intrinsically displayed on the cell membrane, the modification of DNA or RNA sequences on lipid membrane can be achieved by conjugation to an alkyl tail or cholesterol group, which spontaneously inserts into the hydrophobic lipid bilayer. These nucleic acid-displaying lipid vesicles undergo reversible aggregation and fusion in the presence of complementary DNA linkers, in which the repulsive hydration forces between the lipid head groups of bilayers are overcome[50,52]. To gain reversible control over

liposome assembly, membrane-anchored oligonucleotides were incorporated with photoactive azobenzene groups and the system was remotely irradiated with either UV or visible light[55].

Metal ions play an essential role in biology. For example, metal ions serve as catalytic or structural cofactors to maintain the function of proteins. Ion binding or Ca^{2+} influx acts as the first signal driving membrane events[56]. In artificial systems, metal-ligand coordination at the interface of vesicular membranes drives specific interactions that may result in vesicle aggregation, adhesion, and fusion. For example, Lehn et al.[53] designed synthetic lipids bearing a bipyridine head group and incorporated these amphiphilic lipids into LUVs. Upon the addition of metal ions (e.g., Ni^{2+} or Co^{2+}), metal-ligand complexation rapidly led to spontaneous fusion into giant multilamellar vesicles.

Biological recognition between functional motif pairs such as mannose/concanavalin A ($K_a \sim 8.5 \times 10^6\,M^{-1}$)[57], D-Ala-D-Ala/vancomycin ($K_a \sim 10^6\,M^{-1}$)[58], biotin/streptavidin ($K_a \sim 10^{15}\,M^{-1}$)[59] and coiled-coil polypeptides[60] are engineered on the surface of lipid membrane to initiate vesicle aggregation and fusion, as well as liposome-based biosensing. For example, Zasadzinski et al.[54] reported the reversible aggregation of phosphatidylcholine liposomes equipped with biotin upon the addition of streptavidin. Percec et al.[18,19] designed a class of amphiphilic dendrimers that self-assembled into dendrimersomes displaying sugar ligands with a precisely controlled density, offering a platform for biomimetic study of biological interactions.

Electrostatic effect dominates many aspects of biological phenomena such as protein folding and DNA organization. Charge attraction between chemical ligands and surface receptors also contributes to interfacial recognition on lipid membrane. König et al.[61] reported vesicle membranes bearing three amphiphilic artificial binding receptors that recognized phosphate anion,

imidazole derivatives, and ammonium ions through electrostatic interaction. Similarly, lipid vesicles functionalized with bis-zinc cyclen complexes exhibited a high affinity to phosphate anions; as such, they selectively discriminated uridine triphosphate and pyrophosphate via an indicator displacement assay[62].

Mimicking receptor-mediated transmembrane signaling with supramolecular systems

Despite extensive studies of membrane transporters[63] and ion channels[64], the construction of receptor-mediated signal transduction in artificial systems is less explored[65–67]. This is challenging since transmembrane signaling involves a series of precisely designed physicochemical processes such as interfacial recognition, signal conversion from one type into another type, signal transmission from outer membrane to the interior, catalytic signal amplification, as well as downstream responses. Nevertheless, the essential role of RTKs and GPCRs as signaling mechanisms in biology has inspired the rational design of artificial signaling systems in phospholipid membranes.

RTKs coordinate intracellular signaling cascades through the binding of a ligand and the dimerization of cell surface receptors that activates tyrosine kinase activity and stimulates intracellular responses. Artificial signaling systems that mimic the RTK signaling mode have been developed to sense a range of external signals, including potassium ferricyanide[68], diethylenetriammonium[69,70], adenosine triphosphate (ATP)[71], immunoglobulin G antibody[72], and proton[73]. Early work by Matile et al.[74] reported a membrane-spanning ion channel exhibiting a simple mode of RTK signaling where the binding of polyhistidine and copper ions led to the synergistic dimerization of receptors. Hunter and Williams[68] developed a RTK signal transduction system based on cholenic acid-derived membrane-spanning receptors that sensed the external oxidant signal to cluster the receptors and release a secondary signal via thiol-disulfide exchange. Schrader et al.[69,70] designed unsymmetrical transmembrane receptors bearing bisphosphonate dianions as a recognition site outside membrane and a fluorescence resonance energy transfer (FRET) pair on the other end (Fig. 3a). The binding of an external primary messenger (e.g., diethylenetriammonium) triggered receptor dimerization and activated an internal FRET. Target-aptamer recognition is another useful tool to build RTK-mode signaling pathway in artificial membrane. For example, Liu et al.[71] developed a transmembrane signal transducer possessing three functional modules: split ATP aptamers as recognition modules, a hydrophobic transmembrane linker, and a split G-quadruplex as a signal output module (Fig. 3b). The presence of ATP outside the membrane triggers the dimerization of DNA receptors, resulting in catalyzed peroxidation of Amplex red to resorufin.

