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Polymers with Intrinsically Therapeutic Activity: from Membrane-targeted Cytotoxicity to Receptor-topology Remodeling

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Abstract Polymers with intrinsic therapeutic activity have redefined the role of macromolecules in medicine. Unlike conventional polymeric carriers, which primarily improve solubility, prolong circulation, or control drug release, these polymers directly engage in therapeutic processes through their chemical structures, physical organization, multivalent interactions, and stimulus-responsive behaviors. In this review, we discuss the four representative classes of therapeutic polymers. Membrane-active polymers eradicate pathogens, disrupt biofilms, and kill tumor cells by exploiting their charge, hydrophobicity, chain conformation, and disease-associated membrane vulnerability. Immunomodulatory polymers activate or redirect protective immunity by engaging innate immune sensors, glycan-recognition pathways, and engineered immune-cell interfaces. Anti-inflammatory polymers resolve pathological inflammation by scavenging reactive oxygen species, regulating macrophage polarization, inhibiting pyroptosis, and remodeling damaged tissue microenvironments. Receptor-topology-remodeling multivalent polymers reorganize cell surface receptors through nanoscale ligand spacing, receptor crosslinking, mechanical force, and programmable clustering to induce apoptosis or rewire signaling. Taken together, these examples establish that polymer architecture itself can determine therapeutic outcomes across a wide spectrum of conditions, including infection, cancer, inflammatory diseases, and immune-mediated disorders. By comparing these mechanisms, we highlight how macromolecular design parameters, including valency, degradability, assembly state, and disease-triggered activation, can translate into therapeutic potential. We further delineated the key design principles and translational challenges for this emerging class of polymer-based therapeutics.

Keywords Polymers with intrinsically therapeutic activity; Membrane-active polymers; Immunomodulatory polymers; Anti-inflammatory polymers; Receptor-topology-remodeling multivalent polymers

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1 INTRODUCTION

Polymers have long played an important role in biomedical research owing to their structural diversity, tunable physicochemical properties, and ability to interface with biological systems at molecular, cellular, and tissue scales.[1,2] In many classical applications, polymers are designed as drug carriers,[3,4] implants, hy-

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drogels,[5,6] coatings, tissue engineering scaffolds, or surface modifiers. Their major functions include improving biocompatibility; prolonging circulation,[7] enhancing local retention,[8–11] regulating degradation; and optimizing the pharmacokinetics of active small molecules, peptides, proteins, and nucleic acids.[1,2,12–14] This carrier-centered paradigm has greatly advanced polymer-based medicine and is essential for modern drug delivery. However, it does not fully describe a rapidly expanding class of macromolecular systems in which the polymer itself directly contributes to the therapeutic outcome.[15,16] In these systems, therapeutic activity is not merely derived from the encapsulated or conjugated payload, but also from the intrinsic physicochemical features, architecture, dynamic assembly, or biological interactions of the polymer. Thus, the central question shifts from how polymers deliver drugs to how polymer structures function as active therapeutic agents. Here, "intrinsically therapeutic polymers" refers to polymeric or biopolymeric systems in which the macromolecular component directly contributes to therapeutic activity through its chemical structure, physicochemical properties, multivalency, assembly, or interfacial organization, rather than serving solely as a passive carrier. Hybrid systems, polymer-engineered cellular interfaces, and DNA-based nanostructures are included when polymeric or biopolymeric components are essential determinants of therapeutic mechanisms.

This conceptual shift is important because many pathological processes are spatially organized rather than being controlled by a single molecular target. Bacterial envelopes, fungal membranes, biofilms, tumor cell surfaces, immune synapses, inflamed tissues, extracellular matrices, and receptor clusters are dynamic biological interfaces.[17–19] Their pathological behavior depends on charge distribution, membrane composition, cellular organization, mechanical forces, oxidative stress, cytokine dysregulation, matrix remodeling, and receptor proximity. Conventional drugs often regulate disease by binding defined enzymes or receptors, whereas intrinsically therapeutic polymers can act through collective macromolecular mechanisms, including membrane disruption, macromolecular assemblies, steric blockade, receptor crosslinking, and cell surface patching.[16,20,21] These mechanisms provide opportunities to address antimicrobial resistance, tumor heterogeneity, chronic inflammation, insufficient immune activation, and drug-insensitive cellular states. At the same time, they require a more rigorous understanding of structure-activity relationships because efficacy, selectivity, toxicity, tissue residence, and clearance are often governed by the same macromolecular parameters.

Membrane-active polymers represent one of the most direct demonstrations of therapeutic functions dictated by the physicochemical properties of polymers. Inspired by host defense peptides, cationic and amphiphilic polymers can bind anionic microbial envelopes through electrostatic interactions and subsequently induce hydrophobic insertion, membrane disorganization, translocation, or intracellular damage.[17,22] This membrane-targeting strategy has been extended from combating bacteria to tackling more complex systems such as biofilms and fungal envelopes, where a protective extracellular matrix coupled with altered microbial metabolism and upregulated stress responses creates formidable barriers to treatment.[23,24] More recently, the same membrane-targeting logic has been redirected toward tumor cell killing.[25] Owing to the similar membrane compositions of mammalian and tumor cell membranes, tumor-selective membranolytic polymers usually require gating mechanisms based on acidity, enzyme responsiveness, charge shielding, aggregation-controlled pericellular residence, or stimulus-responsive exposure of membranolytic domains.[26–28] These systems show that membrane activity is not simply nonspecific toxicity but a tunable therapeutic function controlled by charge density, hydrophobicity, chain conformation, degradability, stereochemistry, and local activation.

The second category comprises immunomodulatory polymers, whose primary function is to regulate immune recognition to initiate antigen presentation, cytokine production, or effector-cell recruitment, while remaining sufficiently localized and transient to avoid systemic inflammation and tissue damage.[18,29] Natural polysaccharides represent a major family of immunostimulatory polymers, in which repeating carbohydrate motifs, sulfation, acetylation, branching, molecular weight, solubility, and particulate organization influence recognition by pattern recognition receptors, lectins, complement components, macrophages, and dendritic cells.[30,31] Given that receptor engagement, endosomal escape, antigen loading, lymphatic trafficking, and tissue retention can all be independently engineered and recombined, synthetic polymers offer a more modular route for immune activation.[32,33] In addition, polymer interfaces on dendritic cells, natural killer cells (NK), neutrophils, and other immune cells can regulate cell-cell contact, activation duration, residence time, and mechanical persistence.[34] These examples indicate that polymers can serve as programmable immune modulators rather than as inert excipients.

Closely related yet mechanistically distinct are anti-inflammatory polymers, which are designed to intervene in pathological immune microenvironments rather than to amplify immune activation. In chronic wounds, cystitis, spinal cord injury, osteoarthritis, sepsis, postoperative adhesions, excessive reactive oxygen species, persistent macrophage M1 polarization, bacterial biofilms, cytokine amplification, and impaired matrix remodeling collectively create a self-reinforcing pathological barrier that blocks tissue repair.[35–37] Accordingly, recent anti-inflammatory polymer systems have been engineered to scavenge reactive oxygen species (ROS) or inflammatory mediators; reprogram macrophages and fibroblasts; provide adhesive, injectable, or mechanically adaptive residence; and couple anti-inflammation with regeneration, hemostasis, or antibacterial functions.[35,38,39] Natural polymer hydrogels, polyphenol-integrated dressings, macrophage-instructive surfaces, multifunctional local interfaces, and active macromolecular anti-inflammatory therapies together illustrate that polymer-directed anti-inflammatory activity can arise from how cells attach to, sense, remodel, and respond to the material, rather than from the material merely serving as a passive scaffold or drug depot.[36,40,41]

The fourth class comprises receptor-topology-remodeling multivalent polymers and related programmable macromolecular scaffolds. For many membrane receptors, ligand

binding alone is insufficient to define the biological outcome, as the cell interprets the nanoscale organization of engaged receptors, including their spacing, orientation, clustering valency, membrane residence, and cluster lifetime, as distinct signaling inputs. Depending on this spatial code, receptor engagement can trigger activation, suppression, biased signaling, or programmed cell death.[42–44] The nanopatterning of death receptors provides a clear example, in which DNA origami, peptide patterns, or DNA nanostructures organize the spacing of cytotoxic ligands to promote receptor clustering and cell apoptosis.[42–45] Multivalent polymers apply the mechanistic core of drug-free macromolecular therapeutics, using receptor-binding motifs and multivalent macromolecular effectors to crosslink slowly internalizing receptors such as CD20 and CD38.[46,47] Aptamer assemblies, glycol-chitosan-based multi-catcher polymers, nanothreads, cell-surface polymerization, protein cages, and mechanically regulated receptor systems further demonstrate that therapeutic output can be generated by editing receptor proximity, membrane organization, and cell-surface topology.[48–51]

In this review, we summarize four representative classes of polymers with intrinsic therapeutic activities: membrane-active polymers, immunomodulatory polymers, anti-inflammatory polymers, and receptor-topology-remodeling multivalent polymers. Rather than treating polymers as inert matrices, delivery auxiliaries, or passive scaffolds, we emphasize how polymer charge, hydrophobicity, chain architecture, degradability, multivalency, ligand spacing, surface persistence, and dynamic assembly translate into biological functions. Particular attention is paid to the relationship between macromolecular design and therapeutic outcomes, including membrane selectivity, immune activation, inflammatory resolution, tissue repair, and receptor clustering. Together, these examples provide a framework for designing next-generation polymer medicines with intrinsic, programmable, and disease-selective therapeutic activity.

2 MEMBRANE-ACTIVE POLYMERS: FROM PATHOGEN MEMBRANE DISRUPTION TO TUMOR MEMBRANOLYSIS

Membrane-active polymers constitute a distinctive category of therapeutic macromolecules that engage the biological membrane as a primary therapeutic target. Their activity is typically derived from the synergistic integration of cationic charge, hydrophobic insertion, chain conformation, multivalency, and stimulus-responsive exposure. In this section, we trace the progression of membrane activity from microbial membrane-targeting to tumor cell membranolysis, emphasizing how selectivity is governed by bacterial phospholipids, biofilm architecture, tumor acidity, enzymatic activation, and immunogenic consequences.

2.1 Antibacterial Polymers Targeting Microbial Membranes

The antibacterial use of membrane-active polymers originates from the same design logic as that of host-defense peptides: electrostatic attraction to anionic bacterial envelopes followed by hydrophobic insertion and membrane disorganization.[52] This strategy is attractive because membrane disruption is less dependent on a single mutable protein target than conventional antibiotics. Degradable guanidinium-functionalized polycarbonates illustrate how this principle can be translated into a systemic therapy. By tuning the hydrophobic spacer, the optimized butyl-spacer polymer showed rapid activity against multidrug-resistant *Klebsiella pneumoniae*. At high concentrations, it self-assembled to shield its hydrophobic domains from mammalian cells and alleviated lung infection in mice, with limited organ toxicity.[53]

More recent studies have demonstrated that antibacterial selectivity can extend beyond simple charge discrimination. Radially amphiphilic helical polypeptides have been designed to selectively recognize bacterial phosphatidylglycerol (PG) over mammalian phosphatidylserine (PS), although both are anionic lipids.[54] This lipid-level selectivity is schematically illustrated by the radial amphiphilic peptide design and the PG-recognition model shown in Fig. 1. In this system, helicity, radial amphiphilicity, and conformationally masked hydrophobic domains govern peptide assembly on the PG-rich membranes, establishing a higher-order lipid-recognition mechanism. This is an important conceptual advance: membrane-active polymers do not need to behave as nonspecific cationic detergents, and they can be engineered to recognize the composition, curvature, and organization of microbial membranes.

