



Design of therapeutic biomaterials to control inflammation

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Abstract | Inflammation plays an important role in the response to danger signals arising from damage to our body and in restoring homeostasis. Dysregulated inflammatory responses occur in many diseases, including cancer, sepsis and autoimmunity. The efficacy of anti-inflammatory drugs, developed for the treatment of dysregulated inflammation, can be potentiated using biomaterials, by improving the bioavailability of drugs and by reducing side effects. In this Review, we first outline key elements and stages of the inflammatory environment and then discuss the design of biomaterials for different anti-inflammatory therapeutic strategies. Biomaterials can be engineered to scavenge danger signals, such as reactive oxygen and nitrogen species and cell-free DNA, in the early stages of inflammation. Materials can also be designed to prevent adhesive interactions of leukocytes and endothelial cells that initiate inflammatory responses. Furthermore, nanoscale platforms can deliver anti-inflammatory agents to inflammation sites. We conclude by discussing the challenges and opportunities for biomaterial innovations in addressing inflammation.

Inflammation is the body's natural and essential response to signals arising from tissue damage or pathogenic infection¹. Following trauma or infection, inflammation drives the restoration of homeostasis by protecting the host from exogenous pathogens and by repairing damaged tissue². Inflammation usually occurs as a sequence of events, starting with a rapid induction phase, which leads to a pro-inflammatory response, gradually followed by a resolution phase³. Therefore, inflammation is crucial to wound healing. However, if this well-orchestrated response is dysregulated, inflammation may become uncontrolled or chronic, which can ultimately lead to the development and progression of various inflammatory diseases, such as cancer, obesity, sepsis, cardiovascular, neuronal and autoimmune diseases⁴.

Dysregulated chronic or local inflammation occurs in several stages. In the early stage, danger signals, such as damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), which are released from damaged cells or pathogens, activate resident immune cells to generate cytokines, chemokines, proteases, growth factors and oxygen-free radicals⁵. Circulating immune cells then home to the site of the inflamed tissue through endothelial cell adhesion to boost pro-inflammatory responses⁶. This coordinated immune response ultimately restores homeostasis. However, if the response is insufficient or excessive,

upsetting the balance between the innate and adaptive arms of the immune system, it can lead to late-stage inflammation. Such a dysregulated immune response can cause a catastrophic cascade, characterized by local or systemic tissue damage and excessive danger signal production. Shifts in the inflammatory response from acute to chronic can also cause a breakdown of immune tolerance, leading to the progression of inflammatory disease, which may even result in death⁷.

The connection between inflammation and homeostasis is increasingly understood, and a holistic consideration of the inflammatory process offers opportunities for the design of specific and efficacious therapeutic strategies to target and regulate inflammation⁸. Drug therapy is commonly used to treat inflammation, and biomaterials can be applied as drug carrier to enable controlled drug delivery and release with high efficacy and minimal side effects. In addition to drug delivery, biomaterials can also scavenge pro-inflammatory factors or block undesired leukocyte–endothelial cell interactions to inhibit inflammation⁸. Biomaterials can, thus, complement conventional drug therapies, offering design versatility, targeting of different pathways and high spatiotemporal control of anti-inflammatory activities.

In this Review, we discuss three major biomaterials-based strategies for modulating the different stages of dysregulated inflammation (FIG. 1); biomaterials as

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scavengers of danger signals in early inflammation; biomaterials as inhibitors of leukocyte–endothelial cell adhesion in the middle stages of inflammation; and biomaterials as delivery systems for anti-inflammatory agents in the middle and late stages of inflammation. Finally, we highlight future directions and challenges for the clinical translation of anti-inflammatory biomaterials.

The inflammatory environment

Danger signals

PAMPs released by bacteria and viruses trigger inflammation in infection; DAMPs are the endogenous counterpart of PAMPs, inducing sterile inflammation (that is, inflammation owing to trauma rather than infection)⁹. DAMPs and PAMPs are recognized by different innate immune pattern recognition receptors, such as Toll-like receptors (TLRs), which are expressed on immune cells^{9,10}. Upon binding extracellular DAMPs and PAMPs, TLRs activate cytoplasmic adapter molecules that initiate a cascade of activation pathways, including nuclear factor- κ B (NF- κ B), interferon regulatory factor and a link to MAPK pathways, leading to the production of pro-inflammatory cytokines (for example, tumour necrosis factor (TNF), interleukin-1 (IL-1) and IL-6) and chemokines through transcriptional and post-transcriptional mechanisms^{9,10}. Furthermore, reactive oxygen and nitrogen species (RONS) can activate I κ B kinases and/or inhibit phosphotyrosine and phosphoserine/threonine phosphatases to upregulate redox-sensitive NF- κ B, further exacerbating inflammation¹¹. In addition to TLRs, immune cells possess NOD-like receptors (NLRs) to specifically identify pathogenic patterns in the cytoplasm, resulting in an inflammasome-mediated activation of pro-inflammatory cytokine release². An auxiliary mechanism in dealing with inflammation involves cyclic GMP–AMP synthase and its downstream effector, stimulator of interferon genes, which recognizes intracellular DNAs and promotes the release of type I interferons and other inflammatory cytokines¹². Therefore, immune cells can recognize and respond to various danger signals in the initial stage of inflammation and transmit signals to the nucleus for the production of cytokines.

Inflammatory cells

Innate immune cells, that is, monocytes, macrophages and neutrophils, orchestrate early inflammation^{13,14} (FIG. 2). Within minutes of an injury, tissue-resident

macrophages and circulating neutrophils are activated by DAMPs and release inflammatory mediators that recruit circulating innate immune cells to the injury site¹⁵. Additional mechanosignalling is triggered by direct interaction between surface molecules in adjacent cells^{16,17}. In response to macrophage-produced cytokines and PAMPs or DAMPs, released by injured or invading cells, the postcapillary venular endothelium upregulates adhesion molecules involved in the leukocyte recruitment cascade^{18,19}. This cascade involves mechanosignalling between adhesion molecules on the endothelium and various integrins on leukocytes, which can direct the recruitment of circulating leukocytes, eventually leading to their extravasation. Neutrophils are the first immune cells to arrive at the affected site^{16–19}, and intravascular neutrophils adhered to the endothelium can modify the endothelial barrier²⁰. In response to chemoattractants, neutrophils release TNF in close proximity to endothelial junctions to locally increase microvascular permeability^{21,22}. Circulating neutrophils migrate to the site as early as 20 min after injury and accumulate for the next 2 h (REF.²³). Circulating monocytes subsequently infiltrate the site, 24 h after injury, and increase in number for up to 72 h post-injury²⁴. These infiltrating monocytes produce inflammatory mediators, clear dead cells, stimulate extracellular matrix production and angiogenesis, and regenerate parenchymal cells¹⁵. In early inflammation, CD4⁺ T helper 1 (T_H1) cells infiltrate the injury site and release pro-inflammatory cytokines^{24,25}. In late inflammation, regulatory T (T_{reg}) cells and T_H2 cells, along with regulatory M2-like macrophages, increase in number and resolve inflammation by producing anti-inflammatory cytokines, such as transforming growth factor- β (TGF β) and IL-10 (REFS^{26,27}).

Inflammatory mediators

Activated inflammatory cells release acute mediators of inflammation²⁸, such as the pro-inflammatory cytokines TNF, IL-1 β and IL-6, which have profound effects on tissue regeneration, response to infection or pain, and neuronal activity^{28,29} (FIG. 2). When dysregulated, these pro-inflammatory cytokines can contribute to the pathogenesis of diseases, such as systemic inflammatory response syndrome, atherosclerosis, rheumatoid arthritis, multiple sclerosis and septic shock³⁰.

RONS, including oxygen and nitrogen free radicals, such as superoxide radical (O₂^{•-}), hydroxyl radical (•OH) and nitric oxide radical (•NO), are pro-inflammatory molecules that cause lipid peroxidation and oxidative stress^{31,32}. RONS can have deleterious effects on tissues and are, thus, regulated by endogenous antioxidant mechanisms that involve enzymes (superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx)) and antioxidants (ascorbic acid, α -tocopherol and glutathione)^{31,32}. Overproduction of RONS results in oxidative stress and tissue damage.

Enzymes play essential roles in inflammation and wound healing^{33,34}. Cyclooxygenase 1 and cyclooxygenase 2 are upregulated in leukocytes and metabolize arachidonic acid into prostaglandins (PGs) (for example, PGE₂, PGD₂, PGF₂), which regulate vascular permeability, neuron activity, bronchial reactivity and

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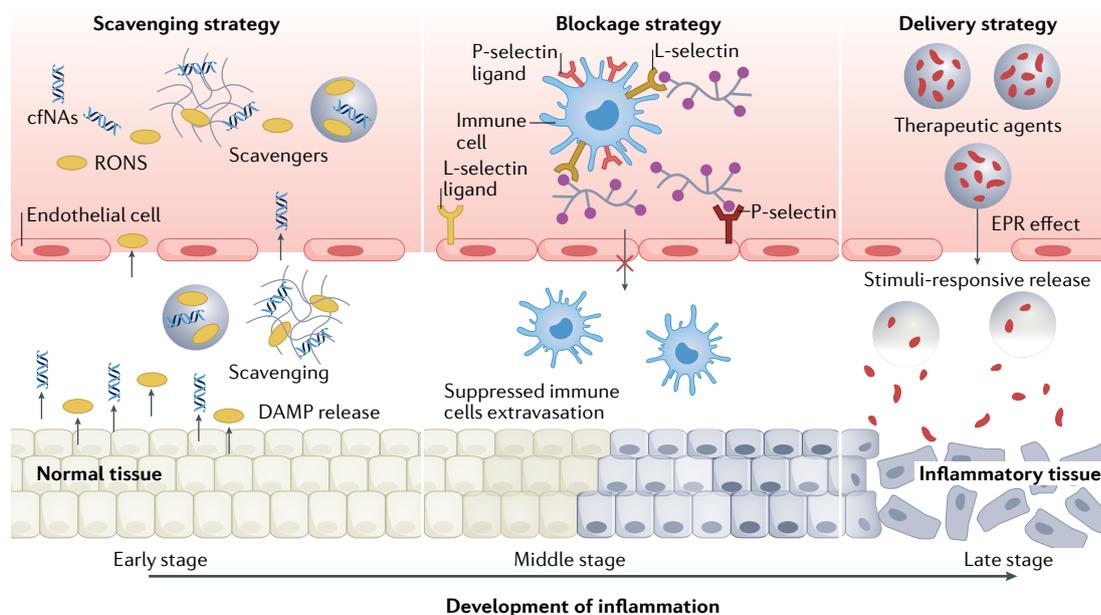


Fig. 1 | **Therapeutic biomaterials to control inflammation.** Biomaterials can be applied to control sterile inflammation in the early stage (scavenging strategy), middle stage (blockage strategy) and late stage (delivery strategy). cfNA, cell-free nucleic acid; DAMP, damage-associated molecular pattern; EPR, enhanced permeability and retention; RONS, reactive oxygen and nitrogen species.

cardiovascular smooth muscles³³. Activated inflammatory cells produce proteolytic enzymes that activate the complement, kallikrein–kinin and coagulation cascades, as well as proteinase-activated receptors, integrins and other adhesion receptors and ion channels, triggering the five cardinal signs of inflammation: increased blood flow and redness, fluid leakage and swelling, pain, heat and loss of tissue function³⁴.