GPCRs are a large protein family that recognize a diverse range of endogenous ligands. The binding of an external signal to a GPCR causes a conformational change of receptor and generates a subsequent interaction between the GPCR and a nearby G protein. Artificial receptors that have similar function as GPCRs were previously reported in organic solvents[75–77]. To better mimic protein receptors, Clayden et al.[78] developed a photo-responsive foldamer consisting of an azobenzene group and a helical synthetic peptide spanning across the lipid membrane. The foldamer sensed light signal to stimulate global conformational changes and a response of solid-state ^{19}F nuclear magnetic resonance. This foldamer was further developed into a synthetic membrane-bound receptor attached with a metal ion-binding pocket that selectively recognized external ligands (Fig. 3c)[79]. In the presence of copper ions (cofactor), the affinity of a chiral ligand to the binding pocket switched the interconverting conformational states and caused a structural

change of fluorophores inside the membrane, which ultimately generated a fluorescence signal.

Apart from RTK and GPCR mode, molecular translocation is used as an alternative mechanism of signal transduction across lipid membranes[80–82]. Lipid bilayer is a dynamic and fluidic phase, in which individual lipids diffuse laterally[83] and move from one leaflet to the other leaflet (flip-flop, $t_{1/2} \sim h$)[84,85]. Williams and Hunter[86] developed a synthetic receptor capable of transmitting a chemical signal across lipid membrane by taking advantage of receptor translocation from one side of lipid bilayer to the other. In their design, two hydrophilic head groups are attached to a steroid core, in which one head group acts as an external sensing site and the other is a pro-catalyst. The receptor is not long enough to span the bilayer and therefore the pro-catalyst is imbedded in lipid membrane. Increasing the external pH removes the charge on the sensing site, allowing the pro-catalyst group to enter the vesicle interior and catalyze the hydrolysis of a fluorogenic substrate. When the receptor is attached with a bipyridine group, its translocation is inhibited by the coordination of copper ions and activated by sodium ascorbate (a reducing agent) and ethylenediaminetetraacetic acid (a competing ligand)[87,88]. By employing this signal transduction mechanism, the lipid vesicles can release an encapsulated molecular cargo in response to an external control signal (Fig. 4a)[89] or undergo a vesicle-to-vesicle communication based on competing biotin-NeutrAvidin binding[90]. In another system[91], the binding of a cadmium(II) cofactor to the exterior pyridine-oxime group generates a catalytically active complex that can translocate to the vesicles interior and stimulates an output signal. In these systems, molecular hydrophilicity is the key factor that governs receptor translocation across lipid membrane. Similarly, artificial receptors bearing photo-responsive groups such as azobenzene and spiropyran are able to change their hydrophobicity through host-guest interaction or photoisomerization, offering new strategies to switch on transmembrane signaling[92,93].

Inspired by human vision, our group developed a photo-transduction system in artificial cells, where an amphiphilic ruthenium-bipyridine complex was designed as a synthetic photoreceptor[94]. The membrane-anchored receptor is installed on the outer leaflet of lipid membrane to harvest visible light and release a catalytic messenger that translocated across the membrane via flip-flop (Fig. 4b–f). The phototransduction eventually led to fluorescence amplification and a liquid-liquid phase separation (LLPS), a mechanism accounted for the formation of membraneless organelles. Coupling receptor-mediated signaling with biological recognition and enzymatic cascade reactions further enabled the construction of protocell signaling-encoded Boolean logic gates.