2.2 Biofilm and Fungal Membrane Disruption

Biofilms and fungal pathogens pose additional barriers, as the target membrane is protected not only by an extracellular matrix but also by altered metabolism and upregulated stress-response pathways. As a representative example, Rotello and coworkers' fluorescent cationic conjugated poly(phenylene ethynylene)s with optimized C11 hydrophobic side chains have been shown to penetrate antibiotic-resistant biofilms, disrupt bacterial membranes, and achieve >99.9% reduction in a murine wound biofilm model, while their intrinsic fluorescence enables direct visualization of polymer-biofilm interactions.[55] To combat fungal pathogens, Boyer *et al.* designed synthetic polyacrylamide peptides that mimic LH, which are active against *Candida albicans* through a broader stress cascade, including endoplasmic reticulum stress, altered glycosylation, mannan-layer damage, and membrane disruption (Fig. 2).[56]

Membrane activity can also be shifted from outright lysis to more subtle mechanisms when selectivity is paramount. Heterochiral poly-β-peptides, for instance, reduce mammalian toxicity by shifting their mechanism from strong membrane disruption to membrane crossing, after which intracellular ROS generation and DNA interaction contribute to bacterial killing.[57] Collectively, these antibacterial, antibiofilm, and antifungal examples demonstrate that the therapeutic window depends on far more than the charge density; parameters such as chain stereochemistry, hydrophobic side-chain length, biofilm penetration, and intracellular trafficking ultimately determine whether a polymer kills pathogens while sparing host cells.

2.3 Tumor-selective Membranolytic Polymers

The same membrane-centered logic has been extended to cancer therapy, where rapid plasma membrane rupture can bypass apoptosis resistance, intracellular drug efflux, and tumor genetic heterogeneity. Host-defense peptide-mimicking anticancer

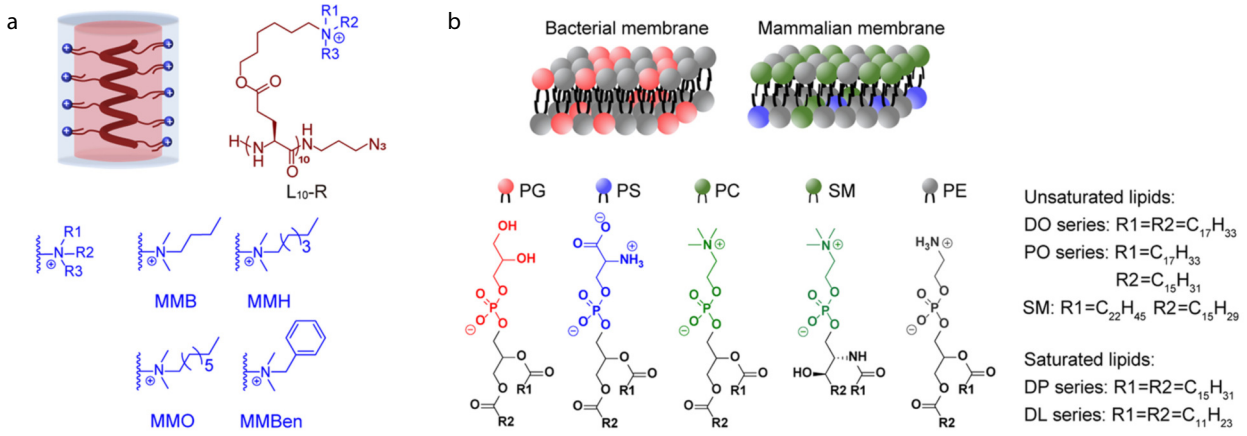


Fig. 1 Radially amphiphilic antimicrobial peptides for selective bacterial membrane recognition. (a) Helical L10-R peptides organize cationic quaternary ammonium side chains and hydrophobic backbones into a radially amphiphilic architecture; (b) Bacterial and mammalian membranes differ in phospholipid composition, enabling selective recognition of phosphatidylglycerol (PG)-rich bacterial membranes over mammalian phosphatidylserine- or zwitterionic lipid-containing membranes. (Reproduced with permission from Ref. [54]; Copyright (2024), American Association for the Advancement of Science, CC BY-NC 4.0).

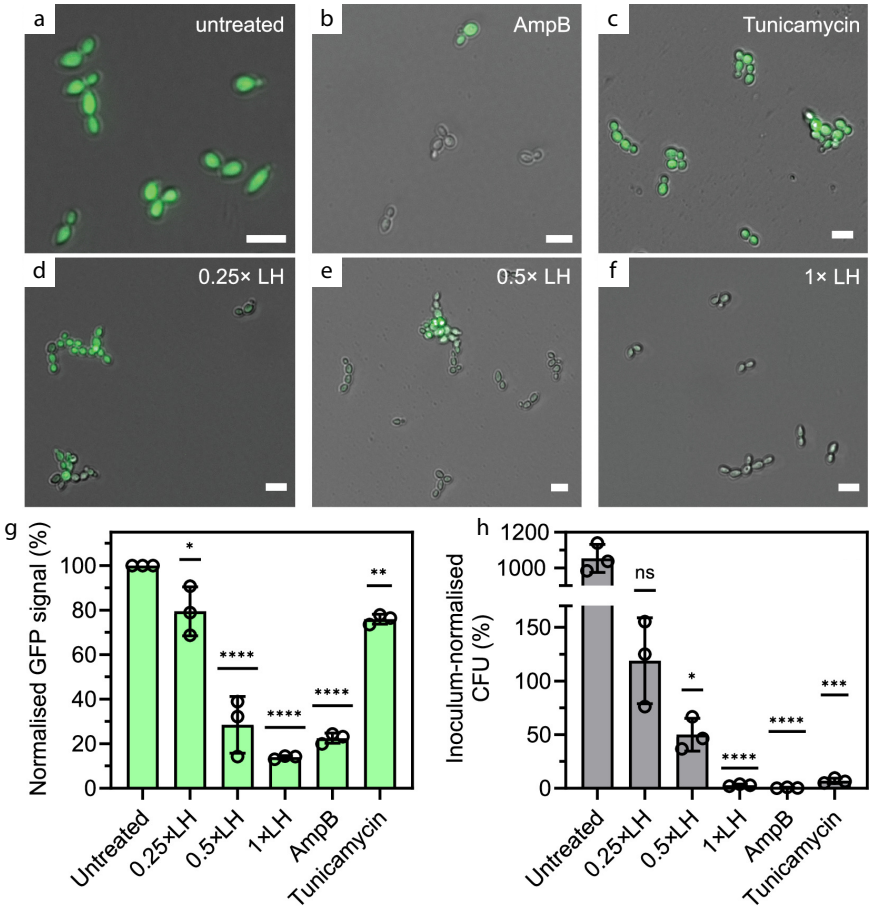


Fig. 2 Membranolytic antifungal activity of synthetic peptide-mimic polymer LH. (a–f) Cytoplasmic GFP imaging of *Candida albicans* shows membrane lysis after treatment with amphotericin B or increasing concentrations of polymer LH, whereas tunicamycin induces fungal death with less prominent GFP leakage; (g, h) Quantification of GFP signal and colony-forming units demonstrates concentration-dependent membrane disruption and loss of fungal viability after LH treatment. (Reproduced with permission from Ref. [56]; Copyright (2024), Springer Nature, CC BY-NC-ND 4.0).

polypeptides provided an early demonstration: the cationic polypeptide ACPP killed diverse cancer cells within minutes *via* membrane lysis. The pH-sensitive zwitterionic derivative DA-ACPP reduced hemolysis at physiological pH, while regaining its

membranolytic activity in acidic tumor environments, thereby suppressing orthotopic breast tumors and melanoma lung metastases.[58] Reviews of oncolytic peptides and polymers have framed these systems as a distinct oncotherapy modality in which the macromolecule itself, rather than an encapsulated drug, acts as a cytotoxic agent.[59]

A central challenge is that tumor cell membranes resemble normal cell membranes far more closely than bacterial membranes, making selective disruption inherently difficult. Consequently, tumor-selective oncolytic polymers typically rely on gating mechanisms. For example, neutrally charged guanidinium-polypeptide nanoparticles mask cationic toxicity through electrostatic assembly with an anionic pH-sensitive carrier, accumulate in tumors, and restore membranolytic activity under acidic conditions.[60] Similarly, pH-activated polypeptide nanoparticles shield cationic oncolytic chains at pH=7.4, but release them at pH=6.8, causing membrane damage, mitochondrial dysfunction, ROS production, immunogenic cell death, and suppression of tumor growth, recurrence, and metastasis.[61] Enzymatic unmasking offers another strategy: alkaline-phosphatase-responsive precursor switches from negatively charged C12-PLL/PA to cationic C12-PLL in tumor tissue, thereby recovering membranolytic activity and inhibiting orthotopic 4T1 tumors with low systemic toxicity.[62]

The most refined systems convert subtle tumor acidity into sharp functional outputs. Xiong *et al.* developed proton-transistor nanodetergents to amplify a 0.1 pH unit input into a >32-fold change in cytotoxicity; at physiological pH, they remain neutral and shielded, whereas tumor acidity induces protonation, morphological transformation, exposure of membranolytic blocks, and cation-π-assisted insertion of benzyl domains into cell membranes.[63] Alternating ultra-pH-sensitive polyesters further improved the structural precision by placing ionizable tertiary amines and hydrophobic groups in an ordered sequence, enabling an OFF-to-ON transition within 0.2 pH units and phosphatidylserine-associated membranolysis at pH=6.8 (Fig. 3).[26] These examples collectively illustrate the broader potential of ultra-pH-sensitive nanoplatforms, where sharp pH-responsive transitions have been exploited in precision therapy, imaging, phototherapy, drug delivery, and immunotherapy.[64]

Tumor selectivity can also be controlled by polymer aggregation and pericellular residence. Poly(vinyl alcohol)-ursodeoxycholic acid conjugates demonstrate that hydrophobicity and negative charge must be balanced rather than maximized. An intermediate degree of grafting forms pericellular aggregates under tumor-acidic conditions and induces

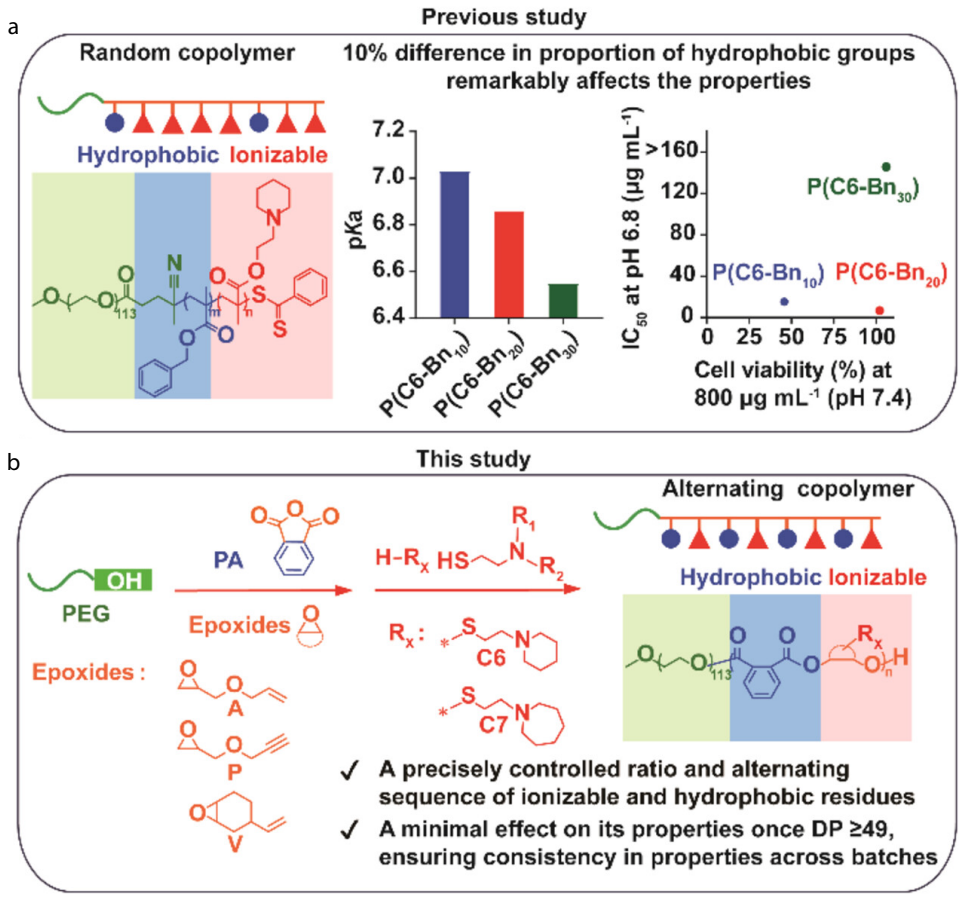


Fig. 3 Alternating pH-ultrasensitive oncolytic polyesters for tumor-selective membrane disruption. (a) Previously reported random pH-ultrasensitive copolymers show strong sensitivity of p*K*a and cytotoxic selectivity to small variations in hydrophobic composition; (b) Alternating oncolytic polyesters precisely arrange ionizable and hydrophobic groups along the polymer backbone, enabling reproducible tumor-acidity-triggered membranolytic activity. (Reproduced with permission from Ref. [26]; Copyright (2024), American Chemical Society).

cell death more selectively, whereas lower or higher substitution favors internalization and reduces pH discrimination.[65] Thus, for cancer membranolysis, the decisive design variables are not only cationic charge and hydrophobicity but also masking, activation threshold, aggregation state, lipid engagement, and the location of polymer action at or within the cell membrane.