Neutrophil extracellular traps (NETs) are large molecular complexes produced by activated neutrophils³⁵. NETs fight infection by immobilizing and killing bacteria, viruses and fungi, ultimately activating the innate immune response and coagulation. Abnormal NETs formation is associated with chronic autoimmunity and sterile and infectious inflammation³⁶.

Biomaterials for inflammation targeting

Biomaterials can be used to target anti-inflammatory therapeutics to desired cells, tissues and organs, to improve drug delivery and anti-inflammatory efficacy, and to reduce toxicity^{37,38}. Targeting strategies can be divided into passive and active targeting.

Passive targeting

Passive targeting is the transport of drug formulations through leaky fenestrated capillaries by passive diffusion or convection³⁹. Enhanced permeability is often observed in vasculatures of inflamed tissue and at tumour sites^{39,40}. Therapeutic nanoparticles can, thus, accumulate in the interstitial space, a phenomenon termed the enhanced permeability and retention (EPR) effect, which was first established in the development of anticancer nanomedicines³⁹. The EPR effect can also be exploited to passively deliver biomaterial–drug formulations to the inflamed site through the leaky vasculature surrounding

inflamed tissue^{39,40}. However, the clinical significance of the EPR effect in cancer is under debate^{41,42} and, thus, the clinical impact of nanoparticle-mediated anti-inflammatory therapy must be viewed with caution. Nevertheless, the EPR effect is well established in animal models. Size-dependent accumulation of nanoparticles has been observed in a variety of inflamed tissues, including intestine, heart and tumour tissue^{40,43,44}. In general, medium-sized (20–200-nm-diameter) nanoparticles are optimal for passively targeting drugs to inflamed tissue⁴⁴. Furthermore, nanoparticle shape can have an effect on endocytosis by immune cells⁴⁵, influencing the binding and phagocytosis by macrophages, as well as binding by targeted dendritic cells through electrostatic interactions⁴⁶. Biomaterial surface charge may modulate or overshadow the effects of nanoparticle size or shape in passive targeting^{47,48} and can affect therapeutic uptake and the toxicity profiles of immune cells⁴⁸.

Active targeting

Active targeting involves the conjugation of moieties that specifically bind inflammatory molecules and cells to the surface of biomaterials-based drug formulations. Inflammatory targets include inflamed vasculature, immune cells, pathogens, enzymes and mediators or products of inflammation.

Vascular inflammation is common in the pathogenesis of atherosclerosis⁴⁹. Vascular inflammation is a result of the interaction between circulating leukocytes and endothelial cells, which is mediated by endothelial cell adhesion molecules (CAMs), including selectins and immunoglobulins, that are expressed on endothelial cells following activation by cytokines⁵⁰. Therapeutic targeting of endothelial CAMs is a promising approach to managing vascular inflammation. P-selectin and

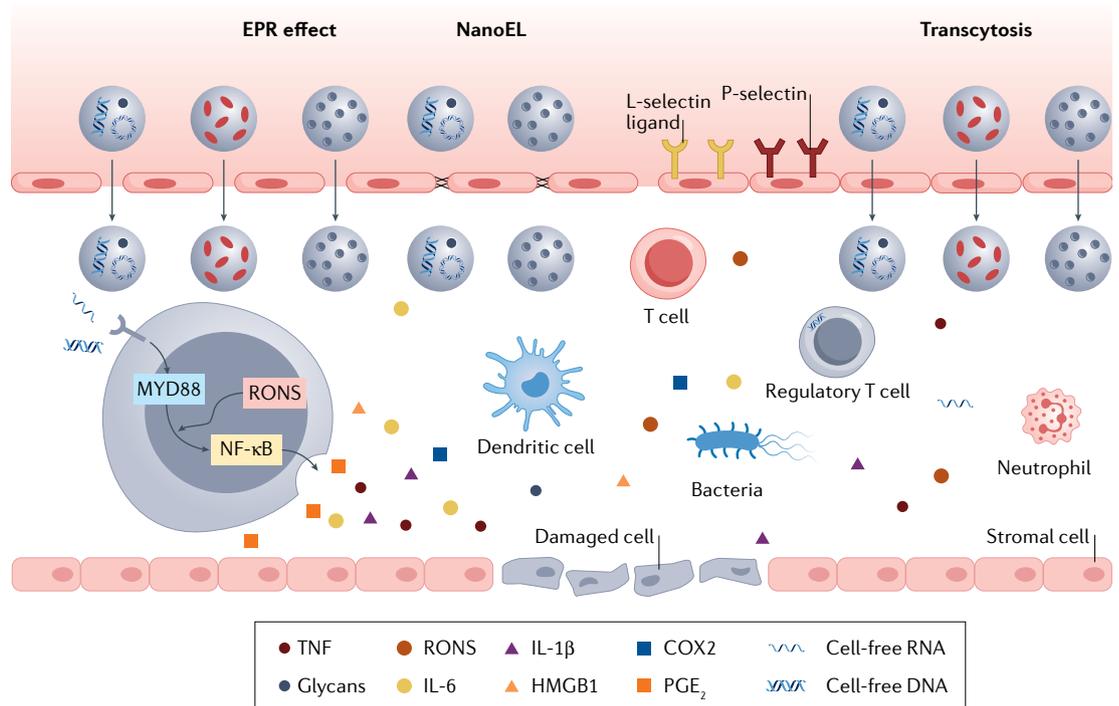


Fig. 2 | The inflammatory microenvironment. The inflammatory microenvironment comprises invasive pathogens, damaged cells and vasculature, infiltrating immune cells, danger signals, such as pathogen-associated molecular patterns and endogenous tissue damage-associated molecular patterns, and a plethora of pro-inflammatory molecules, such as cytokines, chemokines, enzymes, leukotrienes and eicosanoids. In particular, reactive oxygen and nitrogen species (RONS) can activate Toll-like-receptor-mediated nuclear factor- κ B (NF- κ B) and interferon regulatory factor pathways during inflammation. Localized inflammation induces the activation of microvascular endothelial cells, causing changes in vascular permeability to promote leukocyte homing, such as neutrophil adhesion and transmigration, as well as activation of platelets and monocytes. Nanoparticles can accumulate in the inflammatory microenvironment owing to the enhanced permeability and retention (EPR) effect, transcytosis or nanomaterials-induced endothelial leakiness (NanoEL). COX2, cyclooxygenase 2; HMGB1, high-mobility group box 1; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; PGE₂, prostaglandin E₂; TNF, tumour necrosis factor.

E-selectin are usually expressed at low levels on the endothelial surface, but are highly expressed during the early and middle stages of inflammation⁵¹. Vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1) are endothelial transmembrane proteins that are also upregulated during vascular inflammation⁵². Magnetic particles decorated with anti-VCAM1 antibodies can localize specifically to the ischaemically injured brain by targeting inflamed endothelial tissue⁵³. Alternatively, nanoparticles can be coated with leukocyte plasma membranes⁵⁸. Proteins in the leukocyte plasma membrane specifically bind endothelial cell receptors, allowing targeted delivery to inflamed tissues⁵⁴.

Active delivery may also be achieved by cellular transcytosis, enabling nanoparticle delivery and tumour penetration⁵⁵. Here, macromolecules and nanoparticles can permeate the endothelium through endocytosis and exocytosis instead of going through the gap junctions between endothelial cells. Transcytosis is divided into adsorptive transcytosis, which can be exploited for cationic nanoparticles and albumin, and receptor-mediated transcytosis^{56,57}, which involves ligands, such as chlorotoxin, transferrin and TAT peptide⁵⁷. There is ample evidence that inflammation opens up tight junctions

and enhances transcytosis at the blood–brain barrier⁵⁸. The central nervous system endothelium undergoes alterations during neuroinflammation, including disruption of tight junctions, leading to increased permeability, which allows uptake of iron oxide nanoparticles⁵⁹. Inflammation also plays a major role in endothelial dysfunction, contributing to the accelerated endocytosis of iron oxide nanoparticles into the plaque endothelium⁶⁰.

The integrity of vasculature is intrinsically sensitive to biophysical cues spanning the microscale to nanoscale^{61,62}. Some inorganic nanomaterials can randomly enter the nanometre-wide gaps of the adherens junctions between endothelial cells to subsequently produce micrometre-sized gaps between them^{63,64}, leading to a phenomenon called nanomaterials-induced endothelial leakiness (NanoEL). NanoEL is dependent on the physical properties of inorganic nanoparticles (size, density and charge) and facilitates active targeting of nanomedicines^{65,66}. For example, gold nanoparticles with a negative charge and a size of 10–30 nm, as well as silica nanoparticles with a density between 1.57 and 1.72 g cm⁻³ can induce endothelial leakiness⁶³. NanoEL might also promote cancer cell intravasation and extravasation⁶⁶, which raises the question about the risk of cancer nanomedicines. However, given that

inflammation can also cause vascular leakage, NanoEL in an inflammatory but non-cancerous scenario might be beneficial for the delivery of anti-inflammation nanomedicines, such as nanoparticulate scavengers⁶⁷.

