Biomaterials for treating sepsis-induced thromboinflammation

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Sepsis is a common and life-threatening disorder with an alarmingly high mortality rate. Unfortunately, this rate has not decreased significantly over the last decade and the number of septic cases is increasing each year. Despite sepsis affecting millions of people annually, there is still not an established standard of care. The development of a therapy that targets the thromboinflammation characteristic of sepsis is imperative. Until recently, research has focused on uncovering individual pathways to target. As more of the pathophysiology of sepsis has become understood and more biomarkers uncovered, the interplay between endothelial cells, platelets, and leukocytes has emerged as a critical event. Therefore, a multi-targeted approach is clearly required for designing an effective treatment for sepsis. The versatility of biomaterials offers a promising solution in that they can be designed to target and affect multiple pathways and systems and safely inhibit excessive inflammation while maintaining hemostasis. Already, studies have demonstrated the ability of biomaterials to target different processes and stages in sepsis-induced inflammation and coagulopathy. Moreover, some biomaterials offer inherent anti-inflammatory and hemostatic qualities. This review aims to discuss the most recent advancements in biomaterial development designed to address inflammation, coagulopathy, and thromboinflammation.

KEYWORDS

biomaterials, sepsis, inflammation, hemostasis, thromboinflammation, targeted delivery

1 Introduction

Sepsis is as life-threatening host response to infection, characterized by organ dysfunction (Semeraro et al., 2010; Angus and Poll, 2012; Singer et al., 2016), and this condition is estimated to cause almost 50 million cases globally each year (WHO, 2023). The causes for sepsis include any infectious organisms: bacteria, fungi, viruses, and parasites can all lead to sepsis (Rudd et al., 2020). Sepsis is most commonly caused by bacterial pneumonia, but intra-abdominal and urinary tract infections are also frequent underlying causes (Angus and Poll, 2012). These infections lead to uncontrolled inflammation, resulting in tissue damage and coagulopathy, organ dysfunction, and even death. People who are immunocompromised, such as babies, geriatric populations, and those on immunosuppressive treatments such as chemotherapy, are most at risk (Angus and Poll, 2012; Rudd et al., 2020; Weiss et al., 2020). The respiratory and cardiovascular systems are most severely affected. Clinical signs include difficulty breathing and low blood pressure.

Current treatment strategies depend on the individual and their clinical presentation, so a standard of care has not yet been established. Treatment often involves rescuing the cardiovascular and pulmonary systems through mechanical ventilation, vasopressor administration, and obtaining cultures to guide antimicrobial therapy (Angus and Poll, 2012; Weiss et al., 2020). Despite intensive treatment, sepsis remains a significant health concern, accounting for nearly 20% of all global deaths (WHO, 2023), with a high mortality rate of approximately 33% (Bauer et al., 2020). In the United States alone, hospitals spend over $24 billion each year on septic patient care (Rudd et al., 2020). Over the last decade, mortality rates have not lowered significantly (40% in 2009% vs. 34% in 2019) (Bauer et al., 2020) and the frequency of septic cases has risen every year by 13% on average (Tanne et al., 2002; Gaieski et al., 2013). These trends most likely result from increased life expectancies and the rise of antimicrobial resistance, both of which may contribute to sepsis becoming more difficult to treat (Cánovas-Cervera et al., 2023). Moreover, the relatively stagnant mortality rates in sepsis reflect the lack of significant advancements in therapeutics. Biomaterials and the design of multi-targeted therapeutics offer promising solutions to treating this complex disorder.

Biomaterials are most frequently considered for use as drug delivery vehicles with the aims of improving drug stability, prolonging blood circulation, and controlling spatiotemporal drug release to enhance local effects while minimizing systemic side effects. Accomplishing these goals ultimately improves patient outcomes and reduces drug-related toxicities and coagulopathies. Biomaterials offer inherent benefits based on their physical properties. For instance, silver is a natural antimicrobial, and when used as nanoparticles, it can amplify the antibacterial effects of antibiotics (Sun and Gupta, 2020; Vishwanath et al., 2022). This synergy allows for the use of lower antibiotic doses while achieving effective antibacterial responses. Biomaterials can be manipulated extensively to address several different diseases of different bodily systems as well. Material composition, size, shape, charge, molecular weight, and flexibility can all be optimized for specific purposes. With inflammation, nano-sized biomaterials can take advantage of the enhanced permeability and passively accumulate in inflamed tissues. For active targeting, ligands can be conjugated to biomaterials for selective binding. As for drug release, biomaterials can be designed to respond to changes in pH, temperature, shear forces, enzymes, radiation, and even ultrasonography and magnetic forces. For example, superparamagnetic iron oxide nanoparticles (SPIONs) have frequently been studied for drug delivery since they can be directed to specific areas for targeted drug delivery (Friedrich et al., 2021). Given these possibilities, the development of a biomaterial capable of effectively treating severe sepsis and associated thromboinflammation is imminent.

This review delves into investigations of state-of-the-art biomaterials and the challenges in the development of biomaterials for sepsis-induced thromboinflammation, as well as inflammation and hemostasis individually. Anti-inflammatory biomaterials have historically been engineered from either synthetic materials or cells. Excitingly, recent innovative biomaterials incorporate both synthetic and cellular components. Biomaterials addressing coagulopathy have also expanded to reflect

that coagulation is a dynamic process involving both clot formation and lysis. This review will examine biomaterials for modulating the different stages of coagulation, including furthering hemostasis, preventing thrombosis, and enhancing fibrinolysis. Lastly, investigations into multifunctional therapeutic biomaterials for sepsis-induced thromboinflammation will be discussed.