2.4 Membrane Rupture as an Immunogenic Event

Membrane-active cancer therapy is not limited by direct cytotoxicity. Polysulfonium polymers disrupt cancer cell membranes, induce the release of damage-associated molecular patterns (DAMPs), trigger immunogenic cell death, and generate immune memory that suppresses melanoma recurrence and lung metastasis.[66] This establishes a bridge between physical membrane damage and systemic antitumor immunity.

A more complex example is glioblastoma therapy. Polymer-wrapped CuS nanoflakes combine pH-responsive membrane disruption with NIR-II photothermal therapy. Convection-enhanced delivery improves residence within deep brain tumors, while local antigen retention and dendritic cell detention create a self-reinforcing immunotherapy cascade with enhanced T-cell infiltration.[27] Such systems indicate that membranolytic polymers can function as local immune primers: membrane rupture releases tumor antigens and danger signals, whereas polymer architecture and associated nanomaterials help retain, amplify, or spatially organize those signals.

Across antimicrobial and anticancer applications, membrane-active polymers have demonstrated that therapeutic selectivity arises from the coordinated control of cationic charge, hydrophobicity, chain conformation, stereochemistry, and stimulus-responsive exposure. Charge and hydrophobicity must be balanced to engage diseased membranes while avoiding hemolysis, serum protein binding, and nonspecific host-cell damage. Selectivity is achieved through molecular recognition, including bacterial PG recognition, tumor phosphatidylserine engagement, pH-transistor behavior, and enzyme-mediated charge conversion.[26,54,62,63] Thus, membrane activity should be viewed as a tunable therapeutic function that links local interfacial disruption to antimicrobial killing, tumor membranolysis, and, in selected systems, immune activation.

3 IMMUNOMODULATORY POLYMERS: PROGRAMMING IMMUNE RECOGNITION AND CELL FUNCTION

Immunomodulatory polymers are macromolecules that directly regulate immune recognition, activation, suppression, and intercellular communication. Their activity is governed not only by any loaded drugs or antigens[67,68] but also by the inherent composition, multivalency, charge, hydrophobicity, degradability, and surface persistence. In this section, we discuss three representative strategies: natural polysaccharide immunomodulators, synthetic polymers for innate immune activation, and polymer interfaces for immune-cell engineering.[69–71]

3.1 Immunostimulatory Natural Polymers

Natural polysaccharides are the most extensively studied class of immunomodulatory polymers, and their repeating carbohydrate motifs are readily recognized by innate immune receptors. Their immunological outcomes are governed by their molecular weight, branching, sulfation, acetylation, solubility, particulate state, and chain conformation. In these systems, intrinsic immunomodulatory activity is primarily encoded by polymer structural features, such as glycan composition, sulfation, acetylation, branching, molecular weight, and charge density, rather than by an additional therapeutic payload. These structural parameters critically influence macrophage activation, dendritic cell maturation, complement interactions, cytokine secretion, and crosstalk between innate and adaptive immunity.[72,73] β-Glucans exemplify this structure–activity relationship. Through receptors such as dectin-1, complement receptor 3, CD5, and lactosylceramide, β-glucans act as immunoadjuvants capable of enhancing antigen presentation and antitumor or anti-infective immunity, further demonstrating how the glycan architecture can be harnessed for programmable immune potentiation.[74,30]

Sulfated marine polysaccharides constitute the second most important subgroup. For instance, fucoidan activates antiviral immunity *via* the stimulator of interferon genes (STING) pathway, reshapes the gut microbiota and Peyer's patch immune responses in inflammatory bowel disease, and promotes M1-like macrophage differentiation to potentiate chemoimmunotherapy.[75–77] Photopolymerizable fucoidan and carrageenan retain their immunomodulatory activity in biomaterial formats, supporting their application as scaffold-integrated immune regulators, rather than merely as soluble polysaccharides.[78] These findings align with the broader concept of sulfated glycan-immune dialogue, in which charge density and sulfate patterning regulate interactions with both immune cells and soluble mediators.[79] Meanwhile, the immunomodulatory roles of Siglecs and galectins serve as a reminder that glycan recognition is not uniformly stimulatory and, depending on the receptor context, analogous carbohydrate cues can promote inflammation, immune tolerance, or tissue repair.[80,81]

Chitosan (CS) is a cationic polysaccharide with a distinct adjuvant mechanism. It promoted dendritic cell maturation, type I interferon production, and Th1-skewed cellular immunity through mitochondrial stress, cytosolic DNA release, and cyclic GMP–AMP synthase (cGAS)-STING activation (Fig. 4).[82,83] Thus, chitosan is not merely a mucoadhesive carrier but also acts as a polymeric danger signal. Its immune activity critically depends on the degree of deacetylation, molecular weight, charge density, and formulation route, which explains why chitosan-based systems can serve as vaccine adjuvants, antimicrobial immune activators, or broader immunomodulatory biomaterials.[84] A practical design lesson from natural polymers is that biological activity should be standardized against well-defined structural parameters. Source-dependent heterogeneity, endotoxin contamination, and variations in chain conformation can readily obscure the true relationship between polymer chemistry and immune phenotype.

3.2 Synthetic Polymers for Innate Immune Activation and Vaccination

Compared to natural polymers, synthetic polymers allow receptor engagement, endosomal escape, antigen loading, and pharmacokinetics to be programmed independently. STING-active polymer micelles are representative examples. STING-activating micelles (HySTING), developed by Gao *et al.*, combine the im-

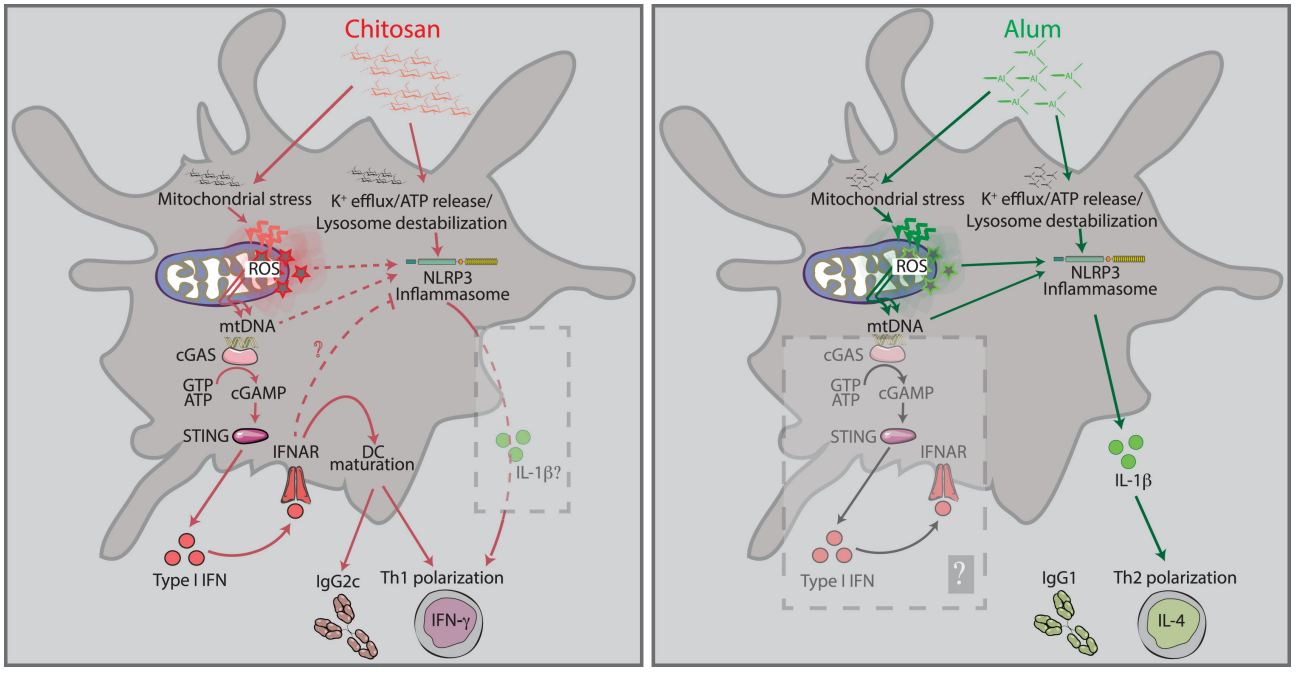


Fig. 4 Chitosan-mediated innate immune activation through the cGAS-STING axis. Phagocytic uptake of chitosan induces mitochondrial stress, ROS production, and mitochondrial DNA release, thereby activating cGAS-STING-dependent type I interferon signaling and promoting Th1-skewed cellular immunity; Alum induces mitochondrial stress and inflammasome activation but does not efficiently trigger the cGAS-STING-type I interferon pathway, highlighting the distinct immune-programming logic of chitosan as a natural polymeric danger signal (Reproduced with permission from Ref. [83]; Copyright (2016), Elsevier).

munostimulatory polymer PEG-*b*-PC7A with secondary carrier polymers of lower p*K*a values, thereby retaining STING activation and membrane destabilization while improving blood circulation, tumor accumulation, cyclic dinucleotide encapsulation, and programmed cell death protein 1 (PD-1) blockade synergy.[85] Mechanistic studies of piSTING, phosphatidylinositol 4-phosphate (PI4P)-associated STING activation, protonation-cooperative STING polymers, heterocycle-tethered branched polymers, polyvalent STING agonists, and STING nanovaccines further showed that ionizable groups, heterocycles, multivalency, and nanoscale clustering can act as polymeric pharmacophores for type I interferon signaling.[33,86–90]

Therapeutic vaccination requires coordinated delivery of antigens and innate stimuli to the same antigen-presenting cells. This principle has recently been demonstrated using a cholesterol azetidine-assisted polymeric nanoparticle (AzeChol NP) that inherently activates Toll-like receptor 9 (TLR9) while transporting tumor antigens to dendritic cells in lymph nodes, eliciting potent $CD8^+$ T cell priming and long-term immune memory.[91] Antigen-folding polymer strategies further improve protein loading and preservation in nanovaccines.[92] These systems satisfy three design requirements: (i) protection of antigens before lymphatic transport, (ii) triggering dendritic cell maturation during antigen processing, and (iii) promotion of cytosolic access or cross-presentation without inducing excessive systemic inflammation. From this perspective, a polymer does not simply replace an adjuvant molecule; rather, it defines the timing and subcellular compartment in which the adjuvant signal is perceived. Spatial control is crucial for cancer immunotherapy. The same type I interferon or inflammatory stimulus that proves therapeutic in antigen-rich tumor tissues can become toxic when systemically disseminated. An additional advantage of synthetic systems is that immune activation can be directly coupled with tumor-associated physicochemical cues. pH-sensitive ionization, micellar disassembly, and protonation cooperativity enable polymers to remain relatively inert in circulation, while becoming active upon cellular uptake or tumor accumulation. This staged behavior mirrors the surface-adaptive logic employed in cancer nanomedicine: the carrier first solves the delivery and then switches into an immune-activating state specifically at the targeted site.