Engineering nanostructures to regulate signal transduction in living cells

Biological recognition on the surface of the plasma membrane requires control over ligand-receptor interaction in space, with precise configuration, orientation and distance. To optimize the ligand-receptor affinity, nanopatterned surfaces produced by nanolithography method or engineered nanoparticles[95,96] were explored to display bioactive ligands in a controlled manner. Supramolecular self-assembly offers an alternative tool to design nanostructures displaying ligands with controlled surface density and spatial arrangement[97]. Here, we will summarize recent advances in using self-assembling structures and nanomaterials of polypeptides, nucleic acids and polymers to trigger signal transduction across the membrane, induce cellular events and stimulate therapeutic effects.
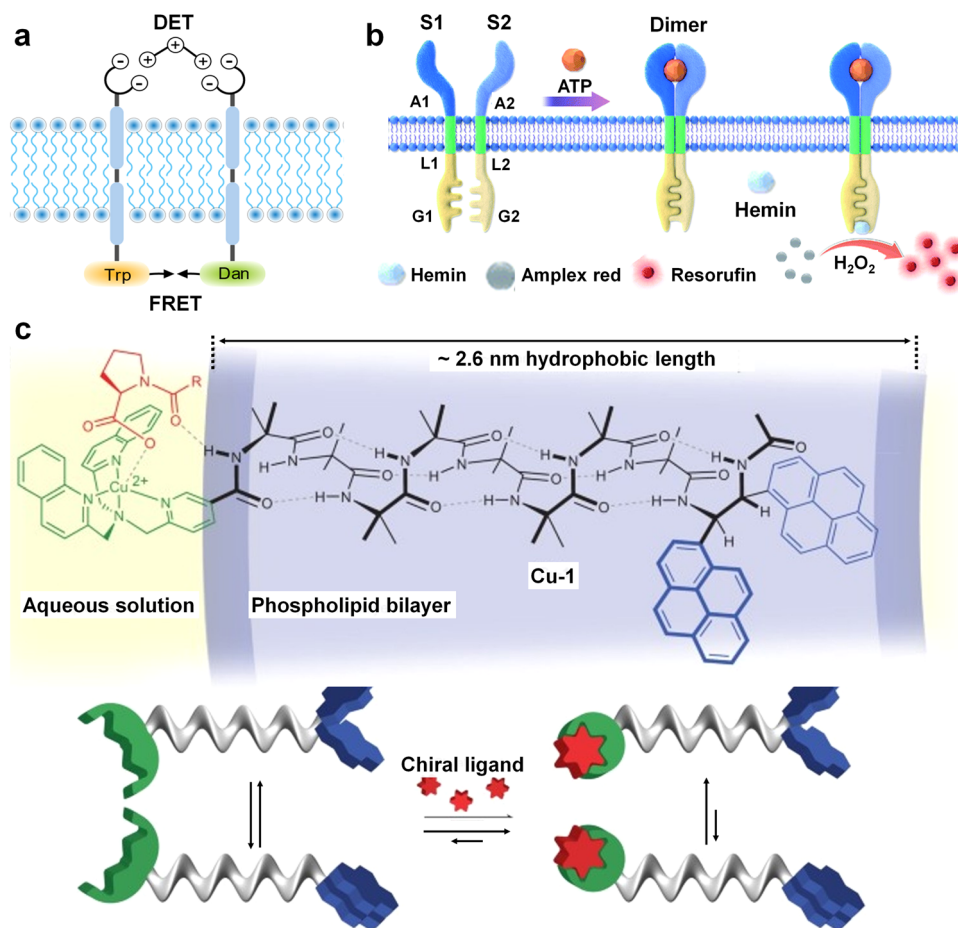
Fig. 3 Artificial GPCR and RTK signaling in supramolecular systems. a Primary messenger (diethylenetriammonium, DET) induces dimerization of two transmembrane receptors and stimulates FRET inside liposomes. **b** ATP-mediated dimerization of DNA-based membrane receptors for transmembrane signaling to activate hemin-catalyzed peroxidation of Amplex red. **c** A synthetic transmembrane receptor Cu-1 comprises three components: a metal-binding site (green), a helical oligomer embedded in the membrane (gray), and a pyrene-based fluorophore (blue). Reversible binding of a chiral ligand triggers the conformational changes from the binding site to the reporter, generating a fluorescence output. **a** Adapted with permission from ref. [69], Copyright Wiley-VCH, 2009; **b** adapted with permission from ref. [71], Copyright Royal Chemical Society, 2021; **c** adapted with permission from ref. [79], Copyright Springer Nature, 2017.

Inspired by the sophisticated structure of natural proteins, chemists have developed polypeptides that contain sequences predisposed to form secondary structures (e.g., α-helix and β-sheet)[98]. Designer polypeptides integrating these subunits can further self-assemble into supramolecular scaffolds fused with bioactive peptide ligands capable of binding to membrane receptors including integrin[99], human epidermal growth factor receptor 2 (HER2)[100], Eph receptor A2 (EphA2)[101], death receptor 5 (DR5)[102] and Met[103,104]. In particular, amphiphilic peptides readily aggregate into fibrillary networks with controlled ligand architectures, geometries, and sequences, forming a versatile platform for mimicking the extracellular matrix. Inspired by the extracellular matrix protein fibronectin that synergistically binds $\alpha_5\beta_1$ integrin, Pashuck et al.[99] designed self-assembled nanofibers and hydrogels with β-sheet motifs, in which the distance of two different peptide epitopes was controlled with sub-nanometer accuracy (0.7 to 6 nm). Endothelial cells, incubated within fibril networks that display Arg-Gly-Asp-Ser (RGDS) and Pro-His-Ser-Arg-Asn (PHSRN) with a 3.2 nm spacing, showed an upregulation in the expression of the alpha 5 integrin subunit (Fig. 5a). Supramolecular self-assembly is highly dynamic and adaptive in physiological environments. Engineered peptide nanoparticles were observed to transform into a fibrillar network upon accumulating at the tumor site, which subsequently