2 Biomaterials for inflammation

The characteristic uncontrolled inflammatory response is initiated by the detection of the invading microbes through their pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS). Additionally, damage inflicted by the invading microbes to the host leads to the release of damage-associated molecular patterns (DAMPs), including high mobility group box 1 (HMGB1). These patterns bind to pattern recognition receptors (PRRs), which are displayed by both circulating innate immune cells and endothelial cells. These PRRs include Toll-like receptors (TLRs), C-type lectin receptors (CLRs), and NOD-like receptors (NLRs) (Lasola et al., 2020; Friedrich et al., 2021; Yu et al., 2022). This detection activates inflammatory signaling pathways, such as nuclear factor-kappa B (NF-κB), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK). Activation of these pathways induces neutrophils, monocytes, and macrophages to phagocytize the pathogens and synthesize pro-inflammatory cytokines and chemokines, such as tumor necrosis factor-alpha (TNFα), interleukin-1 (IL-1), and interleukin-6 (IL-6) (Vuong et al., 2017; Huang et al., 2019). These inflammatory signals recruit more immune cells, induce vasodilation, and increase vascular permeability to promote immune cell infiltration (Semeraro et al., 2010; Jackson et al., 2019). Microbes and cytokines stimulate neutrophils to release neutrophil extracellular traps (NETs), which capture and kill microbes (DeBont et al., 2019). However, in sepsis, the excessive accumulation of immune cells is harmful to the body. The high leukocyte numbers release a "cytokine storm," resulting in tissue damage and paradoxically reduced pathogen clearance (Huang et al., 2019). This is largely due to activated natural killer (NK) cells, which amplify inflammation by secreting interferon-gamma (IFN-γ) and further tissue damage by releasing cytotoxic granzymes and perforins (Guo et al., 2018). NK cells also induce immune cell apoptosis with their ligands, ultimately reducing pathogen uptake and clearance (Michel et al., 2012; Thorén et al., 2012). The activated endothelium also increases its expression of adhesion molecules, including von Willebrand factor (vWF), P-selectins, vascular cell adhesion molecule-1 (VCAM-1), and platelet-endothelial cell adhesion molecule (PECAM)-1 (Greineder et al., 2013; Banka et al., 2023). These molecules enhance the binding of neutrophils, monocytes, and platelets, promoting coagulation and providing targets for site-specific nanoparticles. Biomaterials have also been developed to block inflammation from neutralizing PAMPs and removing reactive oxygen species to altering leukocyte recruitment and phagocytic capabilities and interactions (Lasola et al., 2020) (Figure 1).

2.1 Synthetic biomaterials for inflammation

Traditionally, biomaterials have been synthetic, including polymers, ceramics, and metals. Examples of commonly used
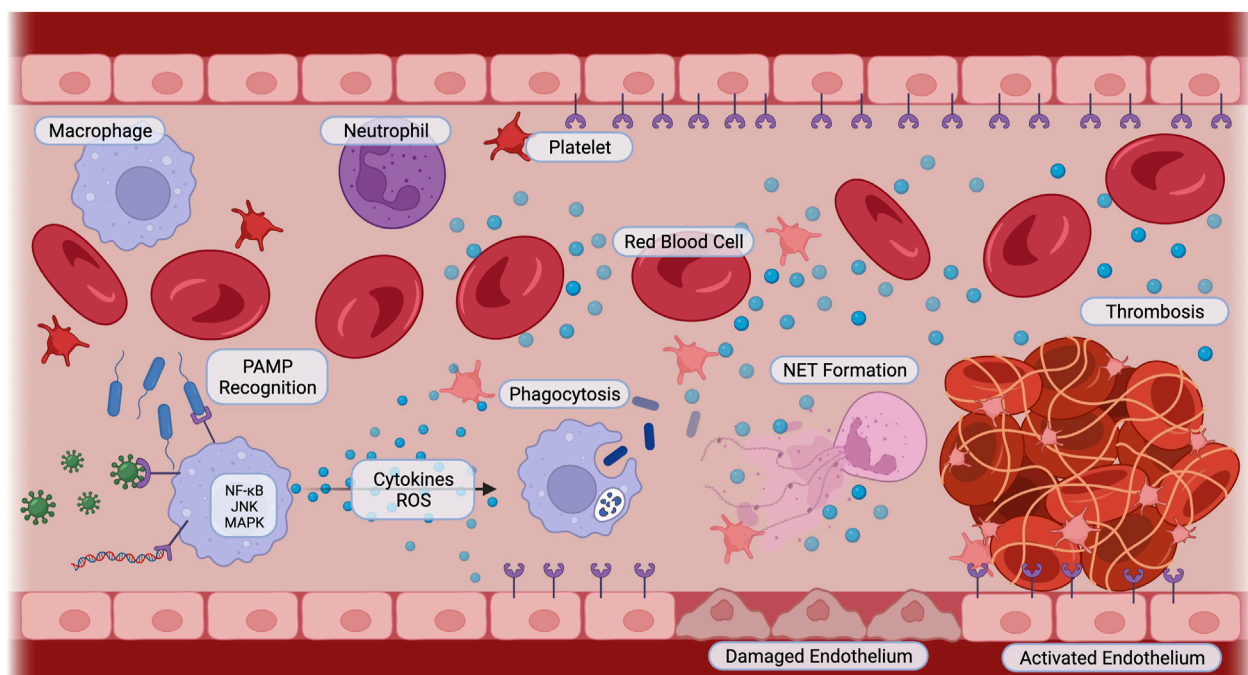
FIGURE 1
Sepsis Pathophysiology. Innate immune cells recognize pathogens such as bacteria, viruses, and parasitic DNA with pattern recognition receptors. Pro-inflammatory signaling cascades including NF-κB, JNK, and MAPK are activated. Cells secrete cytokines and reactive oxygen species, activating immune cells to phagocytize, neutrophils to release neutrophil extracellular traps, and platelets and endothelial cells to switch to a pro-coagulant phenotype. Cellular interactions amplify inflammation, cause endothelial cell damage, and induce thrombosis. Created with BioRender.

synthetic biomaterials for targeted drug delivery include lipid nanoparticles, liposomes, dendrimers, and poly(ethylene glycol) (PEG) conjugates (Greineder et al., 2013). Conjugating PEG to compounds or nanoparticles, also known as "PEGylation," is a common technique to improve the "stealth" of nanoparticles and increase circulation time (Sun et al., 2008; El Mohtadi et al., 2019; Yan et al., 2019; Huang et al., 2021; Nunoi et al., 2022). PEGylation creates a hydrophilic layer, sterically repelling proteins and thereby limiting the adsorption of opsonins that signal to immune cells to uptake and destroy (Kelley et al., 2016; Sobczynski et al., 2017). Moreover, the hydrophilic layer produced by PEGylation can increase drug solubility (Greineder et al., 2013). Of course, PEGylation has a drawback: studies have indicated that PEGylated products can lead to acquired immunogenicity, limiting its use for drugs that require repeat dosing (Kelley et al., 2016). Moreover, the acquired immunogenicity results in accelerated clearance of the particles from the bloodstream, limiting the "stealth" of the materials (El Mohtadi et al., 2019). Therefore, other polymers with stealth capabilities are also being investigated, including poly(propylene sulfoxide) which also has antioxidant properties (El Mohtadi et al., 2019), poly(2-oxazoline) (POx), and zwitterionic polymers (Fam et al., 2020). As of yet, none of these other polymers have been found to induce acquired immunogenicity nor result in accelerated blood clearance.