3.3 Polymer Interfaces for Immune-cell Engineering

Another strategy is to attach polymers directly to immune cells or engineer polymeric interfaces that orchestrate immune cell contact.[93] Dendritic cells, NK cells, and neutrophils are mobile therapeutic units, whose maturation state, cytotoxic potential, and tumor trafficking strongly influence treatment efficacy.[94,95] Polyphenol membrane coatings provide a mild surface engineering method to modulate the function of dendritic cells.[96] Mechanoimmune polymer backpacks sustain dendritic cell maturation during radiotherapy, whereas backpack-activated neutrophils and adhesive polymer micropatches exploit innate cell migration to treat glioblastoma or enhance tumor localization, without relying solely on free nanoparticle accumulation.[97–99] The neutrophil-bearing adhesive polymer micropatch strategy provides a representative example of a polymer interface that converts innate immune cells into drug-free, tumor-targeting therapeutic units (Fig. 5).

Polymer micropatches can also serve as NK cell engagers by physically organizing effector cells and tumor targets, thereby enhancing cytotoxic contact.[100] In these examples, the polymer functioned as a temporary extracellular circuit. It

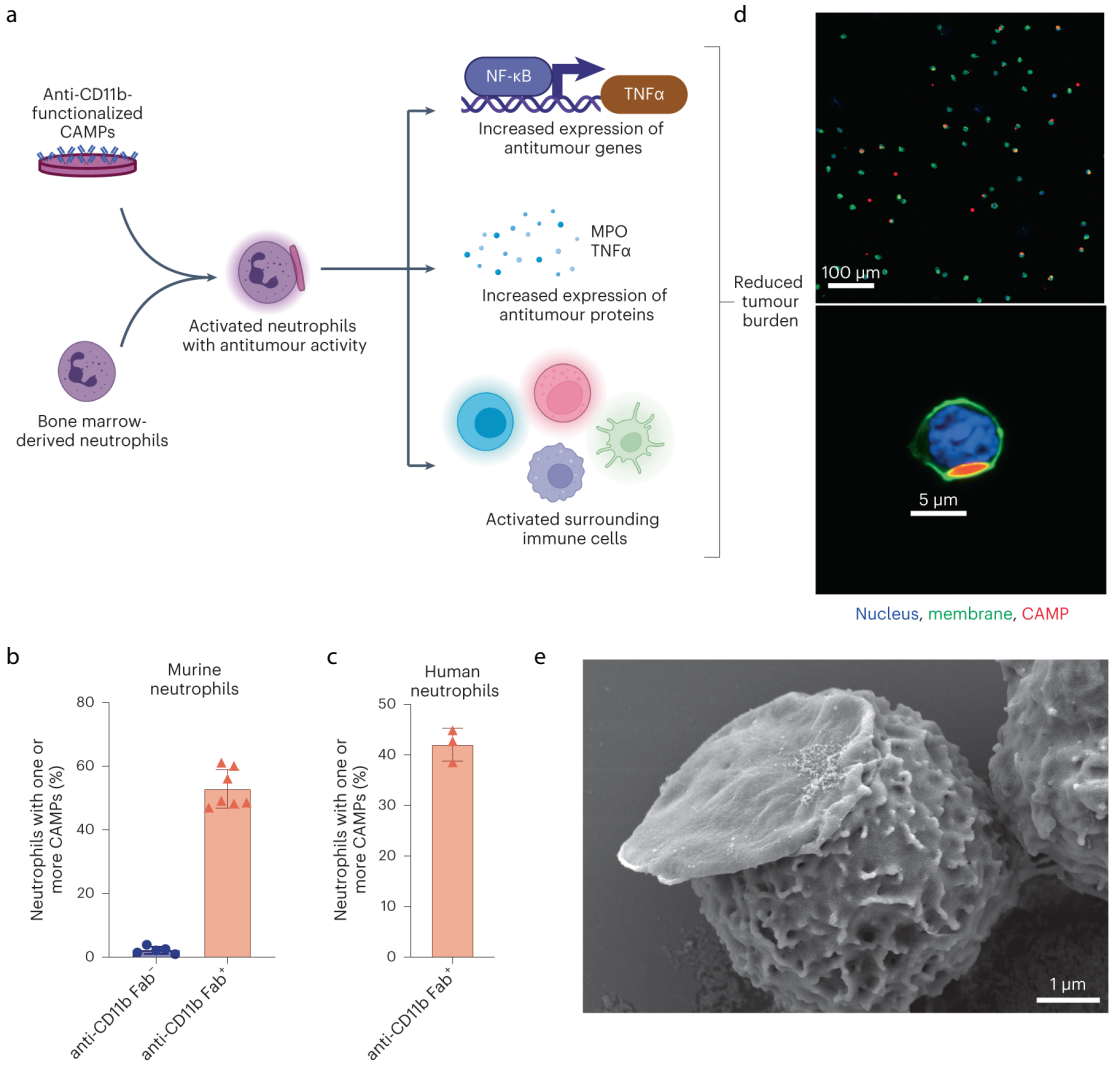


Fig. 5 Neutrophil-bound adhesive polymer micropatches for drug-free cancer immunotherapy. (a) Schematic summary of the neutrophil-CAMP concept, showing that anti-CD11b Fab-functionalized CAMPs attach to neutrophils, activate neutrophil phenotypes, modulate gene expression and protein release, and stimulate immune responses that reduce tumor burden; (b, c) Flow-cytometry analysis of CAMP attachment to murine and human neutrophils; (d, e) Confocal and scanning electron microscopy visualization of surface-attached CAMPs on neutrophils. (Reproduced with permission from Ref. [99]; Copyright (2024), Springer Nature).

controls cell-cell adhesion, residence time, activation duration, and mechanical persistence, rather than simply releasing a payload. This cell-interfacing approach is particularly attractive for tumors or inflamed tissues that are poorly accessed by conventional nanocarriers. It also provides a modular alternative to permanent genetic engineering: immune cells can be armed, guided, or sustained by detachable polymer structures, while retaining their native sensing, migration, and clearance programs. By anchoring onto immune cell surfaces, these polymers confer tumor-homing capacity, prolong intratumoral residence, and amplify effector functions, such as cytotoxicity and cytokine secretion. The resulting immune responses encompass direct tumor cell killing, modulation of the local immune microenvironment, and, in selected systems, generation of systemic antitumor immunity.

Taken together, immunomodulatory polymers show that immune regulation can be encoded in a macromolecular structure, rather than being treated as a secondary biological response. Natural immunostimulatory polysaccharides, synthetic innate-sensor-activating vaccines, and cell-interface engineering platforms depend on chain architecture, ionization, hydrophobicity, sulfation, degradability, multivalency, and surface persistence. Linking the polymer structure quantitatively to the immune phenotype is therefore essential for making antitumor immunity, antiviral defense, and cell-based immunotherapy more predictable therapeutic programs.

4 ANTI-INFLAMMATORY POLYMERS: REMODELING PATHOLOGICAL INFLAMMATORY MICROENVIRONMENTS

Anti-inflammatory polymers are designed to disrupt self-reinforcing pathological inflammatory circuits rather than simply serve as passive barriers or drug delivery platforms. A wide range of difficult-to-treat conditions, including chronic wounds, cystitis, spinal cord injury, osteoarthritis, sepsis, postoperative

adhesions, excessive reactive oxygen species (ROS), persistent macrophage M1 polarization, bacterial biofilms, cytokine amplification, and impaired matrix remodeling. To address these multifaceted challenges, anti-inflammatory polymer systems have been increasingly engineered with multiple integrated functions: (i) scavenging ROS or inflammatory mediators; (ii) directing macrophages and fibroblasts; (iii) providing adhesive, injectable, or mechanically adaptive residence; and (iv) coupling anti-inflammation with regeneration, hemostasis, or antibacterial activities. In this section, polymers are considered intrinsically anti-inflammatory when the polymeric component directly modulates inflammatory processes such as ROS scavenging, macrophage polarization, cytokine regulation, or pyroptosis inhibition, whereas tissue adhesion, mechanical support, hemostasis, and regeneration are regarded as complementary or downstream therapeutic functions.

4.1 Natural Polymer Hydrogels for Local Immune Repair

Natural polysaccharides and proteins provide abundant functional groups and intrinsic bioactivity for local anti-inflammatory therapies. Among these, chitosan-based systems are the most versatile. Slight photocrosslinked chitosan/silk fibroin adhesives restore bladder barrier function in cyclophosphamide-induced hemorrhagic cystitis by combining wet adhesion, rapid hemostasis, biodegradation, and macrophage polarization control.[101] Sulfated chitosan rescues dysfunctional diabetic wound macrophages and accelerates healing, whereas O-carboxymethylated chitosan exhibits *in vivo* anti-inflammatory and analgesic activities, indicating that chitosan derivatives can be tuned from local wound immunoregulation to systemic symptom relief.[102,103] Furthermore, carboxymethyl chitosan integrated with gallic acid generates an injectable, self-healing, adhesive hydrogel that remodels the inflammatory microenvironment after spinal cord injury while supporting neural regeneration.[104]

Other natural macromolecules extend this logic to tissue-specific repair. Hyaluronic acid (HA)-coated collagen nanofibers induce *in situ* M2 macrophage polarization for urethral regeneration, which combines antibacterial and anti-inflammatory functions in wounds, and Antheraea pernyi silk nanofibrils exploit inherent arginine–glycine–aspartic acid (RGD) motifs to promote hemostasis, macrophage transition, and re-epithelialization in diabetic wounds.[105–107] Fucoidan hydrogels provide an injectable and self-healing anti-inflammatory platform based on a sulfated marine polysaccharide, whereas natural melanin/alginate hydrogels facilitate cardiac repair through ROS scavenging and macrophage polarization.[108,109] Collectively, these examples illustrate that natural polymers frequently exert their therapeutic effects through simultaneous matrix mimicry and immune modulation, rather than through a single anti-inflammatory pathway. Their translational appeal lies in their ability to match biological origin with local tissue requirements: adhesiveness for wet organs, fibrillar cues for epithelial or urethral reconstruction, sulfated motifs for immune regulation, and degradable protein or polysaccharide networks for synchronized replacement by a new matrix.

4.2 ROS-scavenging and Polyphenol-integrated Dressings

Because oxidative stress perpetuates inflammation and delays the transition from inflammation to proliferation, ROS-scavenging polymers have emerged as a dominant design strategy. Dopamine-copolymerized transparent hydrogels use catechol chemistry and dynamic phenylboronate ester bonds to combine adhesion, mechanical adaptability, transparency, and ROS scavenging in chronic diabetic wounds, thereby promoting M2 macrophage polarization and reducing pro-inflammatory cytokines.[110] Similarly, polyacrylic acid-based coacervate dressings, tannic acid/ferric ion-decorated hydrogels, and biomimetic Janus patches integrate wet adhesion, self-healing, antibacterial activity, antioxidation, and inflammation suppression for wound or tendon repair.[111–113] Growth factor-free ROS-scavenging hydrogels and antioxidant glycopolymersomes further demonstrated that anti-inflammatory activity can be encoded directly into polymer networks or vesicular glycopolymer assemblies without relying on exogenous cytokines or growth factors.[114,115]

Polyphenol-derived systems are particularly instructive because their catechol-rich structures participate in adhesion, redox buffering, and immune regulation. In these systems, phenolic and catechol motifs directly contribute to intrinsic ROS-scavenging and immunoregulatory activities, whereas functions such as tissue adhesion and regeneration are considered complementary therapeutic effects. Tea polyphenol nanoparticles block pyroptosis in endotoxin-induced sepsis by scavenging broad-spectrum reactive oxygen and nitrogen species and inhibiting gasdermin D oligomerization, thereby coupling antioxidant and antipyroptotic mechanisms.[116] Hydrogel dressings with intrinsic antibiofilm and antioxidative dual functions address infected diabetic wounds, where bacterial biofilms and high ROS levels mutually sustain chronic inflammation (Fig. 6).[117] In these materials, antioxidant capacity is not an accessory property; it is a central immunological input that controls the macrophage state, cytokine release, keratinocyte migration, angiogenesis, and tissue remodeling. A recurring design principle is a multifunctional economy: the same phenolic or glycopolymer motif can simultaneously provide cohesion, radical consumption, microbial suppression, and immune reprogramming, reducing reliance on fragile loaded biologics.