suppressed the dimerization of HER2, a receptor tyrosine kinase overexpressed in cancers, and prevented downstream cell signaling and the expression of proliferation and survival genes (Fig. 5b)[100]. Similarly, a cancer-targeting peptide was shown to bind to transmembrane receptor tyrosine kinase EphA2 and induce the aggregation of overexpressed EphA2 receptors[101], leading to the activation of signal transduction of antitumor pathway and the downstream apoptosis of cancer cells. Futaki et al.[105,106] designed a leucine-zipper coiled-coil polypeptide as an artificial bivalent ligand to stimulate dimerization of epidermal growth factor receptor (EGFR) on plasma membranes.

Nucleic acid self-assembly is a reliable approach to design predictable, programmable, and addressable scaffolds displaying biological ligands or ligand mimics with specific orientation, spacing and organization. The Watson-Crick rules direct bottom-up assembly of DNA nanostructures, where two complementary DNAs form a double helix with a diameter of 2.0 nm and a length of 3.4 nm per helical turn. Moreover, the conjugation of functional groups (e.g., peptide, aptamer and DNAzyme) to oligo-nucleotides endows specific recognition towards membrane receptors or catalytic amplification[107]. So far, receptor-binding aptamers have been screened and developed to recognize Met[108–110], transferrin receptor[111], and transmembrane tumor necrosis factor (TNF) receptors[112]. Among these, hepatocyte
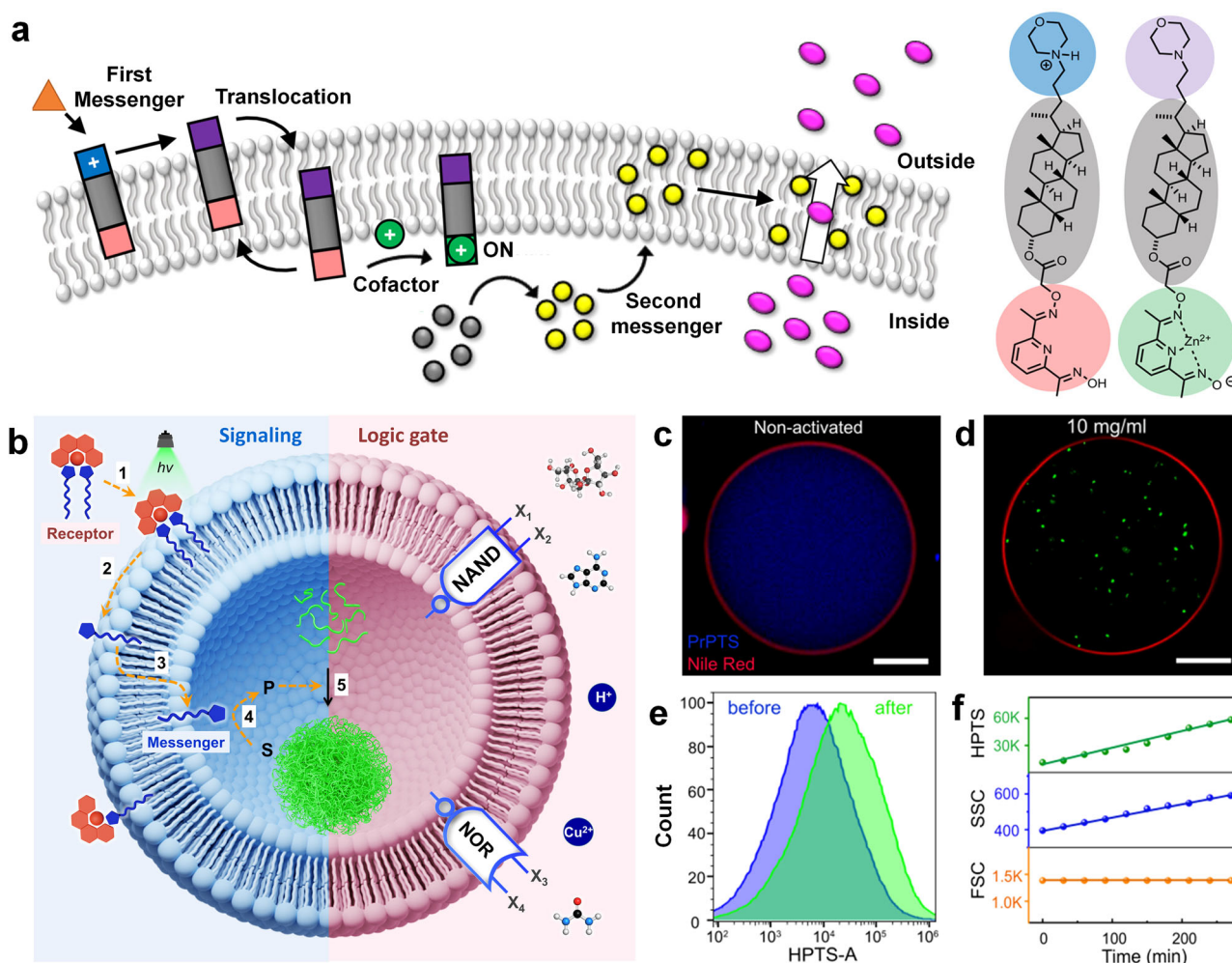
Fig. 4 Signal transduction across phospholipid bilayers via the mechanism of molecular translocation. a A signal transduction mechanism that triggers cargo release from vesicles. Binding of a charged cofactor to the inner head group activates a catalytic hydrolysis and liberates a surfactant that enhances the permeability of the membrane and facilitates cargo release. **b** Schematic illustration of receptor-mediated phototransduction, which involves five essential steps including installation of a photoreceptor on the outer leaflet of lipid bilayers (1), light-triggered release of a messenger (2), flip-flop movement of messenger across the membrane (3), signal amplification through catalytic hydrolysis of an esterase substrate (S) into a fluorescent product (P) (4), and the formation of coacervate droplets (5). Coupling signal transduction with biological recognition and enzymatic cascade reactions leads to the development of Boolean logic gates. **c**, **d** Formation of coacervate microdroplets as artificial organelles inside giant vesicles. **e**, **f** Flow cytometry results show the enhancement of fluorescence intensity and the growth of coacervates through phototransduction. Scale bars: **c** 10 μm, **d** 15 μm. **a** Adapted with permission from ref. [89], Copyright American Chemical Society, 2017; **b**–**f** adapted with permission from ref. [94], Copyright AAAS, 2023.