Receptors or ligands expressed on leukocytes at inflamed sites provide targets for anti-inflammatory biomaterial–drug formulations^{68,69}. A variety of ligands have been targeted to simulate leukocyte–endothelial cell receptor–ligand interactions, track the fate of neutrophils in the inflammatory microenvironment and facilitate targeted drug delivery^{51,70}. Likewise, a variety of membrane proteins, including integrins, folic acid receptors, lipid scavenger receptors, chemokine receptors and CAMs⁷¹, have been used to target and image neutrophils and macrophages. Targeted immunotherapy of atherosclerosis can be achieved using nanoparticles coated with high-density lipoproteins (HDL) with a high affinity for monocytes and macrophages to modulate the CD40–TRAF6 interaction⁷². The impairment of the migratory capacity of monocytes inhibits their recruitment to the inflammatory site, consequently reducing plaque macrophage content, which is helpful to ameliorate inflammation and atherosclerosis. Exosomes or cell membranes containing targeting proteins can also be applied as nanoparticle coatings to achieve selective homing to an inflamed site³⁸. Moreover, engineered nanoparticles can target platelets, T cells, B cells and dendritic cells for the diagnosis and treatment of inflammatory diseases³⁸.

Inflammatory molecules can also be used as stimuli for biomaterials degradation to achieve degradation-mediated targeting. High levels of reactive oxygen species (ROS) are associated with chronic inflammation³². Biomaterials designed with ROS-responsive frameworks can, thus, be degraded in inflamed tissue for the site-specific release of anti-inflammatory drugs⁷³. Inflammatory enzymes can also be exploited to trigger biomaterial activity⁷⁴. For example, myeloperoxidase-responsive biomaterials exhibiting luminescent signals can be applied to estimate neutrophil count and allow specific imaging of neutrophils in inflammation-associated diseases^{75,76}. Similarly, biomaterials with a structure sensitive to proteolytic matrix metalloproteinases, which are abundant in inflammatory sites, can deliver drugs to inflamed tissues^{77,78}. In addition, low pH is a feature of the inflammatory microenvironment^{79,80}. Thus, biomaterials can be designed to be pH-sensitive to respond specifically to inflammatory molecules and achieve precise diagnosis and treatment⁸⁰.

Scavenging strategies

RONS scavengers

RONS are produced as metabolites or signal molecules in living organisms during cellular metabolism or in response to environmental stimulation⁸¹. Low levels of RONS can act as cellular signalling messengers by reversibly oxidizing thiol groups in proteins, thereby, modifying the protein structure and function. However, high levels of RONS disrupt cellular processes by non-specifically attacking proteins, lipids and DNA⁸¹. Excess RONS are produced by cells involved in the host defence response, for example, by polymorphonuclear

neutrophils, and promote endothelial dysfunction by oxidizing crucial cellular signalling proteins, such as tyrosine phosphatases⁸². Under inflammatory conditions, oxidative stress produced by polymorphonuclear neutrophils leads to the opening of inter-endothelial junctions, promoting the migration of inflammatory cells across the endothelial barrier. These inflammatory cells not only participate in the clearance of pathogens and foreign particles but also lead to tissue injury. For example, M1 macrophages contribute to tissue injury by releasing large quantities of highly reactive cytotoxic oxidants to destroy pathogens²⁷. Therefore, regulation of RONS levels by antioxidant therapy can maintain intracellular redox homeostasis and prevent oxidative-stress-related diseases^{82,83}. Scavengers with antioxidative effects serve as enzyme mimetics to remove overexpressed RONS for the alleviation of inflammation⁸². For example, antioxidant enzymes and natural small molecules (for example, vitamin E and vitamin C) can prevent oxidative damage and inflammatory disease⁸². However, these naturally occurring antioxidants are limited in their ability to balance RONS levels, because they are not stable in harsh conditions (for example, acidic pH or redox environment), show poor pharmacokinetics, non-specific tissue accumulation and potentially harmful effects at high doses^{82,84}. Alternatively, biomaterials with enzyme-like catalytic antioxidant activities can protect cells from oxidative damage and reduce inflammation^{82,83,85}. Antioxidative biomaterials fall into two main categories: artificial-selenoenzyme-based scavengers and catalytic-nanomaterial-based scavengers (FIG. 3a).

Artificial-selenoenzyme-based scavengers. Organoselenium compounds are natural molecules (for example, glutathione oxidase and selenium) widely used in organic synthesis. Artificial selenoenzymes that exhibit GPx activity have been used therapeutically to catalyse the reduction of hydroperoxides and maintain a metabolic balance of ROS^{86,87}. The GPx-mimicking drug Ebselen (2-phenyl-1,2-benzisoxselenazol-3(2H)-one)^{86,87} is a promising therapeutic with anti-inflammatory, antioxidant and cytoprotective activity, and is currently being tested in clinical trials as an anti-inflammatory drug (Phase II, NCT04484025 and NCT04483973). Inspired by the success of Ebselen, other organoselenium compounds with GPx activity have been developed, falling into two categories based on their structure: compounds with a direct Se–N–Se–O bond and compounds with intramolecular non-covalent Se...N–Se...O interactions^{87–89}.

Catalytic-nanomaterial-based scavengers. Metal-based, carbon-based and polymer-based nanomaterials with antioxidant-enzyme-like catalytic activity can also serve as RONS scavengers⁸². The antioxidative activities of nanomaterials are affected by many factors, including size, morphology, composition, surface modification groups, substrate selectivity, pH and temperature, as well as the ions or molecules in the reaction system⁸³. Different nanomaterials might have different antioxidative mechanisms^{82,83}. Nanomaterials composed of

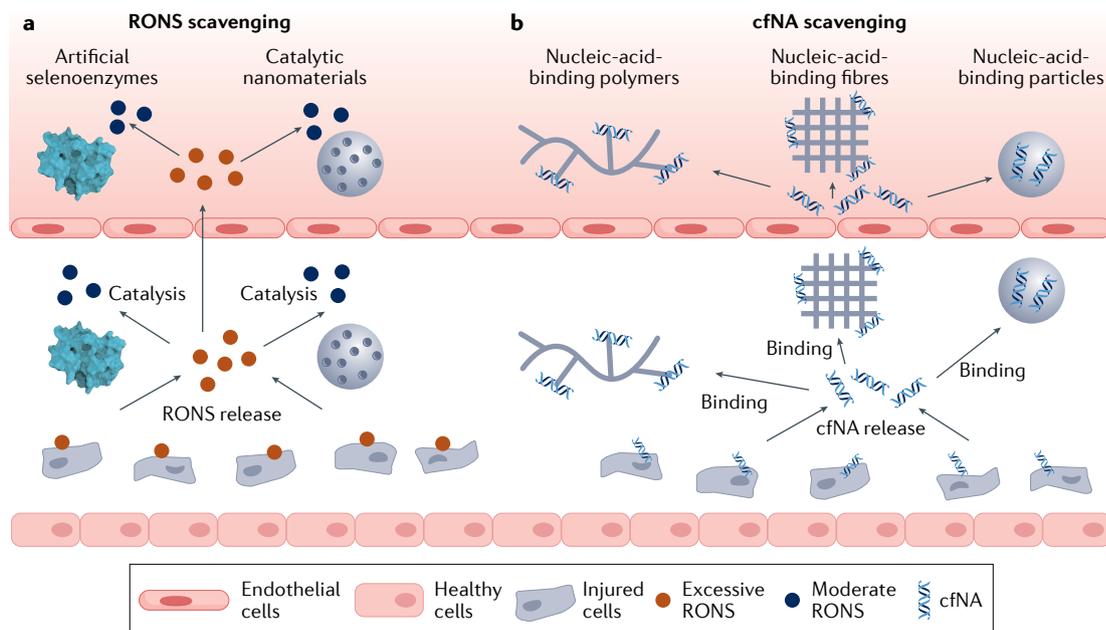


Fig. 3 | **Scavenging strategies to modulate inflammation.** In the early stage of inflammation, pathogen-associated molecular patterns (PAMPs) and endogenous tissue damage-associated molecular patterns (DAMPs) are released from injured cells. Reactive oxygen and nitrogen species (RONS), cell-free nucleic acids (cfNAs) and PAMPs or DAMPs can induce an inflammatory response and the recruitment of immune cells. **a** | RONS scavengers, such as artificial selenoenzymes and catalytic nanomaterials. **b** | cfNA scavengers, such as nucleic-acid-binding polymers, fibres and particles, can reduce the level of RONS and cfNAs in PAMPs or DAMPs and attenuate inflammation development.

noble metals (Pt, Au and Pd) are useful as ROS scavengers owing to their excellent catalytic activity and low cytotoxicity^{90–93}. For example, Pt nanoparticles modified with citrate possess a similar catalytic activity as SOD, CAT and GPx. They have been used to scavenge ROS induced by KRIT1 loss of function in a cellular model of the human cerebral cavernous malformation disease⁹⁰. Au nanoclusters modified with amine-terminated polyamidoamine (PAMAM) dendrimers have CAT-like activity and can, thus, be used to reduce intracellular H₂O₂ levels and protect neuronal cells from H₂O₂-mediated cytotoxicity⁹¹. Pd nanomaterials with CAT-like and SOD-like catalytic activity can moderate mitochondrial injury and protect cells from oxidative damage⁹².

Cerium oxide (CeO) nanoparticles have antioxidative activity owing to the variable oxidation state of cerium (Ce³⁺/Ce⁴⁺) and have been explored as RONS scavengers in treating spinal cord injury, inflammation, sepsis, Alzheimer disease, ischaemic stroke and Parkinson disease (in mouse and rat models)^{94–99}. For example, small, positively charged CeO nanoparticles conjugated with triphenylphosphonium, which targets mitochondria, mitigated neuronal death through ROS scavenging and attenuated reactive gliosis and mitochondrial damage in a mouse model of Alzheimer disease⁹⁶. Nanomaterials containing other metal oxides, such as Fe₃O₄, V₂O₅, Mn₃O₄, MnO₂, Cu_xO and mixed metal oxides, also exhibit enzymatic activity and can, therefore, be used as RONS scavengers^{100–106}. For example, Fe₃O₄ nanoparticles can protect neurons from H₂O₂-induced oxidative damage and ameliorate ROS-induced neurodegeneration in

a *Drosophila* model of Alzheimer disease¹⁰¹. Manganese ferrite and ceria-anchored mesoporous silica nanoparticles can act synergistically to scavenge ROS and generate oxygen, inducing M1 to M2 polarization of macrophages and alleviating inflammation in knee joints in a rat model of rheumatoid arthritis¹⁰⁵.