4.3 Macrophage-instructive Chemistry, Topography, and Architecture

The second design strategy is to direct immune cells through material chemistry, topography, and mesoscale architecture. High-throughput platforms such as ChemoTopoChip screen for synergistic chemistry–topography combinations that direct both mesenchymal stem cell osteogenesis and macrophage phenotype, demonstrating that anti-inflammatory design can be systematically identified through combinatorial screening rather than empirical selection.[118] The ChemoArchiChip extends this concept to micron-scale 3D objects, showing that architecture and polymer chemistry jointly instruct innate immune cell responses.[119] Studies on immobilized monosaccharides and broader immune-instructive polymer libraries further revealed that subtle surface chemistries can drive macrophages toward pro- or anti-inflammatory states and modulate foreign body response *in vivo* (Fig. 7).[120,121]

Cell-instructive polymer systems can also be engineered into regenerative constructs. Multiphasic gel-in-gel materials

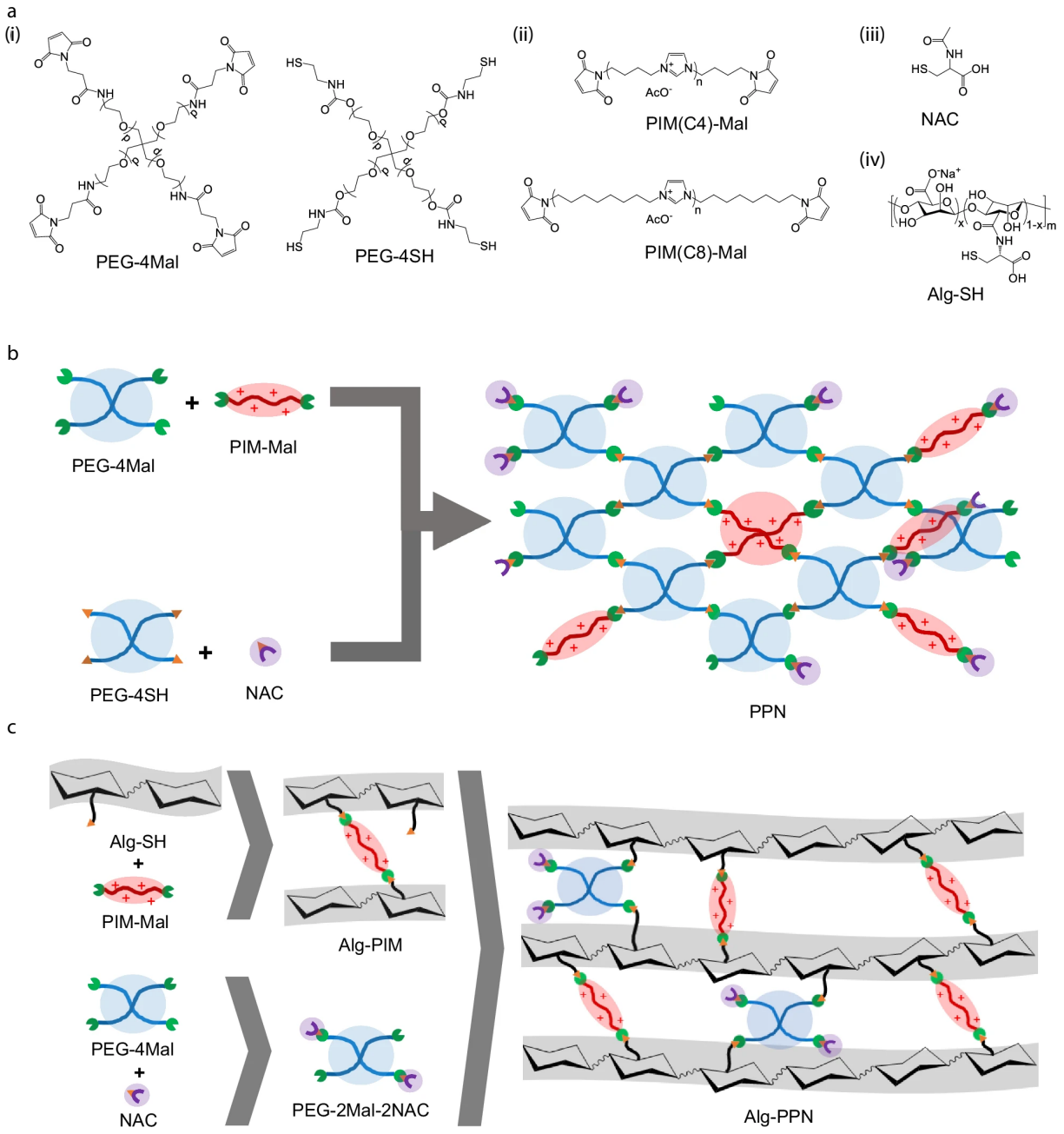


Fig. 6 Dual-functional hydrogel dressings for infected diabetic wound repair. (a) Main chemical components of the hydrogel dressing, including cationic polyimidazolium-maleimide for antibiofilm activity and *N*-acetylcysteine for antioxidant function; (b) PPN film hydrogel formed through thiol-maleimide crosslinking for relatively flat wound surfaces; (c) Alg-PPN fiber hydrogel assembled from alginate- and PEG-based precursors for deep or irregular infected wounds. (Reproduced with permission from Ref. [117]; Copyright (2024), Springer Nature, CC BY 4.0).

spatially organize cell-instructive cues, whereas microparticles decorated with immunomodulatory surface chemistries actively promote wound healing.[122,123] Hydrogel crosslinking itself modulates macrophage and fibroblast behavior as well as intercellular communication during wound healing, emphasizing that network mechanics and bond dynamics are active design parameters rather than passive formulation variables.[124] Thus, the intrinsic anti-inflammatory activity of a polymer can arise from its ability to regulate cell–material interactions and downstream immune cell phenotypes, rather than solely from soluble factors released by the material. This insight is particularly relevant for implantable and regenerative materials, where long-term therapeutic outcomes depend less on the initial burst of anti-inflammatory drug release than on the capacity of the material, which continuously biases the foreign body response toward constructive tissue remodeling.

4.4 Multifunctional Anti-inflammatory Interfaces for Complex Lesions

Clinically relevant inflammatory lesions often require a combi-

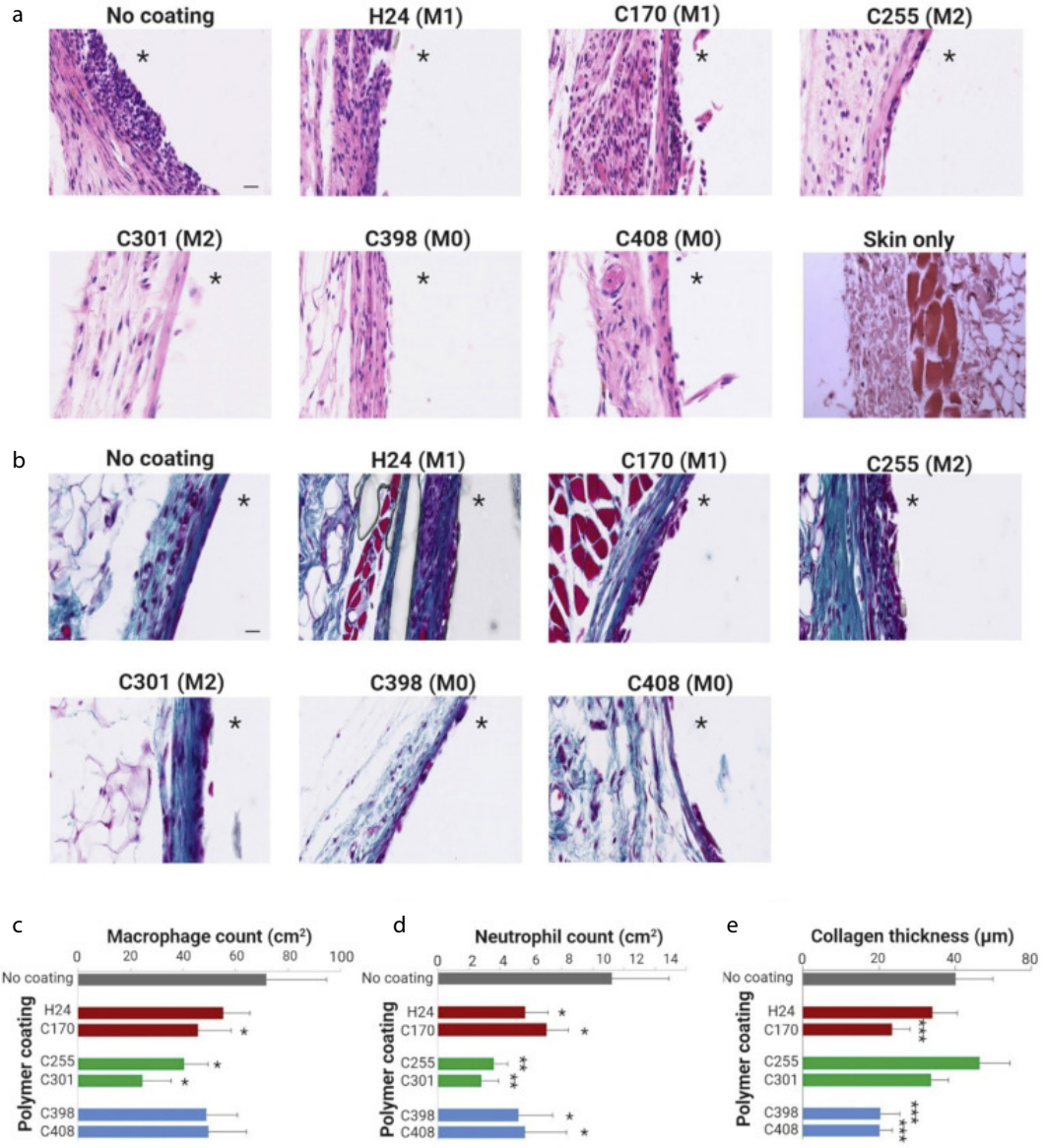


Fig. 7 Immune-instructive polymer coatings regulate macrophage phenotype and the foreign body response. (a, b) H&E and Masson trichrome staining of tissues surrounding implanted polymer-coated catheter segments show distinct inflammatory infiltration and collagen deposition patterns induced by different immune-instructive polymer coatings; (c–e) Quantitative analysis of macrophage infiltration, neutrophil infiltration, and collagen thickness demonstrates that polymer surface chemistry can tune the *in vivo* foreign body response toward different inflammatory or remodeling outcomes. (Reproduced with permission from Ref. [121]; Copyright (2020), Elsevier, CC BY 4.0).

nation of several functions of a single material. Click-crosslinked alginate/chitosan hydrogels treat infected wounds by integrating antibacterial, antioxidant, and anti-inflammatory activities with M2 macrophage induction, angiogenesis, and reepithelialization.[125] Glycopeptide hydrogels regulate wound pH and activate type 2 immune responses through macrophage-T cell crosstalk, whereas dual-crosslinked hydrogel patches promote diabetic wound healing through their adhesive, antibacterial, and immunoregulatory effects.[126–128] Aligned poly(L-lactide) nanofibers inhibit macrophage M1 polarization through Janus kinase/signal transducer and activator of transcription (JAK/STAT) and nuclear factor κB (NF-κB) pathways, illustrating how fiber orientation can influence inflammatory signaling.[129]

Other polymer interfaces have been tailored to anatomically specific inflammatory settings. Electrically aligned polyurethane nerve guidance conduits regulate macrophage polarization to support peripheral nerve regeneration, and hydrogel spinal dural patches combine anti-inflammatory, pain-relieving, and antibacterial properties.[130,131] Sprayable anti-adhesive hydrogels reduce peritoneal macrophage infiltration and inflammation after surgery, whereas microgel-based cream hydrogels prevent postoperative abdominal adhesion by integrating lubricating, anti-inflammatory, and barrier functions.[132,133] Injectable biodegradable piezoelectric hydrogels for osteoarthritis generate localized electrical cues under ultrasound activation and reduce macrophage-derived tumor necrosis factor α (TNF-α), linking mechanotransduction with inflammation control.[134] These systems high-

light that anti-inflammatory polymer design is disease site-dependent: the same material family must be reformulated as a sealant, conduit, patch, cream, or injectable depot according to fluid flow, mechanical loading, cell infiltration, and residence time requirements.