Several synthetic biomaterials are currently being investigated for attenuating inflammation in sepsis models (Table 1). The following studies emphasize the inherent anti-inflammatory abilities of empty biomaterials in ameliorating sepsis-induced pro-inflammatory cytokine release based on their physicochemical properties. Empty polymer nanoparticles, synthesized from poly(lactic-co-glycolic acid) (PLGA) and poly(lactic acid) (PLA), reduced TLR activation and subsequent pro-inflammatory cytokine release in an LPS-induced sepsis mouse model (Casey et al., 2019). Unloaded high-density lipoprotein nanoparticles targeted to VCAM-1 have been shown to inhibit leukocyte adhesion to activated endothelium, reducing proinflammatory cytokine release in an LPS-induced acute lung inflammation mouse model (Yu et al., 2022). Cargo-free liposomes developed from fish roe lipids similarly imparted anti-oxidant and anti-inflammatory effects in LPS-stimulated macrophages (Guedes et al., 2021). Similar in concept, eggshell membrane particles are under investigation for their anti-inflammatory properties, attributed to the proteins and carbohydrates they contain. In addition to reducing NF-κB activity and associated pro-inflammatory cytokines, these particles also increased anti-inflammatory cytokine interleukin-10 (IL-10) (Vuong et al., 2017). Other anti-inflammatory and antioxidant polymers that have demonstrated protection from LPS include N-acetylcysteine gels (Kim et al., 2021), graphene oxide-polypropylene nanoparticles (Fonticoli et al., 2023), and polyphenol gels (Luque et al., 2023), the latter two of which also have antibacterial benefits. In a cecal-puncture and ligation sepsis mouse model, dendrimers scavenged pro-inflammatory cytokines, resulting in a significantly improved survival rate of 100% (Shi et al., 2020). Bioactive glasses have also been examined for their anti-inflammatory and antibacterial potential (Nedelec et al., 2008). Mesoporous bioactive glass nanoparticles (MBGNPs) carrying cerium, an antioxidant, successfully demonstrated anti-inflammatory and antibacterial

TABLE 1 (*Continued*) Biomaterials for Altering Inflammation. The composition, preparation methods, sizes, charges, and investigated anti-inflammatory properties of synthetic biomaterials, cell-derived biomaterials, and combined synthetic and cell-derived biomaterials. PLGA: poly(lactic-co-glycolic acid); PLA: polylatic acid; NAC: N-acetylcysteine; TMOS: tetramethoxysilane; CTAB: cetyltrimethylammonium bromide; PVA: poly(vinyl alcohol); PEG: polyethylene glycol; DAMP: damage-associated molecular pattern; PAMP: pathogen-associated molecular pattern; i.p.: intraperitoneal; i.t.: intratracheal; i.n.: intranasal; p.o.: per os; MHV: mouse hepatitis virus.

	Material composition	Preparation method	Size	Charge	Model	Investigated properties	Reference
	PEG Telodendrimer	Solid-phase synthesis	25 nm–30 nm	Variable	BALB/c mice; cecal ligation and puncture (sepsis) RAW 264.7 macrophages; LPS-stimulated	LPS, cytokine, DAMP, and PAMP adsorption capability: NF-κB transcription factor activity Pro-inflammatory cytokine production Survival, hematology, and body temperature Selected protein adsorption	Shi et al. (2020)
	Loaded mesoporous bioactive glass nanoparticles	Microemulsion-assisted sol-gel condensation, template ion exchange	130 nm–150 nm		MC3T3-E1 preosteoblasts; RAW 264.7 macrophages; LPS-stimulated	Cytotoxicity Anti-inflammatory activity (via nitric oxide concentration) Antibacterial activity	Kurtuldu et al. (2021)
Cell-derived biomaterials	Dexamethasone-loaded macrophage-derived microvesicles	Ultracentrifugation	140 nm		C57BL/6 mice; LPS i.p. (sepsis) RAW 264.7 macrophages, primary glomerular endothelial cells from C57BL/6 mice; LPS-stimulated	NF-κB transcription factor activity Urine and serum enzymes, kidney morphology, collagen-deposition, and leukocyte infiltration Biodistribution Pro-inflammatory cytokine production Cell uptake	Tang et al. (2019)
	Piceatannol-loaded neutrophil-derived extracellular vesicles	Nitrogen cavitation	175 nm–200 nm	−15 to −20 mV	CD1 mice; LPS i.t. (acute lung inflammation) or i.p. (sepsis)	Interference with ICAM-1 endothelial cell expression: Endothelial cell targeting specificity Pro-inflammatory cytokine production Leukocyte infiltration, edema, and survival	Gao et al. (2017)
Synthetic and Cell-derived biomaterials	Gliclazide-loaded monocyte membrane covered PLGA	Extrusion	189.5 nm–292 nm	−10 to −34.1 mV	New Zealand white rabbits; 2% cholesterol (w/w) p.o. (atherosclerosis)	Hemolysis Toxicity Pro-inflammatory cytokine production Blood chemistry, histology, aortic plaque surface area, and macrophage infiltration	Karami et al. (2023)
	Lopinavir-loaded macrophage membrane covered PLGA	Sonication, ultracentrifugation	85.8 nm–102.2 nm	−12.4 to −42.4 mV	BALB/c mice; MHV i.n. (coronavirus) 293 T cells; S-pseudovirus	Pro-inflammatory cytokine production Leukocyte activation and NET formation Biodistribution Lung and liver targeting and accumulation Cytotoxicity Viral load	Tan et al. (2021)