2D transition-metal dichalcogenides, which are graphene analogues with a flexible sheet-like structure, high surface-to-volume ratio and low toxicity in vivo, have also been explored as ROS scavengers¹⁰⁷. For example, MoS₂ nanosheets can scavenge ROS and have been investigated for treating oxidative-stress-related diseases^{108,109}. Similarly, Mo-based polyoxometalate nanoclusters can eliminate detrimental ROS in the treatment of acute kidney injury in mice^{110,111}. In addition, single-atom nanozymes^{112,113}, metal-organic frameworks¹¹⁴ and black phosphorus¹¹⁵ have been explored in antioxidative stress applications. Moreover, carbon-based nanomaterials and naturally occurring biopolymers have been studied as antioxidants in the treatment of inflammation in mouse and rat models^{116–119}.

cfNA scavengers

cfNA-binding polymers. There is growing evidence that cell-free nucleic acids (cfNAs) released by dying cells activate immune cells via TLRs (TLR3, TLR7, TLR8 and TLR9)¹⁰. Overactivation of these TLRs can lead to inflammatory and autoimmune diseases¹⁰. Nucleic-acid-binding polymers can be applied as cfNA scavengers in anti-inflammatory treatments (FIG. 3b). For example, polycationic polymers can attenuate the

activation of all nucleic-acid-sensing TLRs¹²⁰. Upon their systemic administration, these polycationic polymers prevented fatal liver injury in an acute toxic shock mouse model.

cfNAs also activate blood coagulation and, thus, cfNA-binding polymers show anticoagulant and antithrombotic activity *in vitro* and *in vivo*¹²¹. For example, the cationic third-generation PAMAM dendrimer (PAMAM-G3) inhibited thrombosis-induced pulmonary thromboembolism and carotid artery injury in mice¹²¹. Pathologic cutaneous scarring, which affects millions of people worldwide, is strongly correlated with excess cfNAs¹²². In a mouse model, PAMAM-G3 could reduce wound contraction and angiogenesis, while inducing more random collagen deposition and, hence, less scarring compared with untreated mice¹²². cfNAs also play a role in autoimmune disorders, such as lupus erythematosus, by promoting antibody generation. Cationic polymers have been applied as scavengers to limit cfNA-associated autoimmunity¹²³. Furthermore, TLR signalling can induce tumour progression and metastasis by upregulating the secretion of pro-inflammatory cytokines. PAMAM-G3 can reduce liver tumour metastasis in a mouse model of pancreatic cancer by scavenging cfNA and inhibiting the activation of TLRs¹²⁴. The nucleic-acid-binding and TLR-inhibitory activities of PAMAM can be potentiated by grafting PAMAM onto other polymer chains. For example, PAMAM-grafted polycaprolactone platforms were designed with different backbone lengths and charge densities¹²⁵; grafted polymers with long backbones and high charge densities exhibited greater accumulation in inflamed joints of arthritic rats and enhanced therapeutic effects as compared with polymers with short backbones and low charge densities.

Other cationic polymers, such as heparin reversal agents and hexadimethrine bromide, can also act as cfNA scavengers. Heparin reversal agents are composed of a dendritic core with cationic-heparin-binding groups and short poly(ethylene glycol) (PEG) chains on the periphery¹²⁶. The interaction of heparin reversal agents with DNA has been optimized by improving the interaction of DNA with these polymers¹²⁶. Hexadimethrine bromide has a high affinity for mitochondrial DNA, which is similar to bacterial DNA and can provoke inflammation via the TLR9 pathway¹²⁷. Hexadimethrine bromide could, therefore, mitigate the severity of multiple organ injuries in a rat model by scavenging mitochondrial DNA.

Thiazole orange is a cyanine dye that specifically binds nucleic acids and can, thus, be used as cfDNA scavenger. For example, thiazole-orange-modified dextran can be applied as cfNA scavenger to attenuate macrophage infiltration in the infarct area in a myocardial ischaemia reperfusion mouse model¹²⁸.

cfNA-binding nanoparticles and nanofibres. Although nucleic-acid-binding polymers exhibit anti-inflammatory activity, their unfavourable biodistribution and rapid excretion from the body limit their application. Alternatively, nucleic-acid-binding

nanoparticles and nanofibres show higher scavenging capacity, favourable biodistribution and clearance^{129–134} (FIG. 3b). For example, a cationic micelle containing poly(lactic-co-glycolic acid) (PLGA) and poly(2-(diethylamino)ethyl methacrylate) can be applied as anti-inflammatory treatment in animal models with CpG-induced inflammation and collagen-induced arthritis¹²⁹. Intravenous injection of these micelles reduced bone and cartilage damage, as well as ankle and tissue swelling, with significantly better therapeutic results compared with the corresponding soluble polymer. Similarly, polyethyleneimine (PEI)-functionalized, biodegradable mesoporous silica nanoparticles can be designed as cfNA scavengers with different charge densities¹³¹. These silica nanoparticles showed superior performance compared with nucleic-acid-binding polymers in inhibiting cfNA-induced inflammation and subsequent multiple organ injury caused by sepsis in mice. Of note, nucleic-acid-binding nanoparticles exhibited higher accumulation and retention in the inflamed caecum, and a more desirable *in vivo* safety profile, compared with their soluble polymer counterparts. Cationic PEI can also be immobilized onto nanofibrous meshes and electrospun microfibre meshes to produce nucleic-acid-binding fibres^{132,133}. These meshes attenuated an inflammatory response triggered by negatively charged agonists or DAMPs in the serum of post-trauma patients¹³². The nucleic-acid-binding meshes suppressed the NF- κ B response of cells stimulated with DAMPs released from doxorubicin-treated tumour cells *in vitro*¹³³.

Scavengers of other danger signals

In addition to RONS and cfNAs, other danger signals are associated with inflammatory diseases, including lipopolysaccharide (LPS), chemokines, autoantibodies and PAMPs^{135–138}. LPS is a component of Gram-negative bacterial cell walls and is a TLR4 agonist. Inspired by the observation that HDL can bind LPS, a series of HDL-like nanoparticles were synthesized and shown to be effective in scavenging LPS and inhibiting activation of TLR4 receptors¹³⁵. Inflammatory chemokines, including monocyte chemoattractant protein 1 (MCP1) and IL-8, play important roles in chronic inflammation and wound healing^{136,137}. A modular hydrogel based on glycosaminoglycan derivatives and star-shaped PEG was designed for chemokine scavenging and chronic wound treatment¹³⁶. In animal models, this hydrogel outperformed Promogran, a commercial anti-inflammatory product, in reducing inflammation, increasing angiogenesis and advancing wound closure. Nanofibres composed of pullulan, chondroitin sulfate and tannic acid have been used as wound dressings for recessive dystrophic epidermolysis bullosa¹³⁷. The scavenging fibres removed over 99% of the inflammatory MCP1 from the solution *in vitro* within 2 h.

Challenges and opportunities of scavenging strategy

Several challenges remain to be overcome for scavenging biomaterials to optimally control inflammation. The mechanisms by which nanomaterial properties, such as size, shape and surface chemistry, affect its ability to

scavenge danger signals are unclear. Size determines *in vivo* biodistribution, particularly accumulation in inflamed sites¹³⁹, in addition to intracellular trafficking, particularly interaction with endosomal TLR receptors¹³⁹. Shape determines the extracellular and intracellular fate of a scavenger¹⁴⁰. However, shape may be more important than size in terms of scavenging performance; for example, a 2D nanomaterial might be more effective than a nanoparticle in binding a danger signal associated with a protein or embedded in a secreted vesicle. Surface chemistry governs the type of danger signals that can be removed. A structure–property relationship between the composition of scavengers and types of danger signals to be removed would be invaluable for addressing inflammatory diseases that demand diverse scavenging characteristics.

Studies in animal models showed that nucleic-acid-binding polymers and nanoparticles can achieve therapeutic effects in treating inflammatory diseases, ranging from acute liver injury to lupus and sepsis; however, little information is available on the types of danger signals that are neutralized, which is one of the most interesting and pressing questions in biomaterials-mediated inflammation modulation. The design of retrievable scavenging biomaterials coupled with advanced analytical chemistry would be needed to address this question. If successful, such mechanistic studies might identify new biomarkers that would pave the way for the development of potent and precision therapeutics for inflammation therapy. Of note, cationic materials are often toxic, as documented in many non-viral gene delivery studies^{129,130}. Therefore,

the danger-signal-binding affinity needs to be balanced in terms of toxicity, which might require systematic screening and optimization.

Blockage strategies

Blocking leukocyte–endothelial cell interactions

The adhesive interaction of leukocytes and endothelial cells enables leukocyte migration to inflamed sites, an important element in immune surveillance^{18,141}. Calcium-dependent transmembrane glycoproteins, called selectins, are expressed on both endothelial cells and leukocytes, and are involved in their interaction. P-selectin is expressed by platelets and endothelial cells, and L-selectin by leukocytes^{51,142}. Compounds that block these selectins can prevent leukocyte migration and reduce inflammation (FIG. 4a).

Heparin is an anticoagulant that also possesses anti-inflammatory activity by blocking P-selectin and L-selectin¹⁴³. The use of heparin as an anti-inflammatory agent is limited, owing to the risks of heparin-induced thrombocytopenia and uncontrolled bleeding. However, non-anticoagulant heparin-like molecules that block selectin interactions can also reduce inflammation¹⁴⁴.