4.5 Macromolecular Therapies for Systemic Inflammation

In addition to local repair, anti-inflammatory polymers can also be designed as active macromolecular drugs. The hydrolyzable PEG–luminol conjugate HPL self-assembles into micelles that target inflamed tissues and inflammatory cells and suppresses acute lung, kidney, and liver injury as well as endotoxemia by inhibiting the IL-6/JAK2/STAT3 pathway.[135] This strategy differs fundamentally from conventional carrier design: the polymer serves simultaneously as a targeting scaffold, bioactive anti-inflammatory agent, and degradable platform that enables responsive delivery. Together with tea polyphenol nanoparticles for sepsis, HPL indicates that polymer therapeutics can effectively address systemic inflammatory syndromes when bioactivity, tissue localization, and clearance are engineered as a unified macromolecular program (Fig. 8).[116,135] The key challenge is to preserve potency while avoiding prolonged immunosuppression, making hydrolyzability, renal-clearable fragments, and inflammation-responsive accumulation central parameters for next-generation macromolecular anti-inflammatory therapies.

Across these local and systemic examples, anti-inflammatory polymers show that inflammation control extends beyond simply suppressing the immune activity. Effective materials must coordinate ROS scavenging, macrophage instruction, cytokine regulation, tissue adhesion, mechanical adaptability, biodegradation, and disease-site residence, according to the pathological context. In wounds, cystitis, spinal cord injury,

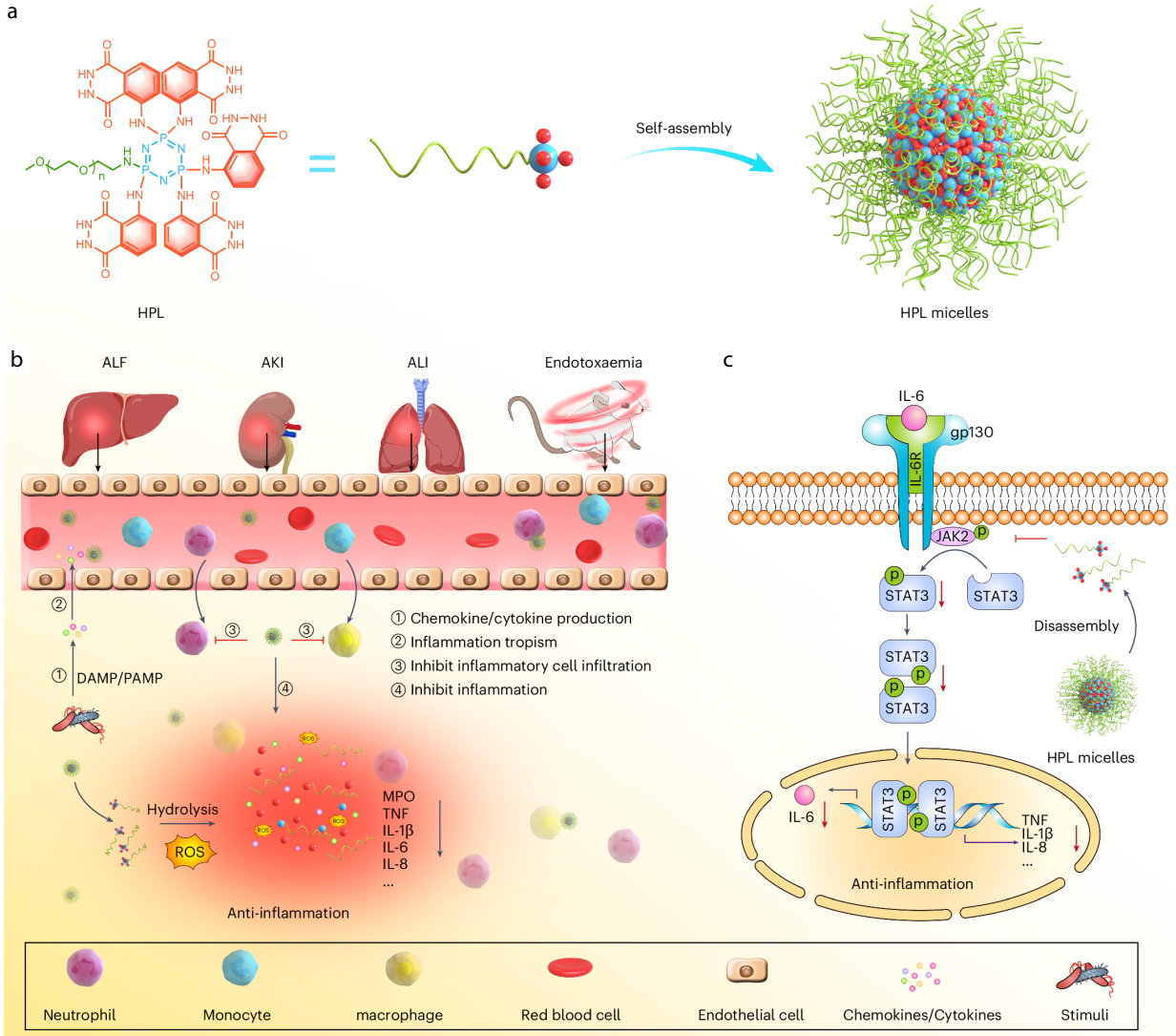


Fig. 8 Macromolecular JAK inhibition for systemic acute inflammation therapy. (a) HPL is constructed by conjugating luminol and PEG onto a hydrolyzable cyclic scaffold and self-assembles into anti-inflammatory micelles; (b) HPL-derived micellar therapy targets inflammatory microenvironments in acute lung injury, acute kidney injury, acute liver failure and endotoxemia, reducing inflammatory cell infiltration and cytokine amplification; (c) The therapeutic effect is mediated by normalization of the IL-6/JAK2/STAT3 signaling axis. (Reproduced with permission from Ref. [135]; Copyright (2025), Springer Nature).

osteoarthritis, postoperative adhesions, and systemic inflammatory injury, the polymer structure determines not only the length of the material remaining at the lesion but also how cells attach to it, remodel it, and transition from inflammatory damage to constructive repair. Therefore, anti-inflammatory polymer design should integrate potency with reversibility, local retention with clearance, and immunosuppression with regenerative guidance. This perspective distinguishes anti-inflammatory polymers from inert dressings or conventional drug depots, and positions them as active regulators of inflammatory microenvironments.

5 REMODELING RECEPTOR-TOPOLOGY-REMODELING MULTIVALENT POLYMERS

Multivalent polymers can treat diseases by reorganizing the spatial organization of receptors on the cell surface, rather than by delivering a cytotoxic payload. This category encompasses synthetic polymers, as well as programmable biopolymeric and macromolecular scaffolds, including DNA- and protein-based assemblies, because their therapeutic functions share common topology-regulating principles involving multivalency, ligand spacing, scaffold geometry, and receptor clustering. In this strategy, the therapeutic output arises from receptor proximity, spacing, orientation, clustering valency, and membrane residence time. Therefore, the key design question is not simply whether a ligand binds its receptor, but also how many receptors are recruited, at what nanoscale distance, for what duration, and whether the resulting topology activates apoptosis, immune signaling, mechanotransduction, receptor sequestration, or cell migration blockade.

5.1 Death-receptor Nanopatterning for Apoptosis

Death receptors provide the clearest example of receptor-topology therapy. TNF-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL) normally require higher-order receptor clustering to initiate downstream caspase signaling; however, their soluble ligands often exhibit only weak agonistic activity. Therefore, DNA origami has been employed as a nanoscale display scaffold to precisely control the ligand number and spacing. For instance, DNA-TRAIL3 trimers organized on rectangular origami promote death receptor clustering and cancer cell apoptosis, revealing that the inter-ligand distance can define whether receptors behave as isolated active units or as part of larger signaling networks.[136] Similarly, Nanoscale FasL organization on DNA origami showed that apoptosis is strongly dependent on ligand spacing and receptor organization, establishing DNA origami as a quantitative ruler for death receptor signaling.[137] The concentration of studies in this area reflects a central feature of death receptors: their signaling threshold is encoded at the supramolecular assembly level. Therefore, polymer and DNA scaffolds provide a unique opportunity to decouple ligand biochemistry from receptor geometry, allowing the same ligand family to be tested as compact trimers, extended arrays, and higher-order clusters.

Peptide and DNA nanostructure systems have extended this principle from biophysical measurements to therapeutic applications. Nanoscale peptide patterns induce death receptor clustering and apoptosis, whereas DNA nanostructure-mediated superclustering enhances cancer cell killing by achieving receptor colocalization far beyond what soluble ligands can achieve.[138,45] A DNA robotic switch adds temporal regulation; cytotoxic ligand nanopatterns can be autonomously displayed in response to programmed stimuli, transforming death receptor activation into a controllable nanoscale event (Fig. 9).[46] These studies indicate that receptor topology is a pharmacological variable. Apoptosis can be tuned by valency, ligand spacing, scaffold rigidity, and kinetics rather than solely by ligand affinity.

5.2 Drug-free Macromolecular Therapeutics by Receptor Crosslinking

Drug-free macromolecular therapeutics (DFMT) represent a polymeric version of receptor-topology remodeling. Instead of carrying a low-molecular-weight drug, DFMT first decorates target cells with a receptor-binding motif and then adds a multivalent macromolecular effector that slowly crosslinks internalizing surface receptors. This strategy has been defined in several comprehensive reviews as a distinct nanomedicine paradigm, in which biorecognition and receptor crosslinking initiate apoptosis in the absence of any conventional cytotoxic cargo.[139–141,47] A key conceptual strength of this approach from the outset has been its modularity: antibodies, Fab fragments, coiled-coil peptides, morpholino oligonucleotides, human serum albumin, or synthetic polymers can be recombined to tune receptor engagement and crosslinking density.[142]

B cell malignancy is the most extensively developed disease model. CD20-targeted DFMT crosslinks receptors in lymphoma or leukemia cells to induce apoptotic signaling. Specifically, human serum albumin-based macromolecular therapeutics induce apoptosis in primary chronic lymphocytic leukemia patient cells through CD20 or CD38 receptor crosslinking, and simultaneous CD20/CD38 heteroreceptor crosslinking further enhances B cell apoptosis both *in vitro* and *in vivo*.[143,50] The therapeutic effect arises from receptor co-clustering, lipid raft redistribution, mitochondrial depolarization, caspase activation, and amplified apoptotic signaling, rather than from drug release. DFMT has also been explored in collagen-induced rheumatoid arthritis, suggesting that receptor crosslinking can be adapted beyond cancer when disease-relevant surface targets are available.[144] This mechanism differs fundamentally from antibody-dependent cytotoxicity or chemotherapy because the polymer neither enters the cell nor releases toxic molecules. Instead, it imposes a new receptor organization on the B-cell membrane, coercing normally dispersed or weakly associated receptors into signaling competent domains.

Spatiotemporal control further enhanced DFMT selectivity. Upconversion nanoparticle-assisted systems enable NIR light-triggered *in situ* crosslinking of aptamer-polymer conjugates, clustering CD20 receptors only at the illuminated tumor site.[145] Such designs address the practical limitation of the two-step DFMT administration paradigm by integrating receptor recognition, macromolecular assembly, and external activation into a single spatiotemporally controlled process. Collectively, these studies show that multivalent polymers can function as topology editors, directly converting the spatial distribution of receptors on the plasma membrane into a therapeutic signal.