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Material composition	Preparation method	Size	Charge	Model	Investigated properties	Reference
Dexamethasone-loaded macrophage-derived exosomes	Ultracentrifugation, electroporation	106.27 ± 11.40 nm	−34.80 ± 6.60 mV	DBA/1 mice; collagen-induced arthritis RAW 264.7 macrophages; LPS stimulated	Pro-inflammatory cytokine production Biodistribution Arthritis parameters (body weight, paw thickness, foot volume, bone density, trabecular thickness) Inflammatory cell infiltration	Yan et al. (2020)
Hexyl 5-aminolevulinate hydrochloride-loaded neutrophil apoptotic body membrane covered mesoporous silica nanoparticles	Centrifugation; hypotonic treatment; sonication; base-catalyzed sol-gel method	200 nm	−15 mV	Sprague Dawley rats; myocardial infarction	Heart targeting efficiency Cardiac function, fibrosis, infarct size Toxicity Macrophage infiltration	Bao et al. (2022)
Neutrophil membrane covered liposomes	Centrifugation; lipid film rehydration	143.6 ± 2.1 nm	−20.2 ± 0.8 mV	C57 mice; myocardial ischemia-reperfusion HUVECs, H9C2 cardiomyocytes, RAW 264.7 macrophages; hypoxia-reoxygenation	Pro-inflammatory cytokine production Apoptosis and proliferation Gene expression levels Neutrophil chemotaxis Biodistribution Cardiac function	Chen et al. (2022)
Microglial membrane covered flavin mononucleotide-coated human serum albumin nanoparticles	Sonication; extrusion	106 nm	−15 to −20 mV	C57BL/6J mice; LPS i.p. (Alzhimer's disease)	Pro-inflammatory cytokine production Blood brain barrier permeability Biodistribution Cognitive ability (open field test, Y-maze test, Morris Water Maze)	Zhang et al. (2023)

activity against both gram-positive and gram-negative bacteria in *in vitro* assays (Kurtuldu et al., 2021). Similarly, MBGNPs loaded with gallium exhibited antibacterial and hemostatic benefits *in vitro* (Kurtuldu et al., 2022). In general, synthetic biomaterials are the easiest drug delivery vehicles to produce and have high manufacturing consistency, but cell-derived biomaterials also offer their own advantages (Witwer and Wolfram, 2021).

2.2 Cell-derived biomaterials for inflammation

Cell-derived biomaterials, including extracellular vesicles and cell-derived products, are being investigated as drug delivery vehicles for their inherent biocompatibility (Table 1). Exosomes are an exciting group of extracellular vesicles known as "natural nanoparticles." Exosomes are particularly promising due to their cell membrane proteins and natural cargo of nucleic acids, proteins, and lipids, meaning exosomes display parent cell-specific targeting and functions (Popowski et al., 2020). These particles' biocompatible membranes are also able to avoid immune recognition and reduce

toxic effects (Lutz et al., 2021). Furthermore, exosome surfaces can be engineered to display ligands for improved targeting and controlled release and their cargo can be altered to carry pharmaceutical drugs (Lutz et al., 2019). In an LPS-induced sepsis mouse model, extracellular vesicles carrying a glucocorticoid reduced renal inflammation and fibrosis, and no side effects common with glucocorticoids were observed (Tang et al., 2019; Lasola et al., 2020). A significant challenge with extracellular vesicles are scaling up production to translating research findings to clinical doses. A potential solution being explored is nitrogen cavitation, which has shown promise by increasing extracellular vesicle production by 16-fold (Gao et al., 2017; Hahm et al., 2021; Ng et al., 2022). Additionally, extracellular vesicles generated using this method retained their ability to efficiently load drugs and deliver them effectively to reduce LPS-induced acute lung inflammation (Gao et al., 2017). Another cell-derived product is heparin, which is especially useful as a biomaterial for sepsis due to its antiviral activity and hemostatic properties (Kemp and Linhardt, 2010). Already, heparin has been found to reduce in-hospital mortality in septic patients by reducing inflammation and rescuing platelet counts over 28 days (Zou et al., 2022; Zhang Z et al., 2023).

Cell-based biomaterials are frequently examined in opposition to synthetic materials, for each type has its own advantages and disadvantages. After all, synthetic materials have more flexibility in terms of composition and designing the sizes and shapes for different applications. In contrast, modification of cell-derived materials are limited to certain sizes and shapes, such as 30–200 nm spherical exosomes (Gurung et al., 2021) or 7 µm discoid red blood cells (Muzykantov, 2013). Still, even with all the design options for synthetic materials, none have been shown to match the four-month lifespan of red blood cells in circulation (Chen et al., 2023). In terms of applications, synthetic materials have been found to provide better intracellular delivery (Muro et al., 2008), and in the context of sepsis, anti-inflammatory drug delivery to damaged tissues is critical. At the same time, red blood cells remain attractive for intravascular drug delivery in sepsis to deliver antithrombotic agents and cytokine inhibitors (Kolesnikova et al., 2013). Due to the unique advantages maintained by each type of biomaterial, research groups are investigating strategies to combine synthetic and cell-derived materials to produce more efficacious drug delivery systems.

One of the products of combined synthetic and cell-derived materials is the development of biomimetic nanoparticles (Table 1). These nanoparticles use membranes from platelets and other blood cells to encapsulate drug-carrying nanoparticles. Karami et al. investigated the ability of PLGA nanoparticles covered in monocyte membrane, carrying the anti-inflammasome drug Gliclazide, to reduce pro-inflammatory cytokine release in monocytes treated with LPS. They also found that in an atherosclerotic rabbit study, these "nanoghosts" shifted macrophages from a pro-inflammatory to anti-inflammatory phenotype and inhibited plaque development (Karami et al., 2023). Macrophage biomimetic nanoparticles have been studied as a therapeutic for COVID-19, which can progress into sepsis. These nanoparticles exhibited both anti-inflammatory and antiviral effects, ultimately resulting in improved survival in a mouse coronavirus model (Tan et al., 2021). However, further research in more relevant models is needed. While research into biomimetic materials specifically for sepsis-based inflammation is limited, many groups have demonstrated the potential of biomimetic nanoparticles for attenuating other inflammatory diseases, including osteoarthritis (Yan et al., 2020), myocardial infarction (Bao et al., 2022; Chen et al., 2022), and neuroinflammation (Zhang M et al., 2023), by suppressing pro-inflammatory cytokine secretion and enhancing the expression of anti-inflammatory cytokines.