Polysulfates. Dendritic polyglycerol sulfate (dPGS), which is widely used in biomaterials research, was initially considered as a heparin mimetic^{144–149}. The dendritic structure and peripheral sulfate groups of dPGS mimic naturally occurring ligands in heparin through a multivalent binding mechanism. dPGS caused a ten-fold shorter clotting time than heparin at concentrations

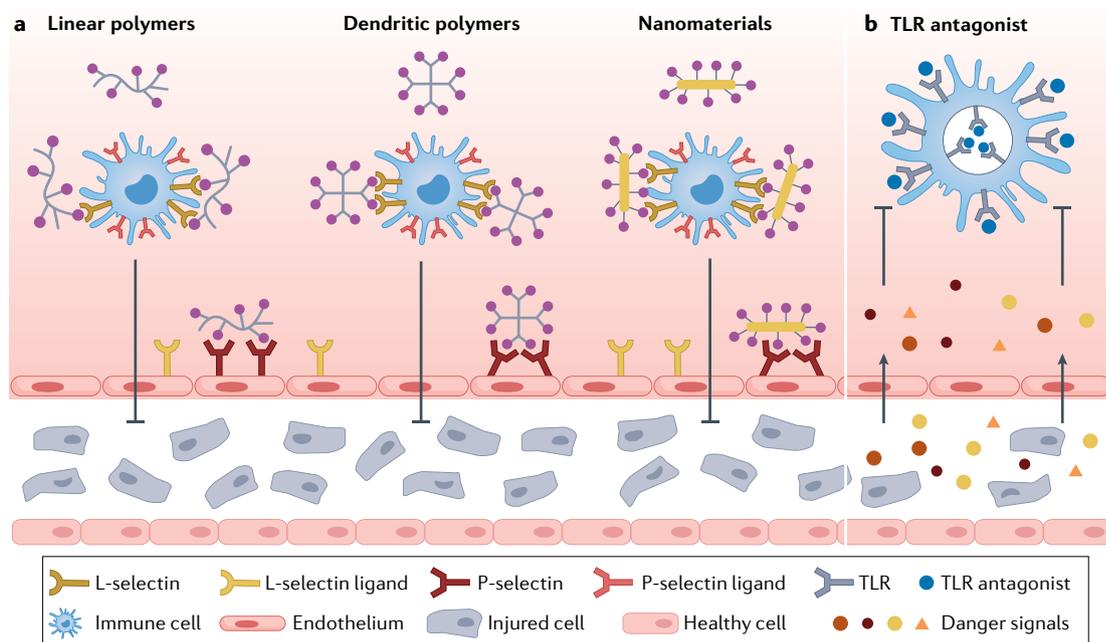


Fig. 4 | Blockage strategies to modulate inflammation. In the middle stage of inflammation, immune cells are recruited to the inflammatory site, generating excessive pro-inflammatory cytokines and inducing severe inflammation. **a** | Anionic biomaterials, such as linear polymers, dendritic polymers and nanomaterials, can block the interaction between L-selectins on leukocytes and L-selectin ligands on the endothelium, or P-selectin on leukocytes and P-selectin ligands on endothelial cells, to inhibit the migration of immune cells to the inflammation sites. **b** | Toll-like receptor (TLR) antagonists can be applied to block the activation of TLRs on immune cells to prevent the activation of immune cells.

above those needed to inhibit inflammation¹⁴⁴. Moreover, dPGS exhibits high multivalent binding affinities to positively charged proteins, such as L-selectin and P-selectin¹⁴⁵. Administration of dPGS could reduce leukocyte extravasation and oedema formation in a contact dermatitis mouse model. Daily treatment of arthritis rats with dPGS is chondroprotective and can inhibit arthritis symptoms and the presence of inflammatory cells in synovial fluid¹⁴⁶.

To increase the biodegradability of dPGS for clearance, a biodegradable form of sulfated poly(glycidol-co-caprolactone) was developed¹⁴⁷, which also has a competitive inhibitory effect on the leukocytic cell adhesion receptor, L-selectin. Similarly, shell-degradable polysulfates can be prepared by incorporating hydrolytically or enzymatically cleavable linkers¹⁴⁸. These shell-degradable dPGS derivatives activate the complement pathway¹⁴⁹; here, rapidly degrading carbamate-functionalized dPGS showed the highest binding affinity to L-selectin.

Anisotropic gold colloids, such as gold nanorods, are ideal contrast agents owing to their non-radiation de-excitation¹⁵⁰. dPGS can be conjugated onto gold nanorods to design compounds with low toxicity and high inflammation-targeting performance, allowing imaging of inflammation in a mouse model of rheumatoid arthritis with high contrast¹⁵¹.

Sulfate interacts with selectins through electrostatic interactions. In addition to dPGS, other polysulfates have been studied for their anti-inflammatory activity, including sulfated PEG dendritic macromolecules¹⁵² and sulfated polysaccharides¹⁵³. These polysulfates inhibit L-selectin binding and sulfated polysaccharides could prevent lymphocyte homing from peripheral blood to the spleen and lymph nodes in mice.

Polyphosphonates. Like sulfates, phosphonates and bisphosphonates are negatively charged and can be used to block leukocyte migration and modulate inflammation^{154–157}. For example, an azabisphosphonate (ABP)-capped dendrimer can specifically target monocytes and induce their anti-inflammatory conversion in mice with rheumatoid arthritis¹⁵⁴. ABP dendrimers can also inhibit the development of autoimmune encephalomyelitis in a mouse model¹⁵⁵. Here, an analogue dendrimer capped with 12 azabiscarboxylate end groups was used as control to confirm the interaction between ABP dendrimers and monocytes¹⁵⁶. The ABP binds to the membrane of monocytes through both non-specific and specific binding, whereas the azabiscarboxylate-functionalized dendrimer showed little binding activity, indicating the importance of the phosphonate in blocking immune cell migration.

Polyanionic macromolecules can also inhibit L-selectin¹⁵⁷, with the inhibition efficiency increasing in the order of carboxylate < phosphate < phosphonate \approx sulfonate < bisphosphonate < sulfate. Although polysulfates, such as dPGS, exhibit excellent L-selectin binding, further research is needed to elucidate the correlation between the microstructure (surface charge and particle size) of the polyanions and their ability to block leukocyte migration.

Polycarboxylates. Little is known about the anti-inflammatory effects of polycarboxylates. A degradable conjugate of dendritic polycarboxylate and morphine has been shown to specifically target peripheral nerve receptors and dampen pain locally without central adverse effects in a rat model¹⁵⁸. In contrast to conventional morphine, the intravenously administered conjugate exclusively activated peripheral opioid receptors to produce analgesia in inflamed rat paws without major side effects, such as sedation or constipation.

Glycoconjugates. Polysaccharides and glycoproteins, such as polyanions, can also selectively bind selectins^{159,160}. The sialyl Lewis^x tetrasaccharide (sLe^x) is a common carbohydrate structure used in selectin-binding studies. For example, sLe^x-modified poly(2-hydroxypropyl) methacrylamide can act as cell adhesion inhibitor, with excellent binding affinity for E-selectin, L-selectin and P-selectin¹⁵⁹. Poly(phosphorhydrazone) dendrimers can be grafted with mannose units¹⁶⁰ to achieve selectin binding, with a G3 dendrimer with 48 trimannosides and a G4 dendrimer with 96 dimannosides showing the highest binding avidity for C-type lectins on dendritic cells.

Blockage of TLRs

Blockage of immune cell TLRs is another promising strategy to reduce inflammation¹⁶¹ (FIG. 4b). For example, peptide–gold nanoparticle hybrids can suppress the activity of several TLRs^{162,163}; here, the hydrophobicity and structure of the amino acids in the peptides are crucial for modulating TLR4 responses. In a murine intestinal inflammation model, peptide–gold nanoparticles improved the disease activity index, reduced weight loss and ameliorated colonic inflammation. The anti-inflammatory activity of the peptide–gold nanoparticles can be further enhanced by modulating the physicochemical parameters of the nanoparticles, in particular, their size¹⁶⁴. Nanoparticles with a 20-nm nanoparticle core exhibit the strongest inhibition of TLR4 activation, which can be attributed to high cell uptake and strong endosomal pH buffering capacity. It was accidentally discovered that adding cigarette smoke extract improved TLR4 inhibition of peptide–gold nanoparticles¹⁶⁵. Cigarette smoke extract components are adsorbed on the peptide–gold nanoparticles, which increases their cellular uptake, thus, avoiding endosomal acidification usually required for TLR4 activation, thereby, enhancing the anti-inflammatory activity of the peptide–gold nanoparticles.

Challenges and opportunities of blockage strategy

Blockage strategies have proven useful in reducing inflammation; however, the mechanisms by which biomaterials interact with selectins and other CAMs have not yet been fully elucidated. Understanding these interactions is important for developing biomaterials that regulate the homing of circulating immune cells to inflammatory sites. Electrostatic forces play an important role in these binding events; however, binding affinity is not simply proportional to the charge density on the biomaterial¹⁵⁷. The types of anions also matter.

For example, polymers with a sulfate group are more effective than those with a phosphate group in binding L-selectin and blocking the recruitment of immune cells to inflammatory sites. Other anionic structures may potentially be even more potent. As in scavenging strategies, the size and structure of the binding group influence the interactions with CAMs; for example, multivalency endowed by a dendritic morphology or surface functionalization of a particle. Interestingly, the softness of the particle may also matter, because the flexibility or shape adaption could facilitate multivalent interactions. However, the exact relation between these interactions and particle size and softness remains elusive. Additionally, most selectin-binding studies are based on electrostatic interactions, which are not specific, similar to nucleic acid scavenging strategies. Non-specific binding, however, cannot claim the benefit of blocking an unspecified upstream signal, as in the case of scavenging, where inhibition of the TLR-ligand interaction attenuates the activation of the MYD88–NF- κ B pathway¹⁶⁶. Using selectin-binding antibodies (against P-selectin, L-selectin and E-selectin) would be a more specific blockage strategy¹⁶⁷. These antibodies would need to be combined with biomaterials to maintain their bioactivity and achieve high blockage efficacy.

Delivery strategies

Unlike scavenging and blockage strategies, which are based on the intrinsic properties of the biomaterials, delivery of anti-inflammatory agents by biomaterials also depends on the drug properties. A variety of materials, including polymers, lipids and inorganic materials, have been explored as drug carriers^{168,169} that deliver anti-inflammatory agents, such as small-molecule drugs,

biomacromolecules (nucleic acids and proteins) and therapeutic gas (FIG. 5).