5.3 Aptamer, Nanoparticle, and Cell-surface Polymer Topologies

In addition to antibody-based DFMT, aptamers and polymer

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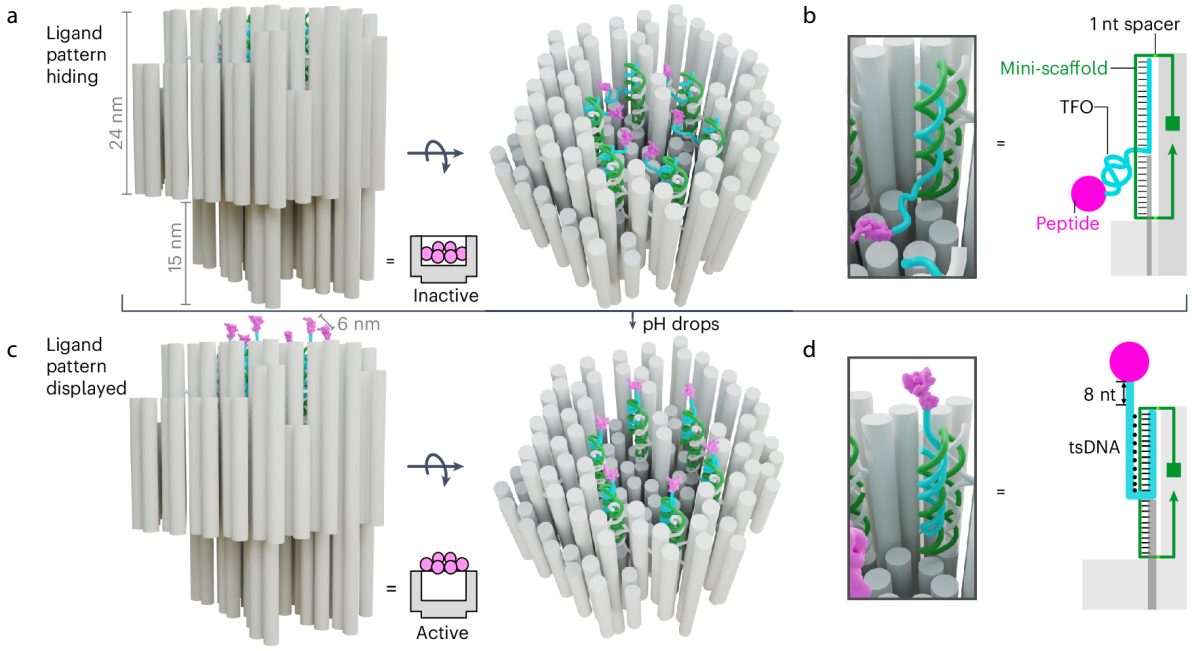


Fig. 9 pH-responsive DNA robotic switch for regulated display of cytotoxic ligand nanopatterns. (a) The three-dimensional DNA origami structure contains a head cavity that physically hides six peptide ligands conjugated to DNA strands; (b) The peptide ligands are retained inside the cavity through the random-coil behavior of triplex-forming oligonucleotide segments; (c, d) Under acidic pH, triplex DNA formation drives the peptide ligands out of the cavity and displays them as a hexagonal cytotoxic ligand pattern on the origami surface. (Reproduced with permission from Ref. [46]; Copyright (2024), Springer Nature, CC BY 4.0).

scaffolds offer programmable control over receptor-binding geometry. For example, multi-catcher glycol-chitosan polymers bearing aptamers and cholesterol anchors stabilize nucleolin clusters on cancer cell membranes, triggering calcium influx, mitochondrial apoptosis, and tumor inhibition.[51] Programmable atom-like DNA nanoparticles precisely prescribed aptamer valence and directionality on tetrahedral frameworks, demonstrating that biased directional arrangements can increase cell-surface binding even when the aptamer copy number is held constant.[146] Studies of ligand-functionalized DNA nanostructures have further identified key determinants of cell interactions, including ligand density, spatial distribution, scaffold geometry, and membrane accessibility.[147]

Cell surface engineering offers an alternative route by directly constructing a topology on living cells. Site-selected *in situ* polymerization enables cytocompatible polymer formation at the cell surface, where subsequent receptor clustering modulates the cell fate.[148,149] This site-confined polymer growth provides a synthetic route to remodel the cell-surface interface itself, rather than simply decorating preformed scaffolds with ligands (Fig. 10). In a related strategy, C-X-C chemokine receptor 4 (CXCR4)-targeted nanothreads patch the cancer cell surface and inhibit metastasis, illustrating that multivalent polymers can block or reorganize receptor-mediated migration rather than directly inducing apoptosis.[48] In this case, receptor remodeling is employed not to activate cell death directly, but to reshape CXCR4 organization and interrupt the metastatic cascade (Fig. 11). Furthermore, surface-patterned DNA origami rulers revealed that epidermal growth factor receptor (EGFR) activation is dictated by nanoscale ligand distance, whereas engineered receptor-mediated transmembrane signaling in artificial and living cells shows that synthetic surface assemblies can rewire intercellular communication across membranes.[150,49] These examples expand the scope of receptor-topology remodeling by inducing cell death to reprogram broader cell behaviors. A polymer or DNA scaffold can serve as a membrane-resident organizer, altering the lifetime, lateral mobility, or local density of receptors before canonical intracellular signaling begins.

5.4 Mechanical, Immune, and Antibody-assembly Control of Receptor Organization

The receptor topology is not purely chemical; it can be regulated mechanically. Optoregulated molecular motors apply local forces to receptors, such as integrins and T-cell receptors, producing physiologically relevant mechanotransduction, focal adhesion maturation, and T-cell activation under spatiotemporal light control.[151] This paradigm expands the design of multivalent polymers from static clustering to force-gated receptor remodeling, where ligand engagement and mechanical pulling jointly determine the signaling output.

Immune recognition systems are another topology-sensitive model. The designed proteins can assemble antibodies into modular nanocages, thereby controlling antibody spatial organization and effector architecture.[152] Similarly, Hapten-decorated DNA nanostructures decipher how antigen spacing controls antibody organization during mast cell activation, revealing that immune receptor activation is dictated by nanoscale antigen geometry to a degree comparable to the total ligand dose.[153] Extending this logic to intracellular signaling complexes, proximity-induced caspase-9 activation on DNA origami-based synthetic apoptosomes shows that combining multiple caspase-9 molecules on a defined scaf-

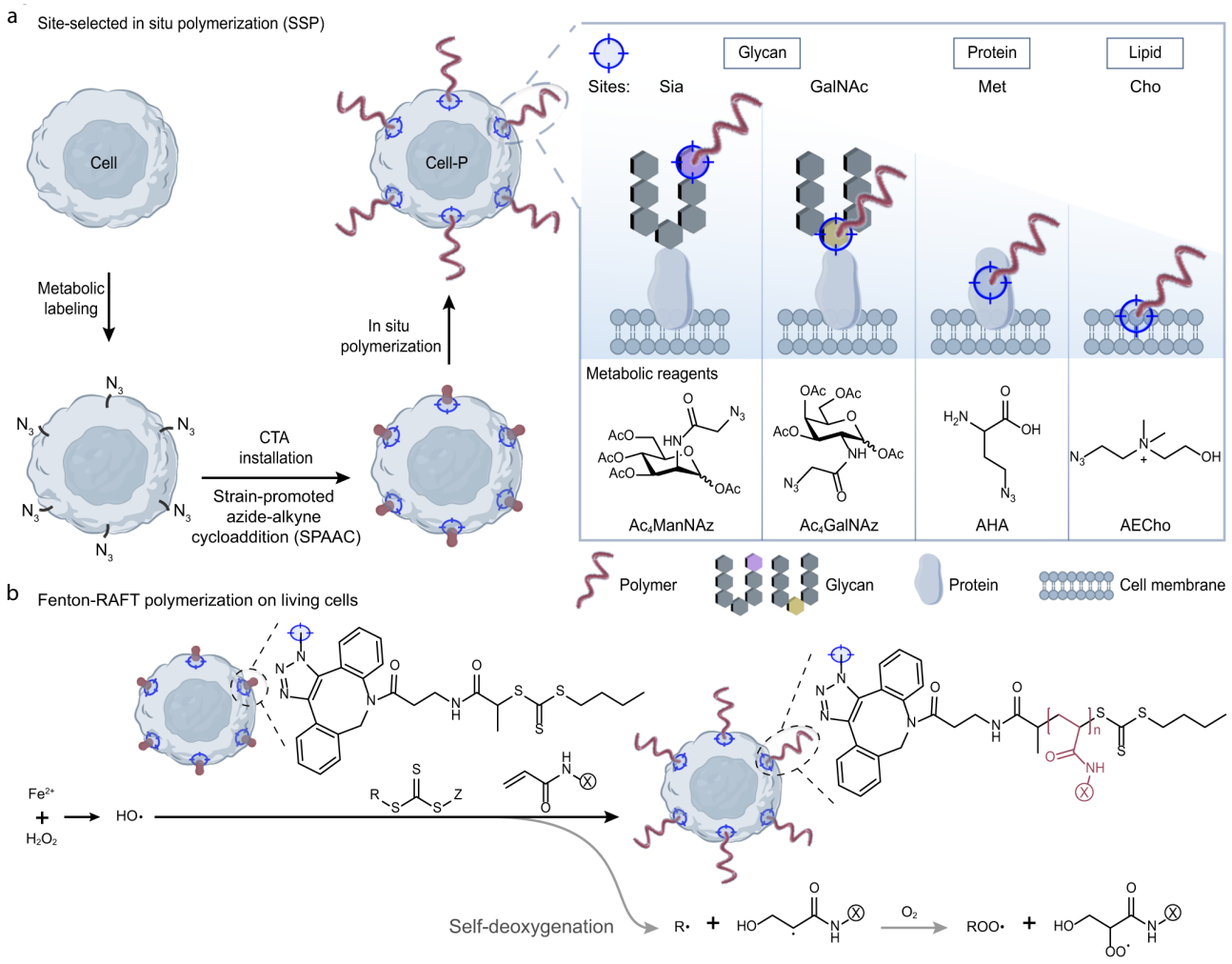


Fig. 10 Site-selected *in situ* polymerization for living cell-surface engineering. (a) Metabolic labeling confines chain-transfer-agent installation to selected glycan, protein, or lipid sites on the living cell surface, enabling spatially controlled polymer growth; (b) Self-deoxygenating Fenton-RAFT polymerization proceeds from the installed chain-transfer agents under cytocompatible conditions, generating site-defined polymer coatings that remodel the cell-surface interface and modulate cell fate. (Reproduced with permission from Ref. [148]; Copyright (2023), Springer Nature, CC BY 4.0).

fold is sufficient to trigger enzymatic function.[154] In immune systems, this spatial precision is particularly important given that receptor activation is often digital and threshold-like: insufficient clustering remains functionally silent, whereas excessive or persistent clustering may cause off-target inflammation. Therefore, synthetic scaffolds act as both calibration tools and candidate therapeutics.

Across these systems, receptor-topology-remodeling multivalent polymers show that the binding affinity alone is insufficient to define therapeutic outcomes. Valency, directionality, ligand spacing, scaffold rigidity, mechanical force, cluster lifetime, and membrane residence time collectively determine whether receptor engagement is activated, inhibited, apoptotic, or migration-blocked. Topology can therefore be harnessed either to activate signaling, such as in death receptor or CD20/CD38 crosslinking, or to suppress disease phenotypes, such as CXCR4 surface patching. External triggers such as light, force, and proximity-responsive assembly introduce an additional layer of spatiotemporal control; however, they also raise translational demands with respect to synthesis, dosing, and *in vivo* validation. These considerations ultimately establish receptor topology as a programmable therapeutic variable, rather than a passive consequence of ligand binding.