2.3 Challenges for anti-inflammatory biomaterials

Despite the wide range of biomaterials investigated recently for controlling inflammation in sepsis, several obstacles persist in pre-clinical studies. Firstly, the models used for sepsis are too narrowly focused (Choi et al., 2023). Many studies rely on LPS-induced sepsis models and are limited to *in vitro* studies using monocytes and macrophages (Jin et al., 2019; Kong et al., 2019; Lee et al., 2020; Hemmingsen et al., 2021). Due to the extensive literature on the role of LPS in sepsis, it is obviously understandable to pursue investigations in an established model. However, sepsis can result from various infectious organisms, including viruses, fungi, and

parasites and it would be remiss not to broaden studies to include these. With the advent of SARS-CoV-2, several studies have investigated COVID-19-related sepsis, but more sepsis models from different causes remain to studied. Moreover, LPS is specific to gram-negative bacteria and does not account for the pathogenicity and different inflammatory pathways activated by gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) (Dickson and Lehmann, 2019). Even within bacterial species, different strains carry unique lipid A endotoxins, leading to varying interactions with cells and levels of toxicity (Dickson and Lehmann, 2019; Harm et al., 2019). Additionally, pre-clinical models often expose animals to their first infectious agents, while human sepsis patients must also combat opportunistic pathogens and underlying comorbidities. Another challenge is the need to shift research toward developing multitargeted biomaterials. Current strategies often focus on single-target approaches to minimalize side effects. However, sepsis is a complex disorder that affects multiple body systems and processes, necessitating a multitargeted solution.

3 Biomaterials for coagulopathy

One of the processes severely affected by sepsis is hemostasis. Under normal conditions, endothelial cells maintain an anticoagulant state and secrete platelet antagonists to prevent adhesion (Sloos et al., 2022). During sepsis or any inflammatory event, thrombosis is stimulated (Jackson et al., 2019). As previously noted, inflammation also activates the endothelial cells to increase their expression of adhesion proteins, thereby increasing the binding of neutrophils, monocytes, and platelets. Furthermore, the NETs released by neutrophils ensnare platelets as well as bacteria, promoting coagulation and clot formation. When injured, endothelial cells shift to a pro-coagulant state and secrete tissue factor, thrombin, and plasminogen activation inhibitor-1 (PAI-1) (Dudnick et al., 1991). The vasculature initially constricts, increasing platelet interactions with endothelial collagen (Cánovas-Cervera et al., 2023). The platelets activate and aggregate in a process known as primary hemostasis. Following, secondary hemostasis involves interactions between coagulation factors to stabilize the clot with fibrin formation (Raghunathan et al., 2022). In normal circumstances, once the damaged endothelium is repaired, the clot becomes subjected to fibrinolysis with tissue-plasminogen activator (tPA) converting inactive plasminogen to plasmin, which degrades and removes the clot. During sepsis, clot formation may be aberrant, resulting in clots that are either too weak to fulfill hemostasis or too strong to undergo lysis (Dudnick et al., 1991). Therefore, there is a need for biomaterials that can safely act on the endothelium to promote hemostasis and stimulate clot lysis as appropriate.

3.1 Hemostatic biomaterials

Currently, there are several pharmacologic treatments that are used to stabilize hemostasis, including desmopressin, aprotinin, and tranexamic acid. However, there is a need for drugs that directly promote hemostasis (Dudnick et al., 1991; Sloos et al., 2022). Another pro-hemostatic option is whole blood or platelet transfusions.

TABLE 2 Biomaterials for Coagulopathies. The composition, preparation methods, sizes, charges, and investigated hemostatic, anticoagulant, and fibrinolytic properties of biomaterials. pNIPAm: poly(N-isopropylacrylamide); AAC: acrylic acid; ULC: ultra-low crosslinked; DSPC: distearoylphosphatidylcholine; DSPE: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine; VBP: vWF binding peptide; CBP: collagen binding peptide; PAH: poly(allyamine hydrochloride); BSA: bovine serum albumin; FMP: fibrinogen-mimetic peptide; TDI: 2,4-toluene diisocyanate; TCP: thrombin-cleavable peptide; i.v.: intravenous.

	Material composition	Preparation method	Size	Charge	Model	Investigated properties	Reference
Hemostatic biomaterials	pNIPAm-AAc ULC microgel with fibrin antibody fragments	Precipitation polymerization, EDC/Sulfo-NHS chemistry	1 μm		Sprague Dawley rats; femoral vessel injury	Enhancement of fibrin and clot formation: Fibrin-binding capabilities Fibrin clot formation and collapse Clot structure Clot contraction and stability	Brown et al. (2014)
	pNIPAm-co-AAc ULC microgel with fibrin knob B mimicking peptide	Precipitation polymerization, EDC/Sulfo-NHS chemistry	150 nm–1 μm		C57BL/6 mice; liver laceration	Facilitate fibrin B:b knob:hole binding to enhance clot formation and contraction: Clot fiber density, stability, and retraction Clot polymerization and degradation rates Blood loss and fibrin deposition in a liver laceration model Biodistribution Hematology Complement activation	Nandi et al. (2021)
	DSPC-DSPE liposomes with phosphatidylserine ligands	Thin-film rehydration and extrusion	100 nm–150 nm		C57BL/6 mice; anti-CD42b-induced thrombocytopenia C57BL/6 mice; cardiac puncture Sprague Dawley rats; liver laceration	Enhance thrombin and fibrin generation: Plasmin-specific targeting Thrombin and fibrin generation Fibrin clot formation and stability Bleeding time and blood loss, survival, thrombosis, and clot lysis	Sekhon et al. (2022)
Hemostatic biomaterials	Thrombin-loaded DSPC Liposomes with VBP and CBP	Maleimide-thiol reaction	175 nm		C57BL/6 mice; tail-clip C57BL/6 mice; liver laceration	Bind vWF and collagen to release thrombin and enhance clotting: Platelet activation and aggregation NET formation Complement activation Fibrin generation Bleeding time and blood loss vWF and collagen binding specificity Endothelial cell activation Clot formation time and rate	Girish et al. (2022)
	Hyaluronic acid with VBP and CBP	EDC/Sulfo-NHS chemistry			BALB/c mice; tail vein laceration	Bind activated platelets and promote accumulation at sites of endothelial injury: Platelet binding specificity Platelet accumulation and aggregation Bleeding time and blood loss	Gao et al. (2020)