Small-molecule drug delivery

Small-molecule drugs (for example, resveratrol, dexamethasone, irbesartan and celecoxib) are not only suited for intracellular targets but also applicable to cell-surface or extracellular targets for anti-inflammatory therapy¹⁷⁰. However, their bioavailability and bioactivity are limited by poor water solubility and rapid metabolism. More importantly, their off-target toxicity (for example, immunosuppression and gastrointestinal toxicity) can cause serious side effects and is a major cause of failure in clinical trials¹⁷¹. Drug delivery platforms based on biomaterials as drug carriers can help to overcome these limitations^{172–175}.

PLGA is biocompatible and biodegradable, and can be used for the design of drug delivery carriers for treating inflammatory diseases, including osteoarthritis, nasal polyp, inflammatory bowel disease and myocardial ischaemia–reperfusion injury^{176–178}. Dexamethasone sodium phosphate a synthetic corticosteroid, has been widely applied to alleviate inflammation and reduce the loss of cartilage extracellular matrix. ROS-responsive hollow microspheres, composed of dexamethasone sodium phosphate and PLGA, can be locally injected into inflamed osteoarthritic tissue to treat arthritis and joint destruction in mice¹⁷⁷. Liposome-based nano-platforms allow targeted delivery of anti-inflammatory small-molecular drugs (for example, morin, dexamethasone, quercetin and resveratrol) for the treatment of rheumatoid arthritis, sepsis, vascular inflammation and inflammatory liver disease in animal models^{179–181}. Other synthetic polymer-based carriers, including

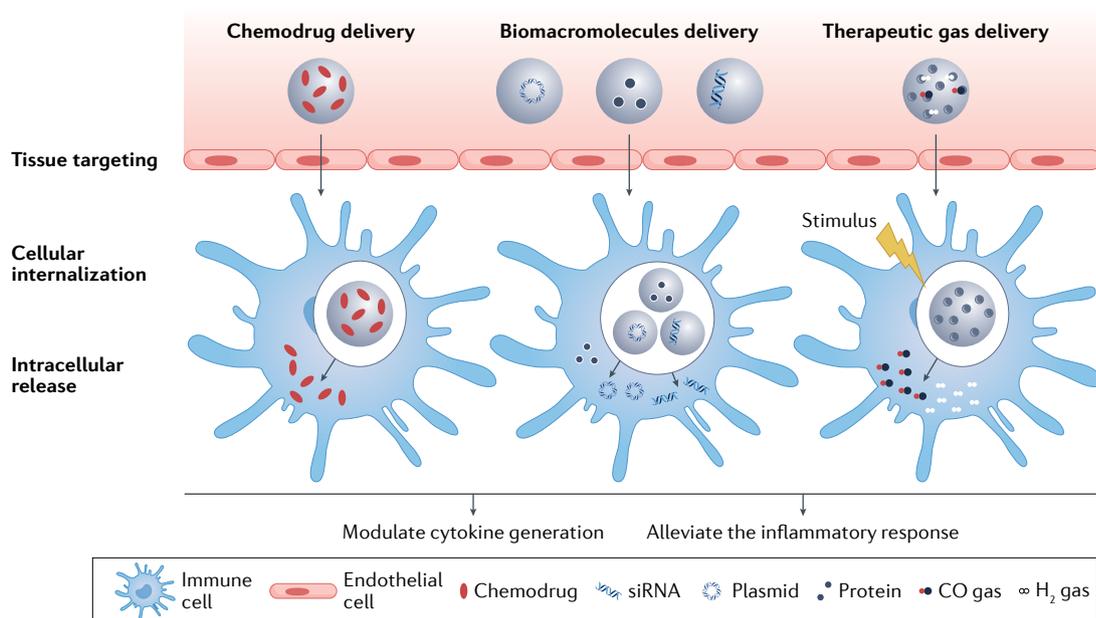


Fig. 5 | **Delivery strategies to modulate inflammation.** In the final stage of uncontrolled inflammation, an excess of immune cells produces an inflammatory response, which can result in a cytokine storm. Biomaterials can be applied as drug delivery platforms, in particular, as nanocarriers, to extracellularly or intracellularly deliver therapeutic agents to the inflammatory sites through the enhanced permeability and retention effect, transcytosis or nanomaterials-induced endothelial leakiness.

poly(ϵ -caprolactone) nanoparticles, poly(ester amide) microspheres, parylene-C nanostructured films, PAMAM dendrimers and polydimethylsiloxane-based 3D scaffolds have also been explored for the delivery of anti-inflammatory drugs^{182–185}.

Compared with synthetic polymers, natural biopolymers tend to have higher biocompatibility and their biodegradation is less likely to cause tissue irritation compared with the acidic breakdown products of PLGA^{186–190}. For example, alginate hydrogels can be used to deliver mesenchymal stem cells for implantation, preserving the viability of the cells and delivering anti-inflammatory agents to improve the interaction of mesenchymal stem cells with T lymphocytes and, thus, tissue regeneration¹⁸⁸. A pH-responsive, dexamethasone-loaded DNA platform can deliver therapeutic agents to macrophages, resulting in inhibition of sterile inflammation after ischaemia–reperfusion injury in mice^{189,190}.

Compared with polymer-based carriers, inorganic drug carriers such as mesoporous silica nanoparticles have a higher surface-to-volume ratio, higher drug loading capacities and different controlled release profiles because of their porous structure¹⁹¹. For example, mesoporous silica nanoparticles can serve as excellent stealth nanocarriers for the delivery of hydrophobic anti-inflammatory drugs¹⁹². Similarly, resveratrol can be encapsulated in silica nanoparticles to improve the transport of the drug across the tight junctions of the Caco-2 (human epithelial colorectal adenocarcinoma cell) monolayer¹⁹³.

Delivery of therapeutic biomacromolecules

Nucleic acid delivery. Inhibition of pro-inflammatory cytokine generation by siRNA delivery is a promising therapeutic approach to control inflammation. PEI-based cationic nanomaterials are widely used for nucleic acid delivery^{194–199}. Multi-shell nanoparticles containing a calcium phosphate core and PLGA/PEI layer allow intrarectal delivery of TNF, keratinocyte-derived cytokine and interferon gamma-induced protein 10 siRNA to inhibit their gene expression and reduce intestinal inflammation in a mouse model¹⁹⁴. Signal transducer and activator of transcription 1 siRNA, cyclooxygenase 2 siRNA and NF- κ B siRNA can also be delivered for inflammation treatment^{195–197}. Co-delivery of drugs and siRNA has shown better anti-inflammatory performance than drug or siRNA delivery alone^{198,199}. The cationic lipid 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) can be mixed with TNF siRNA and then covered with poly-(1,4-phenyleneacetone dimethylene thioketal), a polymer consisting of ROS-sensitive thioketal linkages²⁰⁰. Owing to the high ROS levels at sites of inflammation, the DOTAP nanoparticles release encapsulated siRNA in inflamed tissues following oral administration in mice with ulcerative colitis. Similarly, acid-responsive DOTAP-containing nanoparticles enable delivery of siRNA to inflammatory sites, avoiding unwanted burst release²⁰¹. A DOTAP-containing PEG-*b*-PLGA cationic-lipid-assisted nanoparticle allows delivery of Bruton's tyrosine kinase siRNA for the treatment of rheumatoid arthritis²⁰². To reduce

the toxicity of positively charged gene delivery vectors, pH-sensitive nanoparticles²⁰³ can be designed with multi-armed PEG and acid-responsive linkers to alleviate inflammation-induced liver damage in mice.

Plasmids and the CRISPR gene editing system can also be delivered to modulate inflammation. For example, endothelial nitric oxide synthase, a pro-angiogenic enzyme, promotes angiogenesis and reduces IL-6 expression^{204,205}, and endothelial nitric oxide synthase plasmid can be delivered together with IL-10 in an elastin-like polypeptide-based injectable system²⁰⁴. Cholesterol-modified PAMAM allows co-delivery of resveratrol and haem oxygenase 1 plasmid²⁰⁵. Inhalation of the cholesterol-modified PAMAM nanoparticle achieved a therapeutic effect in animals with acute lung injury. Cationic-lipid-assisted nanoparticles can deliver CRISPR–Cas9 mRNA and gRNA to suppress NOD-, LRR- and pyrin domain-containing 3 (NLRP3) expression²⁰⁶, demonstrating promising therapeutic efficacy for NLRP3-dependent inflammatory diseases in vitro and in vivo. Despite promising results in preclinical studies, several issues should be taken into careful consideration for clinical translation, including the large size of plasmids, the potentially high off-target effects owing to the persistent expression of the Cas9 enzyme and delivery inefficiency of non-viral vectors²⁰⁷.

Protein delivery. Anti-inflammatory proteins can also be delivered to control inflammation. Several interleukins, including IL-4 (REFS^{208,209}), IL-10 (REFS^{210,211}) and IL-27 (REF²¹²), induce the transition of macrophages to the anti-inflammatory M2 phenotype. For example, IL-4 can be delivered by mesoporous silica nanoparticles with an ultra-large pore size (30 nm) to extend the relatively short bioactivity of IL-4 and improve its anti-inflammatory therapeutic efficacy²⁰⁸. Alternatively, using microfluidics, a microchannel can be engineered in a hydrogel, surrounded by a porous membrane, which can then be dried; subsequent reswelling of the hydrogel triggers the release of IL-4 and dexamethasone, and the release can last for up to 96 h (REF²⁰⁹). A variety of nanocarriers have been used for IL-10 delivery for inflammation modulation, including pluronic-based nanocarriers, mineral-coated microparticles and hyaluronan and heparin-based hydrogel systems^{210,211}.

Neurotrophin 3 (NT3), stromal-derived factor 1 α , TGF β 1 and other proteins^{213–216} have also demonstrated anti-inflammatory activity. For example, an NT3/fibroin-coated gelatin sponge scaffold was engineered for spinal cord injury therapy in rat and canine models²¹³. An N-desulfated heparin-containing PEG-diacrylate hydrogel was developed to deliver stromal-derived factor 1 α ²¹⁴. Biomaterial scaffolds that enable local delivery of proteins such as TGF β 1 can improve the transplantation of islets in a mouse model by reducing local cytokine production and leukocyte infiltration²¹⁵. Furthermore, temporal control of the immunomodulatory microenvironment is important. In an in vitro study, staged delivery of pro-inflammatory cytokines, such as MCP1 and interferon gamma, followed by the release of the anti-inflammatory cytokines IL-4 and IL-10, could polarize macrophages from an M1 to an M2 phenotype

to direct an initially pro-inflammatory response, which is beneficial for wound healing by clearing debris and preventing infection at the site, to a subsequent pro-healing response²¹⁷. This was accomplished with a two-compartment biomaterial system containing a magnetically responsive biphasic ferrogel, which can be externally activated to trigger the release of the cytokines on demand. Although these findings have to be validated *in vivo*, this study highlights the potential advantages of biomaterials in the temporal-spatial control of inflammation, which cannot be easily achieved by conventional drug therapy.