6 CONCLUSIONS AND PERSPECTIVES

Polymers with intrinsic therapeutic activities are evolving from passive biomedical materials to active macromolecular medicines that directly regulate biological processes. The four categories discussed above, membrane-active polymers, immunomodulatory polymers, anti-inflammatory polymers, and receptor-topology-remodeling multivalent polymers, collectively demonstrate that polymer therapeutics can act through mechanisms fundamentally distinct from conventional small-molecule drugs. Rather than relying solely on molecular inhibition or cargo delivery, these materials exploit multivalency, nanoscale organization, dynamic assembly, stimulus respon-

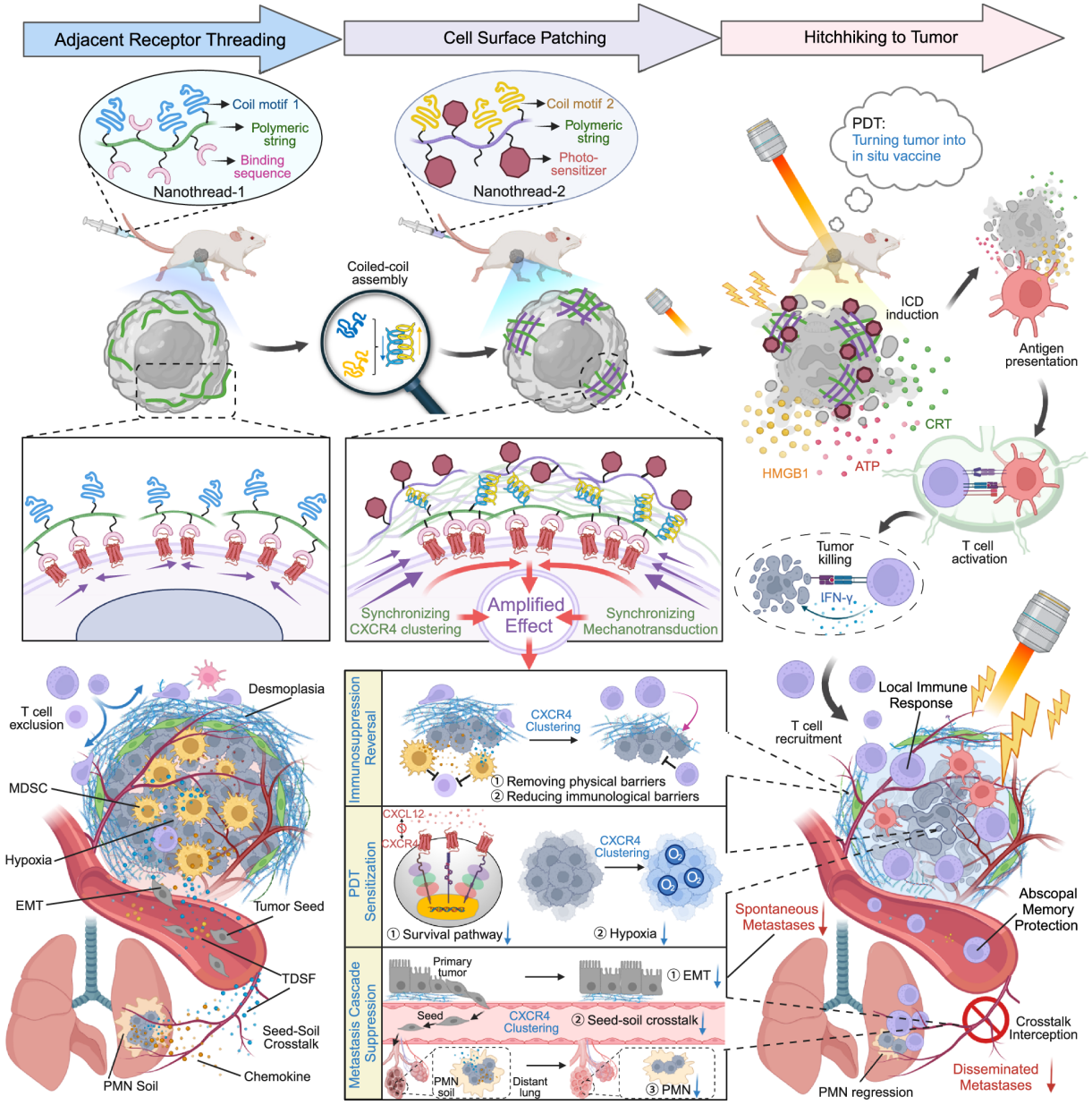


Fig. 11 CXCR4-targeted nanothread patching for cell-surface remodeling and metastasis inhibition. A stepwise nanothread strategy first uses Nanothread-1 to recognize and multivalently bind CXCR4 on the cancer cell surface, then recruits Nanothread-2 through complementary coiled-coil interactions to form a supramolecular network. This cell-surface patching promotes CXCR4 clustering, perturbs downstream pro-metastatic signaling, and delivers photosensitizers for localized photodynamic therapy and immunogenic cell death, thereby suppressing primary tumor growth and metastatic dissemination (Reproduced with permission from Ref. [48]; Copyright (2024), Springer Nature, CC BY 4.0).

siveness, and cell-surface interactions to reshape disease microenvironments and cellular decision-making.

Membrane-active polymers illustrate how physicochemical selectivity can translate into therapeutic activity. In antimicrobial systems, cationic charge, hydrophobic insertion, helicity, and molecular recognition of bacterial lipids enable the disruption of microbial membranes, biofilms, and fungal envelopes. In cancer therapy, the same interfacial logic has been redirected toward tumor cell membranes, where pH activation, enzyme-triggered unmasking, phosphatidylserine engagement, and aggregation-controlled pericellular residence provide selectivity. Importantly, membrane disruption is not merely cytotoxic; in tumors, it can also induce immunogenic cell death and convert local membrane damage into systemic anti-tumor immune responses.

Immunomodulatory polymers further expand the therapeutic role of macromolecules by engaging innate immune sensors, glycan-recognition pathways, dendritic cells, macrophages, neutrophils, and natural killer cells. Natural polysaccharides, such as chitosan, β-glucans, fucoidan, and carrageenan, demonstrate how polymer composition and supramolecular presentation can regulate cGAS-STING activation, lectin signaling, macrophage polarization, and vaccine adjuvanticity. Synthetic polymers provide additional preci-

sion through pH-sensitive STING activation, TLR9-active vaccine platforms, inflammasome-tunable nanostructures, and immune cell surface engineering. These systems suggest that immune activity is not a binary material property but a programmable therapeutic output determined by chemistry, architecture, dose, tissue context, and cell state.

Anti-inflammatory polymers show a complementary direction; instead of amplifying immune responses, they suppress, redirect, or spatially confine pathological inflammation. Hydrogels, glycopolymers, polyphenol nanoparticles, chitosan derivatives, fucoidan networks, and macromolecular JAK inhibitors have demonstrated that polymers can scavenge ROS, block pyroptosis, regulate macrophage phenotype, modulate fibroblast-immune communication, prevent postoperative adhesion, and treat systemic inflammatory injury. These examples highlight a central design principle: effective anti-inflammatory polymers should not simply inhibit inflammation but guide the transition from inflammatory damage to constructive repair.

Receptor-topology-remodeling multivalent polymers represent a particularly sophisticated form of polymer therapeutic activity. By controlling ligand spacing, valency, directionality, force, and membrane residence, these systems reorganize receptors, such as death receptors, CD20, CD38, nucleolin, CXCR4, EGFR, integrins, and immune receptors. DNA origami, protein cages, aptamer scaffolds, cell-surface polymerization, DFMT, and light-controlled crosslinking systems have demonstrated that receptor clustering itself can become a therapeutic modality. This strategy reframes the cell surface as a programmable signaling interface.

Recent studies have further illustrated the continued expansion of intrinsically therapeutic polymers across different therapeutic mechanisms. For example, gasdermin-mimicking synthetic polymers can directly perforate cellular membranes and induce immunogenic pyroptosis, which can integrate self-assembly with intrinsic pattern-recognition receptor activation, and tannic acid-cross-linked nanogels can exert ROS-scavenging and anti-inflammatory effects, even in the absence of loaded anti-inflammatory drugs.[155–157] Collectively, these advances further support the concept that therapeutic functions can be directly encoded into polymer composition and architecture across membrane-active, immunomodulatory, and anti-inflammatory applications.

However, despite these advances, several challenges remain. First, structure-activity relationships must become more quantitative. Parameters such as polymer dispersity, chain length, degradability, ligand spacing, receptor cluster lifetime, membrane residence, and immune-cell specificity should be reported with the same rigor as the efficacy endpoints. Second, safety evaluations must move beyond cytotoxicity and hemolysis to include complement activation, inflammasome stimulation, cytokine amplitude, immune memory, tissue retention, and long-term biodegradation. Third, translation requires scalable synthesis, batch reproducibility, sterilization compatibility, and predictable pharmacokinetics, particularly for complex DNA, protein, and multivalent polymer architectures.

The most powerful therapeutic polymers will likely integrate several modes of action within one material platform: membrane selectivity with immune activation, anti-inflammatory repair with tissue adhesion, receptor clustering with external control, or cell surface engineering with localized drug-free therapy. The convergence of polymer chemistry, immunology, synthetic biology, and nanoscale biophysics will enable the design of macromolecules that sense disease cues, reorganize cellular interfaces, and generate therapeutic signals with high spatial and temporal precisions. In this sense, polymers with therapeutic activity are not merely alternatives to conventional drugs; they represent a new therapeutic language in which the macromolecular structure is translated directly into biological functions.

BIOGRAPHIES

Jun-Bin Chen received his B.S. degree from Southern Medical University in 2019. He then obtained his Ph.D. degree from the South China University of Technology (SCUT) in 2025 under the supervision of Prof. Xian-Zhu Yang. He is currently a postdoctoral fellow at SCUT and continues his research in Prof. Yang's group. His research focuses on nanomaterials with adjuvanticity in cancer immunotherapy.

Xian-Zhu Yang received his B.S. degree from the Hefei University of Technology in 2006 and completed his Ph.D. degree at the University of Science and Technology of China (USTC) in 2011. He then pursued postdoctoral research at USTC before joining the Hefei University of Technology as a professor and doctoral supervisor in 2013. Since 2017, he has been a professor and doctoral supervisor at the South China University of Technology (SCUT). His research interests include nanomedicine and the development of innovative polymeric drug delivery systems.

Conflict of Interests

The authors declare no interest conflict.

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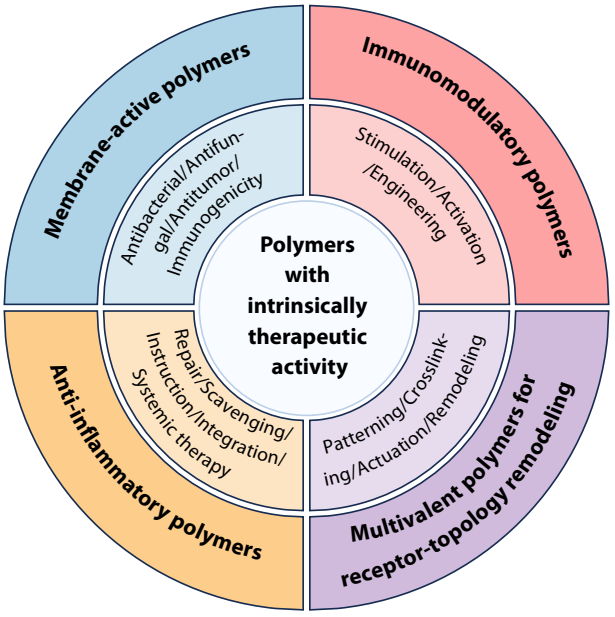
Graphical Abstract

Polymers with Intrinsically Therapeutic Activity: from Membrane-targeted Cytotoxicity to Receptor-topology Remodeling

Ze-Kai Xiao, Ji-Hong Wang, Jun-Bin Chen, and Xian-Zhu Yang

South China University of Technology, Guangzhou International Campus; South China University of Technology

Polymers with intrinsic therapeutic activity act as bioactive macromolecules rather than passive carriers. This review highlights four major classes and their roles in membrane-targeted cytotoxicity, immune modulation, inflammation control, and receptor-topology remodeling, while summarizing the key design principles, translational challenges, and future opportunities in polymer-based therapeutics.



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