growth factor (HGF) induces dimerization of the cell surface receptor c-Met to stimulate cell proliferation, survival, and migration[113]. Sando et al.[114] designed a 50-mer DNA aptamer as an oligonucleotide-based HGF mimetics that inhibits HGF-induced c-Met signaling. This 50-mer DNA inhibitor is further dimerized with a complementary DNA strand to generate an agonist that binds to two receptors and activates the Met signaling (Fig. 6a)[115]. To increase the specificity of Met activation, a bispecific DNA aptamer was developed to simultaneously recognize Met and non-cognate ligands (e.g. thrombin), in which Met phosphorylation was only observed when both aptamer and thrombin were present (Fig. 6b)[116]. A similar strategy was applied to generate a bispecific aptamer that can induce protein-pairing for selective inhibition of receptor function[117]. In addition, aptamer-based growth factor mimetics was demonstrated to exert therapeutic effects in a target tissue for in vivo applications[118] and allow for strategy-guided design of synthetic growth factor surrogates with fine-tuned agonism[119]. Nie et al.[109] designed an ATP-responsive DNA nanodevice that responded to external

stimuli to trigger DNA strand displacement, inducing the dimerization and activation of c-Met to cognate for hepatocyte growth factor (Fig. 6c). This method allows for the manipulation of the behaviors of multiple cell populations simultaneously. Li et al.[120] reported a reversible control of membrane receptors at the cell surface with a self-assembled DNA nanospring, allowing for the regulation of cell protrusions and mRNA expression (Fig. 6d). Recently, a DNA origami structure that precisely scaffold the patterning of TNF-related apoptosis-inducing ligand-mimicking peptides at nanoscale level was demonstrated to stimulate human breast cancer cells[112]. It was found that ~5 nm is the critical inter-ligand distance between hexagonally patterned peptides to induce death receptor clustering and produce apoptosis.