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	Material composition	Preparation method	Size	Charge	Model	Investigated properties	Reference
						Biodistribution Histology, hematology, and blood chemistry to assess toxicity Survival time	
	PAH and BSA with VBP, CBP, and FMP	Layer-by-layer	235 nm–240 nm	−16 to −25 mV	BALB/c mice; tail clip	Recruit activated platelets to sites of endothelial injury: Activated platelet and endothelium targeting specificity Shear-dependent aggregation Bleeding time Biodistribution Off-target microthrombi formation	Anselmo et al. (2014)
Anticoagulant biomaterials	Heparin and TDI	Interfacial polyaddition reaction with inverse miniemulsion	180 nm	−50 mV	HeLa cervix carcinoma cells, MCF-7 breast cancer cells, PC3 prostate cancer cells	Bind and activate ATIII: ATIII binding specificity Clotting time Cellular uptake	Baier et al. (2015)
	Heparin-coated colloidal mesoporous silica nanoparticles	Sol-gel synthesis	50 nm	−30 to −35 mV	*In vitro* assays	Bind and activate ATIII: ATIII binding specificity Heparin activity Coagulation time	Argyo et al. (2012)
	Hirudin and fibrin antibody fragment with factor Xa cross-linker	Cloning with M13 phage system			*In vitro* assays	Thrombin inhibition: Factor Xa-mediated hirudin release ATIII activity Clot size	Peter et al. (2000)
	Hirudin-loaded acrylamide and TCP nanogel with Clot-targeted peptide	One-pot synthesis, single emulsion polymerization	77 nm	Neutral	C57BL/6 mice; thromboplastin i.v. (pulmonary embolism) C57BL/6 mice; FeCl₃ topical (carotid arterial and mesenteric thrombosis)	Thrombin inhibition: Clot targeting TCP-mediated hirudin release Histology, collagen and fibrin deposition, survival, and bleeding time Hemolysis	Xu et al. (2020)
	Elastin-based protein micelles with GPIIb/IIIa antibodies	One pot transpeptidation with evolved sortase A	75 nm	−14 mV	C57BL/6J mice; laser-induced thrombosis	Thrombin inhibition: Clot targeting Platelet accumulation Thrombus formation	Kim et al. (2015)
	Serine Protease Inhibitor with GPIbα Antibody	Cloning			*Ex vivo* assays	Thrombin inhibition and interference with vWF binding: Thrombin and fibrin generation Platelet binding to vWF, agglutination, and aggregation ATP secretion	Sanrattana et al. (2022)

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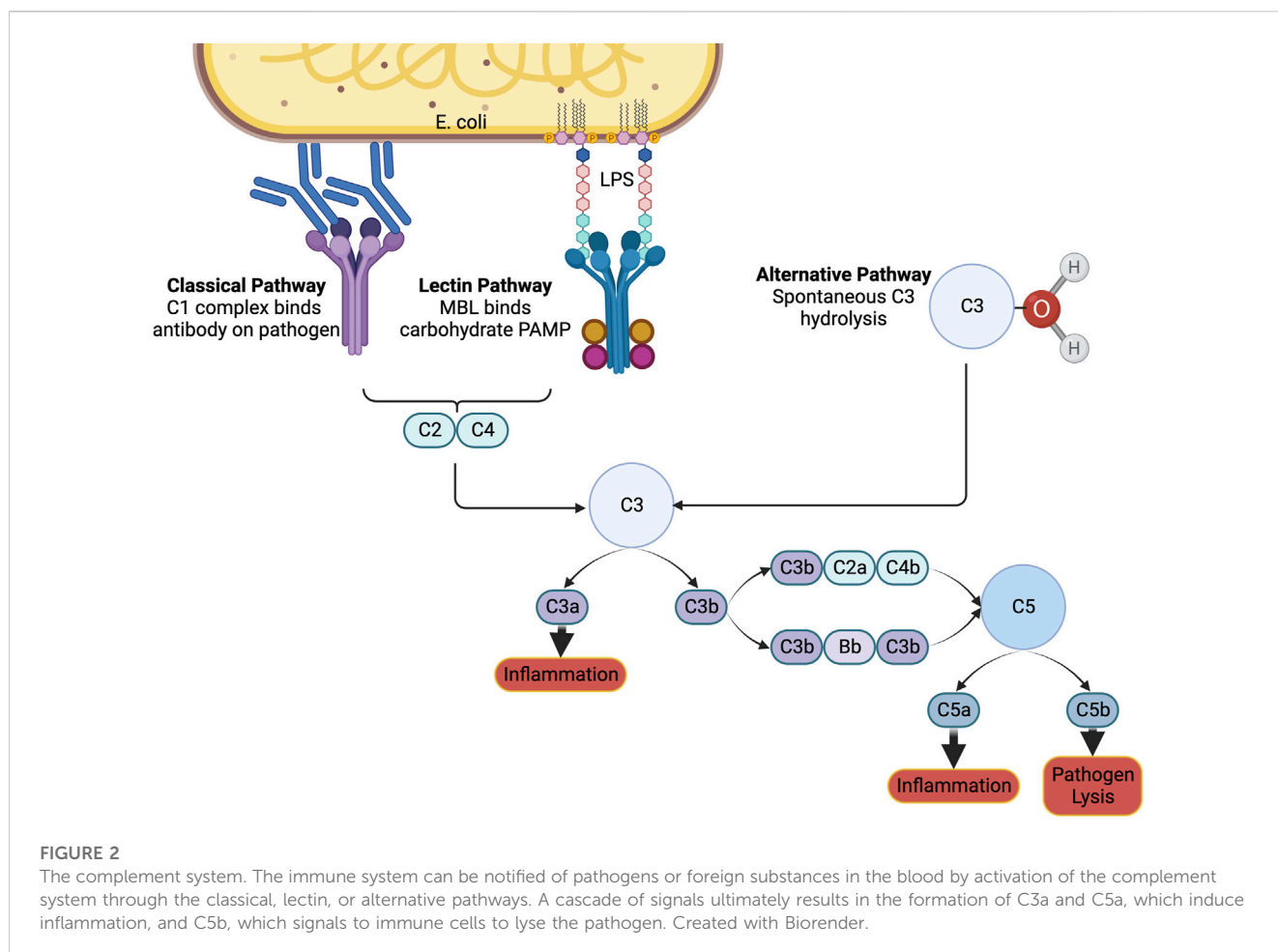|	Material composition	Preparation method	Size	Charge	Model	Investigated properties	Reference
	Hydroxychloroquine-loaded DSPE with P-selectin and neutrophil-elastase binding peptides	Thioether reaction, amide chemistry	200 nm		C57BL/6J mice; LPS i.v.	Inhibit neutrophil activation: Binding specificity to neutrophil-platelet complexes Circulation time Cytotoxicity NET formation Survival and thrombus weights in deep vein thrombosis model	Cruz et al. (2023)
Fibrinolytic biomaterials	Nattokinase-loaded polydopamine microspheres	Oxidative polymerization	>1 μm		*Ex vivo* assays	Fibrin degradation and plasmin generation: Activated platelet targeting Fibrinolysis Clotting time Platelet aggregation	Ye et al. (2018)