Delivery of anti-inflammatory gas

Gas therapy using carbon monoxide (CO)^{218–223}, hydrogen (H₂)^{224–227} or hydrogen sulfide (H₂S)²²⁸ can be applied for the treatment of inflammatory diseases. CO selectively inhibits the generation of pro-inflammatory cytokines (for example, TNF, IL-1 β and macrophage inflammatory protein 1 β) and increases the expression of anti-inflammatory cytokines (for example, IL-10). Despite its promising therapeutic activity, the use of CO in clinical applications is limited, owing to a lack of targeting and potential toxicity. Photoactive CO-releasing nanoplatfoms can overcome this limitation. For example, ferritin-containing protein cages and 3-hydroxybenzo[g]quinolone frameworks^{218,219} release CO under light irradiation, and the amount of released gas can be regulated by the duration of irradiation. Alternatively, esterase and pH-responsive CO prodrugs can be administered for the treatment of LPS-induced systemic inflammation in a mouse model²²⁰. Prolonged CO release can be achieved by a syringe-injectable peptide hydrogel, enabling a CO-releasing half-life of 20.2 \pm 0.6 min, which is longer than the commonly used CO-releasing molecule Ru(CO)₃Cl(glycinate) ($t_{1/2} \approx 3.6$ min)²²¹.

H₂ gas can downregulate pro-inflammatory cytokines and transcription factors, thereby, alleviating inflammatory-response-induced tissue injury. Semi-conducting polymer dots and liposomes enveloping chlorophyll a, 1-ascorbic acid and gold nanoparticles can deliver H₂ gas^{224,225}. Both nanoplatfoms reduced ROS and the concentration of pro-inflammatory cytokines in the paws of mice. High H₂ concentration can also be generated in inflammatory tissue by cyclic passivation and activation of Mg in Mg-PLGA microparticles²²⁶.

Challenges and opportunities of delivery

These lipidic, polymeric and inorganic nanocarriers all have distinct advantages and disadvantages in drug delivery applications^{168,169}. Lipidic nanoparticles are easy to formulate, and many different lipids are available with well-defined composition and properties, which can be screened to identify the ideal lipid mixture for optimal delivery performance²²⁹. The efficacy of the COVID-19 mRNA vaccine is partly related to such an optimized lipid formulation²³⁰. However, encapsulating small hydrophilic drugs and functionalization of lipid nanoparticles remain challenging, but could be addressed through modification of lipids. Polymeric nanoparticles show high compositional and structural diversity,

in terms of molecular weight and architecture, enabling the encapsulation of almost any drug. In addition, biodegradability, stimulus responsiveness and targeting can be incorporated into polymeric nanoparticles. However, batch-to-batch variations in composition and molecular weight of the polymeric carrier may be problematic for clinical translation. For example, a wide molecular weight distribution leads to polydispersity in nanoparticle size and surface potential, which, in turn, promotes aggregation and affects performance. Inorganic nanoparticles are usually more uniform in size, composition and structure, and can possess electrical, magnetic or optical properties for external control release or imaging. Inorganic nanoparticles with a porous structure, such as mesoporous silica nanoparticles, allow loading of drug molecules into the internal pores with high efficiency^{231,232}. If drug loading is confined to surface immobilization, however, the loading level is lower, and surface-exposed drugs are more prone to degradation.

Several strategies can be applied to improve the delivery performance of nanocarriers^{168,169}. For example, more specific inflammation targeting can be achieved by designing carriers that respond to inflammatory molecules. Furthermore, the delivery of multiple cargoes with one vehicle (all-in-one drug delivery platform) at different stages of inflammation would be valuable to treat inflammation. For example, by adapting to the characteristics of the inflammatory microenvironment at different stages, the delivery system could initially release scavengers to remove cfDNA or mitigate RONS, followed by the release of drugs that can block leukocyte–endothelial cell interactions, supported by anti-inflammation agents to strengthen the therapeutic efficacy at the late stage of inflammation. To reduce the complexity associated with multiple drugs, a proactive carrier could be designed that can perform scavenging and blockage functions in addition to delivery.

In addition to inflammatory molecules, other targets could be explored; for example, cells and cellular communication of the microvascular compartment, which collaborate to recruit leukocytes to inflamed tissue. Local signals regulating inflammation are transmitted between cells by paracrine signalling, mechanosignalling, direct signal transduction via gap junctions (connexins) and tunnelling nanotubes, and through release and uptake of cell-derived vesicles, such as exosomes. The recruitment of circulating leukocytes is directed by mechanosignalling between integrins on leukocytes and adhesion molecules on the endothelium. Distinct leukocyte populations and vascular beds express different combinations of adhesion molecules, which could inspire the design of drug delivery platforms to realize tissue-specific targeting²³³. Connexins are membrane proteins that form gap junctions and enable direct signal transduction between adjacent cells by allowing rapid transfer of ions, second messengers and metabolites. Connexin 43 channels in gap junctions are involved in the communication between leukocytes and epithelial cells in the lung and intestine²³⁴. The synthetic peptide ACT1, which mimics the carboxyl terminus of connexin 43, stabilizes gap junctions and decreases infiltration of inflammatory neutrophils into wounds²³⁵. These connexins can be

targeted to modulate the communication between epithelial or endothelial cells and leukocytes²³⁶. Cell-cell signalling can also involve exosomes that shuttle proteins, lipids, microRNA and mRNAs between cells²³⁷. Exosomes are released from most cell types, including leukocytes and endothelial cells, in response to various stimuli, including inflammation. As drug delivery vehicles, exosomes could be designed to express surface molecules to deliver them to specific vascular beds in a targeted manner²³⁸.

Perspectives

Infectious diseases and sterile inflammatory diseases exhibit common pathophysiological features, such as monocyte recruitment, macrophage polarization and enhanced vascular permeability^{1,2,6}. cfNAs released by dead or damaged cells can recruit immune cells and trigger inflammatory responses³⁵. Furthermore, many pathogens, including viruses and bacteria, can activate immune cells by themselves^{5,9}. Pathogen-induced inflammation can be alleviated through eradication of pathogens; however, elimination of sterile inflammation that can develop into chronic inflammation, which is a cause of tumour occurrence, is more difficult^{2,7}. Inflammation can be classified into local and systemic inflammation, depending on the sites of the inflammatory response.

However, local and systemic inflammatory responses are connected^{239,240}, and many local inflammatory diseases, including hepatitis, pneumonia and periodontitis, can induce serious systemic inflammation if they are not controlled at an early stage^{239,240}. Subsequent systemic inflammatory responses, such as a cytokine storm, can lead to multi-organ failure and even death.

The complexity, variability and heterogeneity of the inflammatory environment and corresponding immune response can lead to heterogeneous treatment responses among patients^{1,7}. Inflammation is a highly dynamic process⁷, and, thus, an anti-inflammatory treatment would be desirable that can adapt to the progression of inflammation. For example, sepsis is a complex condition induced by infection and underpinned by an intricate interplay of pro-inflammatory and anti-inflammatory responses¹³¹ (FIG. 6a). Patients with sepsis first undergo a phase of excessive systemic inflammation mediated by various pro-inflammatory mediators of the innate immune system, followed by either recovery or re-entering of the inflammatory phase. Therefore, immunostimulation and immunosuppression need to be balanced for sepsis therapy.

Homeostasis and dysregulation of inflammation are the result of multiple interactions of various cell types with their microenvironment. Real-time monitoring of