Clustering of cell surface receptors requires specific and strong ligand-receptor affinity, which is usually achieved with engineered macromolecular scaffolds that display multivalent ligands with varied density, orientation, and spatial organization[121–123]. In this context, a therapeutic platform that mimics the
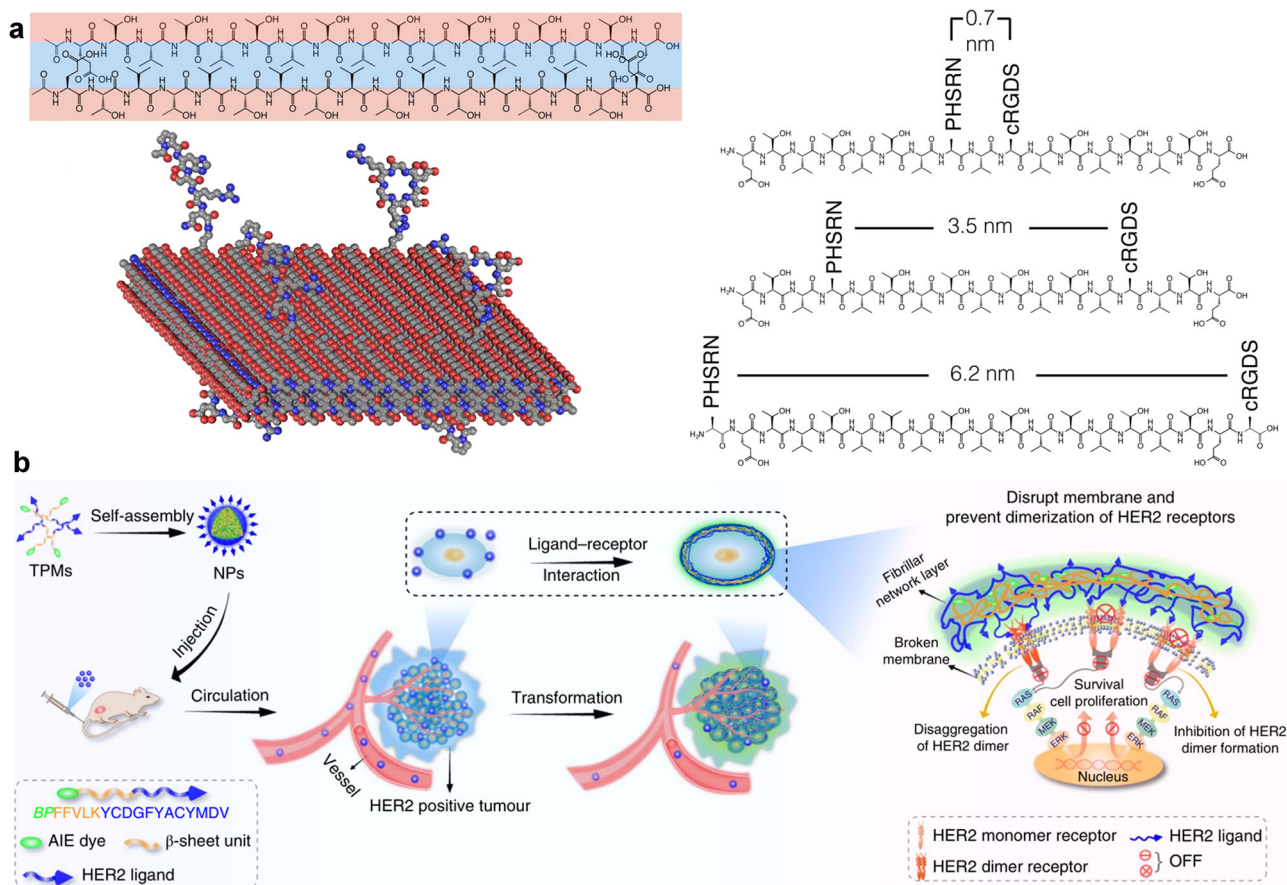
Fig. 5 Interfacing supramolecular peptide nanostructures with membrane receptors. a Schematic illustration of supramolecular fibrils displaying RGDS and PHSRN with defined spacing of 0.7 nm, 3.5 nm and 6.2 nm. RGDS and PHSRN motifs are attached to the rigid backbone of a β-sheet peptide. **b** Transformable peptide monomers (TPMs) self-assemble into nanoparticles (NPs) to arrest HER2 signaling in mice. TPMs are comprised of three discrete functional domains: a bis-pyrene moiety with aggregation-induced emission (AIE), a β-sheet-forming domain derived from β-amyloid and a disulfide cyclic peptide of HER2-binding domain. **a** Adapted with permission from ref. [99], Copyright American Chemical Society, 2016; **b** adapted with permission from ref. [100], Copyright Springer Nature, 2020.

mechanism of immune effector cells was developed to crosslink surface receptors of target cells and induce apoptosis[124]. To achieve this, an antibody-DNA hybrid was developed by conjugating an anti-CD20 Fab' fragment to a single-stranded oligonucleotide, which recognized CD20 on the surface of malignant B-cells. A linear polymer was grafted with complementary oligonucleotides that bind to antibody-DNA hybrids, leading to the clustering of CD20 antigen and apoptosis. Similarly, Kolmar et al.[125] designed DR5 binding constructs comprising varied copies of DR5 targeting peptide covalently bound to a protein scaffold and demonstrated their remarkable effect in inducing apoptotic signaling.