Unfortunately, this option is not always available due to donor shortages, high costs, and the risk of immunogenic reactions (Dudnick et al., 1991; Gao et al., 2020). Moreover, when available, platelets face a short storage life of only five to 7 days (Dudnick et al., 1991; Fernandez-Moure et al., 2018; Raghunathan et al., 2022; Gao et al., 2023). Lyophilization of blood products has been explored as a method to extend storage life and improve accessibility by enabling storage at higher temperatures. Lyo-protectants and cryo-protectants preserve platelet morphology and function. In several animal models, lyophilized platelets have been found to reduce bleeding time and blood loss (Cap and Perkins, 2011). Unfortunately, lyophilized platelets have been found to only last roughly 36 h in circulation before being cleared by macrophages, so while they may be useful in acute trauma, lyophilized platelets have limited use as a prophylactic (Raghunathan et al., 2022). Therefore, a branch of research has focused on developing biosynthetic blood cells, particularly platelet mimetics (Kelley et al., 2016). Some groups use platelet membranes to coat their nanoparticle surfaces, but as with extracellular vesicles, they face scale-up challenges. In this case, the lack of platelet availability from which to derive membranes was the primary obstacle (Raghunathan et al., 2022). To overcome the challenge of platelet membrane availability, some research groups coat nanoparticles with hemostatic proteins found on platelets, including fibrin knob B (Nandi et al., 2021), fibrin antibodies (Brown et al., 2014), phosphatidylserine (Sekhon et al., 2022), vWF-binding peptides, and collagen-binding peptides (Gao et al., 2020; Girish et al., 2022; Gao et al., 2023) (Table 2). These platelet-mimicking particles promote clotting, reduce blood loss, and decrease bleeding time in various models, including liver laceration, tail-clip injury, hemophilia, and human plasma from patients with coagulopathy.

3.2 Anticoagulant biomaterials

During systemic vascular injuries such as sepsis, blood clots can form and become lodged in the microvasculature, blocking blood flow, and causing ischemia. In clinical cases of thrombosis, anticoagulants are commonly administered. However, available anticoagulants have narrow therapeutic ranges and can interfere with hemostasis, posing a bleeding risk. As a result, the administration of anticoagulants, including heparin, antithrombin-III (ATIII), hirudin, activated protein C, thrombomodulin, and tissue factor pathway inhibitor, comes with a risk of bleeding, which can be equally life-threatening. Heparin is an attractive anticoagulant due to its binding with antithrombin-III, rending clots weak and easily lysed (Baier et al., 2015). Furthermore, heparin inhibits the complement system, thereby imparting "stealth" properties to nanoparticles hidden within and increasing blood circulation time (Argyo et al., 2012). Although studies have shown that heparin nanoparticles and heparin-coated nanoparticles increase clotting times, heparin carries a bleeding risk and also induces thrombocytopenia (Peter et al., 2000; Xu et al., 2020). Hirudin, a thrombin inhibitor independent of ATIII, is a potential heparin replacement. Hirudin can achieve anticoagulant activity without inducing thrombocytopenia and the magnitude of hirudin's effects is directly proportional to its dosage. In pulmonary embolism and arterial thrombosis mouse models, hirudin-loaded nanogels demonstrated clot-dependent release, inhibiting clot formation. Importantly, bleeding times were not significantly prolonged in tail-clip injuries (Xu et al., 2020). In these studies, the nanogels controlled hirudin release using thrombin-cleavable peptides.