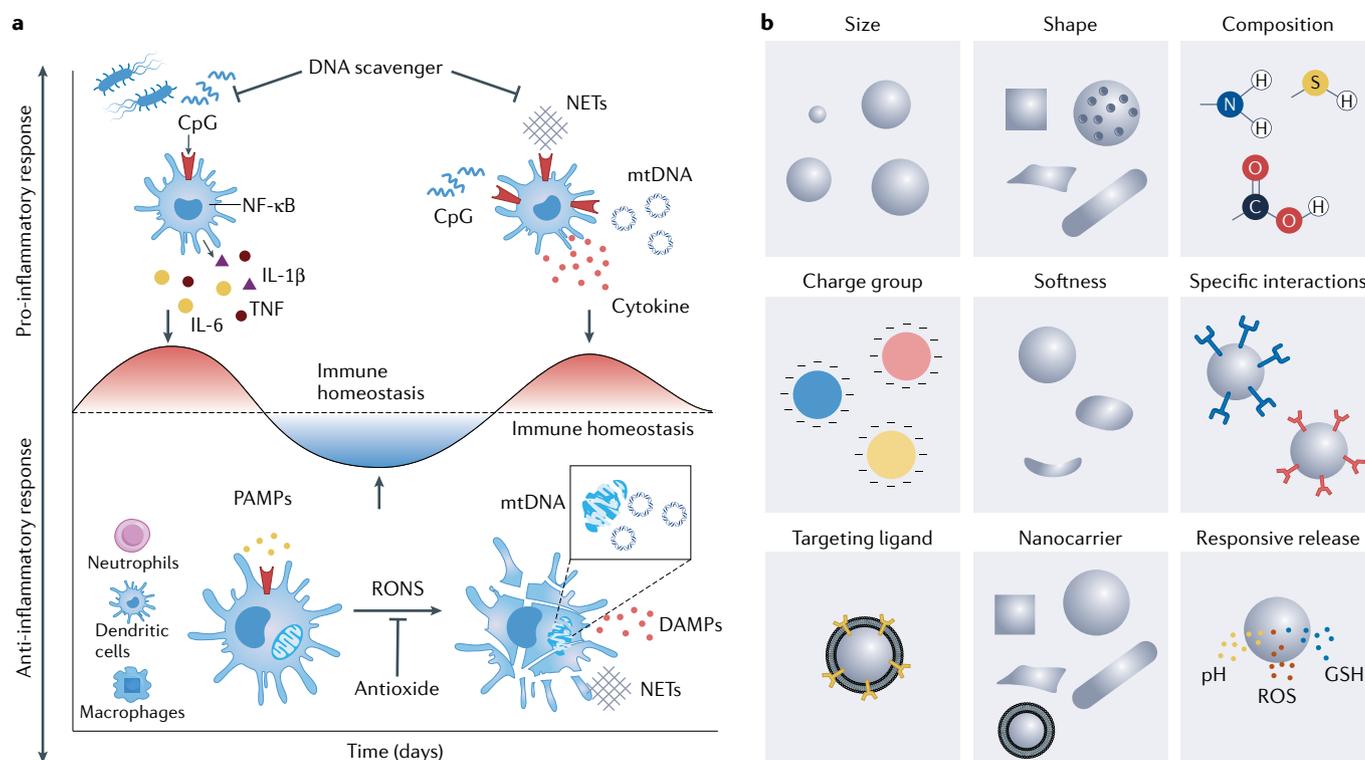


Fig. 6 | Anti-inflammatory biomaterials design. a | Inflammation is a highly dynamic process, exemplified here by the development of sepsis. Sepsis is characterized by an intricate interplay of pro-inflammatory and anti-inflammatory responses. An optimal anti-inflammatory therapy should, therefore, adapt to the progression of inflammation. **b** | Various parameters of biomaterials can be designed for scavenging, blockage and delivery strategies for inflammation modulation. Composition, size, shape, charge and mechanical compliance affect the behaviour of the biomaterial in vitro and in vivo, including tissue distribution, trafficking and cellular

interactions. The mechanical compliance of biomaterials, whether as scaffold to interact with leukocytes or as a nanoparticulate injectable to interact with cells and tissues, is also relevant. Finally, biomaterials can play a passive or active role in inflammation-modulation strategies. DAMP, damage-associated molecular pattern; GSH, glutathione; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; mtDNA, mitochondrial DNA; NET, neutrophil extracellular trap; NF- κ B, nuclear factor- κ B; PAMP, pathogen-associated molecular pattern; RONS, reactive oxygen and nitrogen species; ROS, reactive oxygen species; TNF, tumour necrosis factor.

these interaction dynamics would allow the design of therapeutic strategies tailored to the different stages of the inflammation. Biomaterials offer a vast parametric space to design inflammation-modulation strategies (FIG. 6b), including chemical properties, such as hydrophobicity and charge characteristics, physical properties, such as size, shape and softness, as well as environmental responsiveness to achieve active targeting.

The chemistry of biomaterials is related to their immune-modulatory activities and can, thus, be tailored to different anti-inflammatory strategies. Biomaterials with antioxidant-enzyme-like catalytic activity can be used for RONS scavenging, the potency of which is affected by many factors, including size, morphology, composition, surface modification, pH, temperature and the ions and molecules in the reaction system^{82,83}. Most cfNA-scavenging materials are positively charged to bind negative cfNA through electrostatic interactions¹²⁰. Negatively charged materials can also interact with nucleic acids through metal coordination. Negatively charged biomaterials can be applied to block P-selectin and L-selectin on leukocytes^{144,145} to inhibit their homing; here, the blockage efficiency is not directly proportional to the charge density or zeta potential of the material¹⁵⁷. Nanomaterials used for anti-inflammatory drug delivery are often amphiphilic to allow the formation of nanoparticles through self-assembly to encapsulate drugs or biomacromolecular agents^{168,169}. These nanoparticles can then release the loaded drugs in response to the intracellular microenvironment in the targeted disease area. Materials can also be designed to generate therapeutic gas under external stimuli or to react with intracellular components^{220,224}. Furthermore,

different anti-inflammatory strategies may be incorporated into the biomaterial design to achieve a synergistic effect.

Biomaterials can be designed to passively or actively target specific features of the inflammatory environment for therapeutic and diagnostic applications⁸. Biomaterials with nucleic-acid-binding, ROS-neutralization and mediator-absorption activities can be used to scavenge danger signals and block early inflammation. Biomaterials that block CAMs can prevent leukocyte-endothelial cell adhesion to reduce immune cell recruitment during the middle stage of inflammation. Biomaterials capable of delivering anti-inflammatory drugs in a stimuli-responsive manner can best regulate the inflammatory environment during the middle and late stages of inflammation (FIG. 6b).

However, the vast parametric space of nanomaterial properties makes the establishment of structure-property relationships challenging. To limit the number of animal experiments and to increase the relevance to human responses, microphysiological systems or human tissue chips can be applied for nanomaterial testing. Often constructed with human-induced pluripotent stem cells, engineered 3D tissues can be connected with physiologically relevant flows to form tissues on a chip^{241,242}, which can be applied for disease modelling and drug discovery. Inflammation models can then be generated by adding the appropriate stimulus; for example, addition of TNF to the culture medium perfusing a tissue-engineered blood vessel activates the endothelium and significantly increases transendothelial events of immune cells²⁴¹. Similarly, an ex vivo multi-organ model of ulcerative colitis can be designed by connecting

Table 1 | Representative clinical trials of biomaterials for inflammation-related diseases

Mode of action	Biomaterial	Condition or disease	Recruitment status	First posted	Identifier
Scavenging strategy	Polyethyleneimine-coated membrane for haemofiltration versus polymyxin B-immobilized fibre column	Inflammatory conditions in septic shock	Completed	24 September 2013	NCT01948778
	Membrane composed of copolymer of acrylonitrile and sodium methylsulfonate with polyethyleneimine-treated surface and adhered heparin	Cardiac-surgery-associated acute kidney injury	Recruiting	7 August 2015	NCT02518087
	Copolymer of acrylonitrile and sodium methylsulfonate with polyethyleneimine-treated surface	Septic acute kidney injury	Completed	13 February 2013	NCT01790620
	Chewing gum with chitosan	Gingival inflammation	Completed	2 August 2017	NCT03237624
Blockage strategy	Nebulized heparin	COVID-19-induced lung injury	Enrolling by invitation	21 May 2020	NCT04397510
	Low-dose unfractionated heparin	Inflammation in sepsis	Completed	12 May 2014	NCT02135770
	Low-molecular-weight heparin	Paediatric cataract surgery	Completed	29 September 2009	NCT00986076
	Unfractionated heparin	Severe sepsis with suspected disseminated intravascular coagulation	Recruiting	13 January 2016	NCT02654561
Delivery strategy	PEG-liposomal prednisolone sodium phosphate (Nanocort)	Atherosclerosis	Recruiting	23 July 2012	NCT01647685
	Liposomal GSH for glutathione and N-acetylcysteine delivery	Obesity, hyperlipidaemia, insulin resistance, hypertension	Completed	12 March 2012	NCT01550432

GSH, glutathione; PEG, polyethylene glycol.

microphysiological systems of the human gut, liver and circulating T_{reg} cells and T_H17 cells²⁴². Such physiologically relevant *in vitro* and *ex vivo* systems allow the investigation of the relationship between metabolism, immunity and tissue homeostasis. However, there is ample room to improve such tissue chips; for example, including blood vessel endothelium in the chip design would enable the study of transendothelial immune cell migration^{241,243,244}.

Biomaterials, however, face different challenges to conventional drugs in terms of clinical translation. The majority of approved drugs have a low molecular weight and are uniform in size and composition. By contrast, biomaterials are macromolecular and can range from the nanoscale to the macroscale, with a wide distribution in molecular weight and size⁶. Therefore, considerations of biocompatibility and toxicity of biomaterials are more complicated. For example, biodegradability is beneficial for biomaterials intended as scavengers and drug carriers to avoid long-term complications⁸. However, the optimal biodegradation rate may vary depending on the application; if the biomaterial degrades too fast, the scavenging or delivery function may be compromised, and storage and shipping may be more costly than for non-degradable biomaterials; for example, if an anhydrous packaging is required. Finally, the complexity and heterogeneity of patient-specific inflammation pose a challenge for the clinical translation of biomaterials⁸.

Several biomaterials are currently in clinical trials for inflammation-related diseases (TABLE 1), with only a few approved by the US Food and Drug Administration. In some cases, in particular, for scavenging biomaterials, only *ex vivo* trials have been conducted thus far. In addition to using microphysiological systems based on induced pluripotent stem cells, relevant animal models would be required to enable clinical translation²⁴⁵. Many diseases, including cancer (origin, progression and

metastasis), Alzheimer disease and acute organ injuries (for example, COVID-19-induced lung injury), are tightly linked to local or systemic inflammation^{7,239,246}. Anti-inflammatory therapies for these diseases could be preclinically investigated in sophisticated animal models.

As the concept of biomaterials-assisted inflammation control develops, a future research focus should be on applications, for which such strategies provide a unique advantage, for example, in cancer therapy. A drug carrier could deliver a chemodrug in a controlled manner and, at the same time, also scavenge pro-metastatic factors. The spatiotemporal control of inflammation, which can be achieved by biomaterials-assisted strategies, is also particularly important for cancer treatment. Similarly, the dual functionality of a biomaterial, that is, delivery and scavenging, could be advantageous for the treatment of infectious diseases.

Biomaterials are not passive entities but active participants in the inflammation process. Therefore, a holistic consideration of interactions between biomaterials and the inflammatory microenvironment can inform the design of multifunctional biomaterials to tackle inflammation. Biomaterials could be engineered to induce a therapeutic or immunologic response by themselves, including biomaterials that have been optimized for drug delivery and tissue engineering. Initial translational barriers, such as toxicity, lack of biocompatibility, robustness and manufacturing, have been addressed for many implants and drug delivery devices. This wealth of knowledge can provide the basis for the clinical translation of biomaterials for inflammation treatment. Building on preclinical successes, bridging the gap between preclinical research and clinical translation will pave the way for biomaterials-based anti-inflammatory therapies for various diseases.

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Author contributions

Z.T., D.S. and K.W.L. conceived the manuscript; Z.T., Y.Z., D.S. and H.H. wrote the draft; Z.T. and D.S. designed the figures; H.H., R.H., M.S., J.L., B.S. and K.W.L. edited the manuscript.

Competing interests

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