Modulation of cellular signaling with external stimuli

Manipulating ligand-receptor interaction with external stimuli offers an alternative approach to regulate transmembrane signaling and coordinate cellular behaviors. The use of light as a non-invasive stimulus offers temporal and spatial control with varied irradiation time, wavelength and intensity. For example, Aida et al.[126] described a dendritic molecular glue with multiple pendant guanidinium ions that adhered to HGF and suppressed its affinity towards c-Met. Upon exposure to 365 nm light, the glue was photocleaved at a linkage in the dendrimer framework, and HGF was liberated and retrieved its intrinsic affinity towards c-Met (Fig. 7). Photo irradiation was also applied to increase the ligand affinity to target proteins. Kohata et al.[127] developed

another photoreactive glue that adhered to aptamer/c-Met complex. Upon exposure to UV light, the temporarily stabilized aptamer/c-Met conjugate reacts with the photoexcited benzophenone group of molecular glue and the nitrene species, resulting in the covalent permanent stabilization of the aptamer/c-Met complex, which efficiently inhibited HGF/c-Met interactions and suppressed cell migration.

To modulate cell signaling in a biocompatible manner, a visible-near Infrared (NIR) laser was considered to be advantageous over UV light since the former can penetrate into deep tissue and causes less damages. Qin et al.[128] applied pulse laser to heat plasmonic gold nanoparticles to deactivate protease-activated receptor 2 in target cells, which is a G-protein-coupled receptor involving in a pathway that leads to pain sensitization release. Similarly, NIR irradiation was demonstrated to release a DNA agonist from gold nanorods, which dimerized DNA-modified chimeric or native RTK on cell surfaces and activated downstream signal transduction to control cytoskeletal remodeling, cell polarization, and directional migration[110].

Challenge and outlook

The cell membrane functions as a physical barrier to protect the interior and regulates cellular behaviors via transmembrane signaling. Signaling information is transmitted from the receptor on the plasma membrane across the cytoplasm to stimulate cellular responses. Research into signal transduction provides new
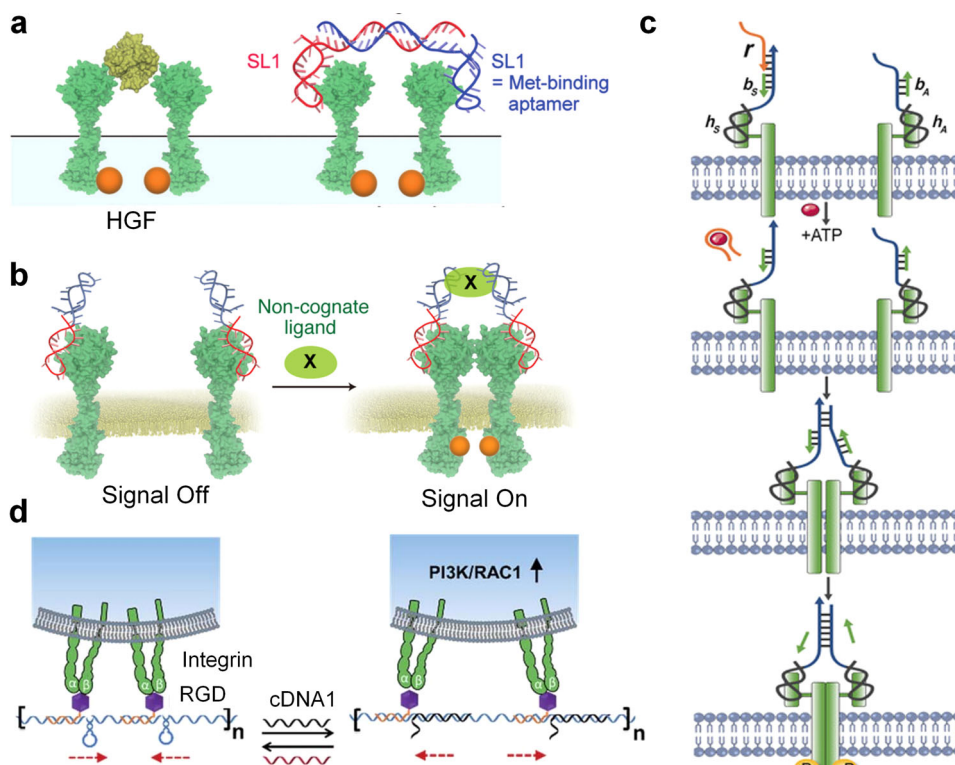
Fig. 6 DNA structures mediated receptor clustering. a Oligonucleotide-based HGF mimetics induces Met dimerization. **b** Reprogramming of the ligand specificity of growth factor receptors with bispecific DNA aptamers as non-cognate ligands. **c** ATP-responsive DNA-mediated chemically induced dimerization. **d** Reversible control of integrin clustering and de-clustering with a DNA nanospring, which allows for regulation of intracellular signaling pathways and cell morphology. **a** Adapted with permission from ref. [115], Copyright Wiley-VCH, 2016; **b** adapted with permission from ref. [116], Copyright American Chemical Society, 2017; **c** adapted with permission from ref. [109], Copyright Wiley-VCH, 2018; **d** adapted with permission from ref. [120], Copyright Royal Chemical Society, 2017.
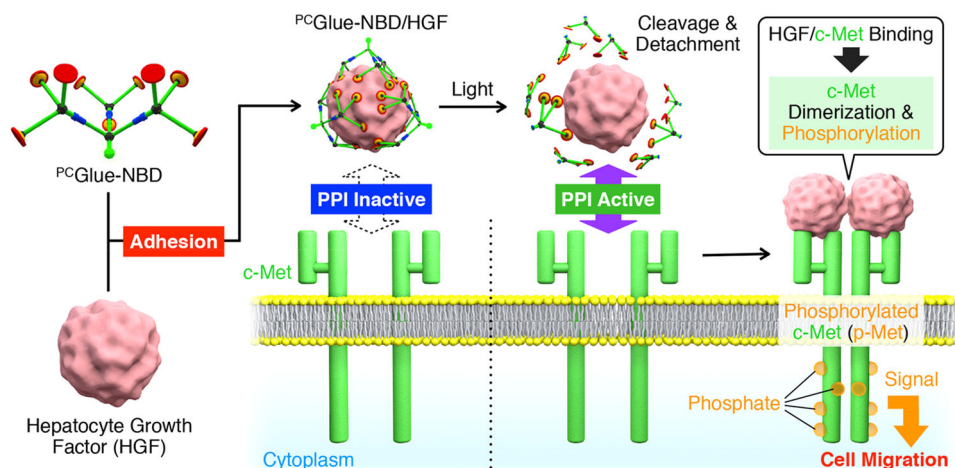

Fig. 7 Photo-controlled protein-protein interaction. Proposed mechanism of a supramolecular glue-mediated off/on switching of ligand-receptor interaction between HGF and c-Met. The glue molecules adhere to HGF and suppress the affinity between HGF and c-Met. Upon exposure to UV light, the glue on HGF is degraded at photocleavable linkages to reduce the multivalency and weaken adhesion, which activates HGF binding to c-Met and initiates dimerization and phosphorylation of receptor. Adapted with permission from ref. [126], Copyright American Chemical Society, 2019.

opportunities to the development of novel therapeutic materials and methods. Biomimetic signal transduction systems have been broadly explored in both synthetic bilayers and living cells.

Key to the development of artificial signaling system is the design of synthetic receptors that sense the external cues, translate this signal into another kind and amplify the signal to elicit downstream responses. A prerequisite for artificial receptors is the ability to recognize specific messengers via monovalent or multivalent interactions. Recent progress has witnessed the development of artificial signaling systems that are capable of sensing small molecules, pH, metal ions, albeit with the binding of low specificity. However, it remains challenging to develop synthetic receptors capable of sensing biologically relevant endogenous ligands such as hormones and neurotransmitters.

Besides, cells can respond to a variety of physical clues such as mechanical stimuli and electrical pulses, which remain largely unexplored in synthetic systems.

Three main mechanisms, i.e., receptor dimerization, GPCR mode and molecular translocation, have been explored to realize signaling across the synthetic lipid membranes. Among these, signal transduction using artificial membrane-spanning GPCR receptors remains challenging since it requires precise control over receptor conformation and orientation inside the membrane. In this regard, computer-aided analysis (e.g., molecular dynamics simulation and machine learning) will help to gain a deep understanding of intramolecular forces and receptor-lipid interactions. Another unmet challenge is to generate an amplified signal output in artificial cells. In biology, cells use enzymes (e.g., protein kinases) to amplify the chemical signal and trigger a downstream cellular response. In synthetic systems, signal amplification is mainly achieved with small catalytic groups, where the magnitude of signal amplification is far less than that achieved with natural enzymes. To tackle this challenge, it is essential to develop enzyme-like catalytic compounds or nanomaterials with comparable activity.

In living cells, reprogramming ligand-receptor interactions represents a powerful tool to regulate transmembrane signaling and downstream cellular responses. In a biologically relevant context, polypeptides and aptamers are selected as recognizing motifs through phage display and Sequential Evolution of Ligands by Exponential Enrichment (SELEX), respectively. To boost the efficacy of interfacial recognition, precise control over spatial organization, orientation, and conformational freedom of bioactive epitopes is demanded to optimize ligand-receptor interaction. Such complex recognition scenarios are achievable with sequence-specific polymers or precisely controlled self-assembly of DNA and polypeptides.

Reporting summary. Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data that support the findings of this study have been included in the manuscript. Any additional data are available from the corresponding author upon reasonable request.

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