Another approach to target active clot formation sites is to decorate delivery vehicles with antibodies or antibody-fragments specific to proteins expressed exclusively during endothelial injury. This method, nor its use in sepsis research, is new (Colman et al., 1988), but as understanding of sepsis and coagulopathy pathophysiology improves, novel targets and targeting ligands have recently developed. Polymeric micelles with a single-chain fragment variable antibody (scFv) that binds to GPIIb/IIIa, a glycoprotein receptor found only on activated platelets, accumulated at platelet-rich thrombi. When loaded with thrombomodulin, they effectively inhibited thrombus formation (W. Kim et al., 2015). Another strategy involved blocking platelet glycoproteins with an scFv to prevent
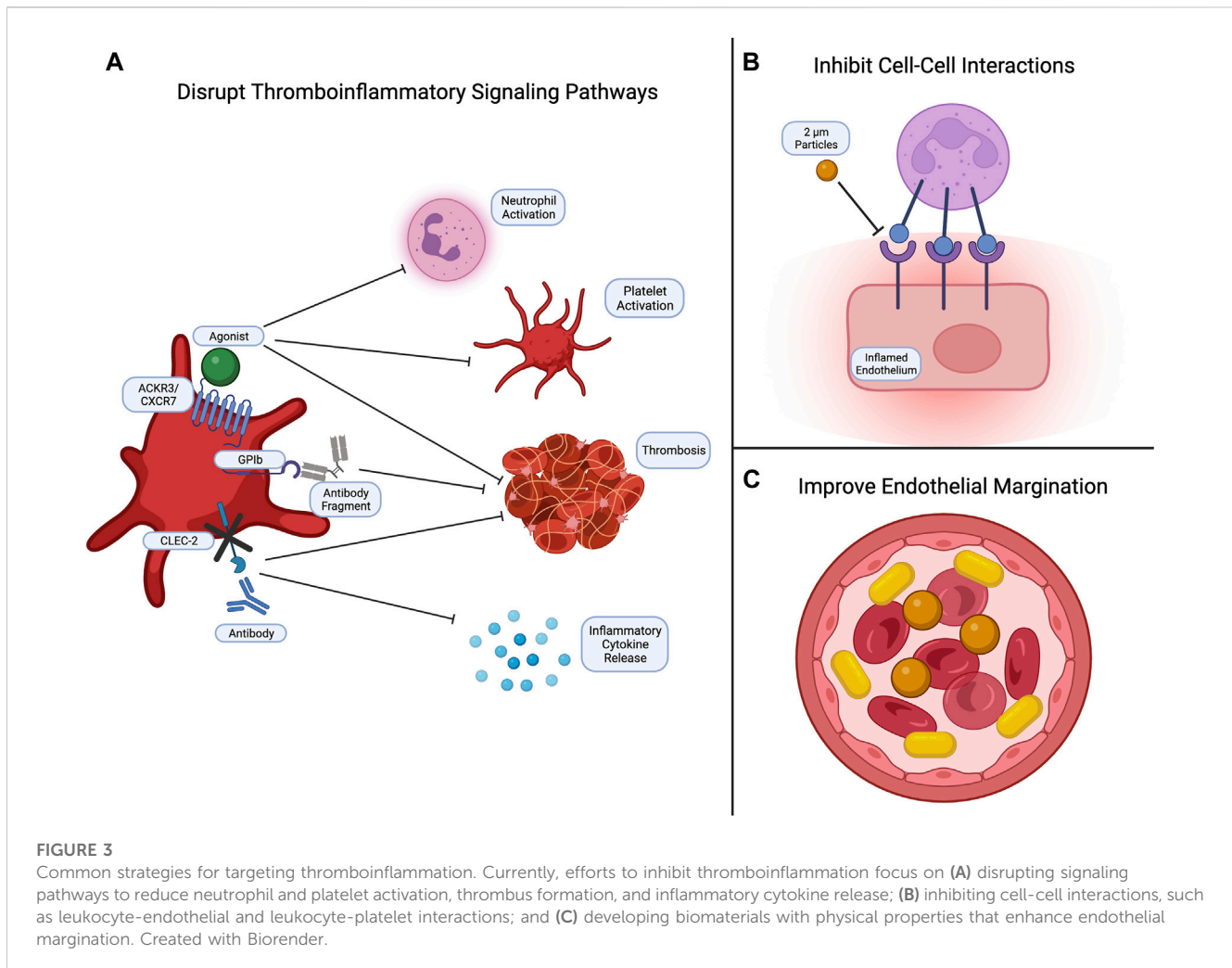
FIGURE 2
The complement system. The immune system can be notified of pathogens or foreign substances in the blood by activation of the complement system through the classical, lectin, or alternative pathways. A cascade of signals ultimately results in the formation of C3a and C5a, which induce inflammation, and C5b, which signals to immune cells to lyse the pathogen. Created with Biorender.

platelet interactions with thrombin and inhibit thrombus formation. Additional loading of an antithrombotic, an α1-antitrypsin variant, enhanced clot inhibition (Sanrattana et al., 2022). This particular set of studies is notable due to its multi-targeted strategy in both blocking platelet binding with scFv as well as inhibiting thrombin with the α1-antitrypsin variant. Following this multitargeted approach, a research group targeted clot formation from the trapping of activated platelets in NETs. This group developed nanoparticles with antibody fragments to selectively target and inhibit activated neutrophils from forming NETs. The nanoparticles were also loaded with hydroxychloroquine to inhibit platelet aggregation and adhesion, thereby inhibiting clot formation through two separate mechanisms (Cruz et al., 2023). Antibody fragments offer advantages such as avoiding cellular activation, minimizing immunogenicity, and binding with high specificity. However, it's important to note that while scFv-bound antithrombotic drugs localize at clots, their accessibility diminishes, potentially limiting their effectiveness and the ability to use lower dosages to reduce bleeding risk (Greineder et al., 2013).

3.3 Fibrinolytic biomaterials

Anticoagulants prevent thrombus formation, while fibrinolytics dissolve existing clots. The most common fibrinolytics are plasminogen activators, mainly tPA and urokinase. Unfortunately, as with anticoagulants, administration of plasminogen activators is associated with increased bleeding risk (Wang et al., 2020; Helms et al., 2023). Moreover, plasminogen activators are notorious for extremely short circulation times making their administration impractical in most cases. Delivery in a biomaterial vehicle can resolve both of these issues. Already, fusing tPA to PEG increases circulation time up to five times as long as naked tPA (M. Sun and Gupta, 2020) but doesn't affect tPA-induced hemorrhage (Greineder et al., 2013). When conjugated to an anti-fibrin antibody, tPA potency and selectivity improved, meaning further investigation is necessary to determine if a subclinical dose of tPA-bound anti-fibrin antibody could effectively dissolve clots and avoid bleeding (Runge et al., 1987). Thus far, delivery of subclinical tPA doses has yet to be examined, and this may be due to the discovery of nattokinase. Nattokinase, a plant-derived fibrinolytic with anti-inflammatory and antioxidant activities, directly degrades fibrin in clots without causing bleeding and inhibits platelet aggregation (Ye et al., 2018; Wu et al., 2020). Therefore, nattokinase overcomes the limitations of tPA without the need for additional modifications. Nattokinase is still a relatively novel fibrinolytic, so it is definitely a compound to keep an eye on as more studies examine its potential and establish its limits. As for urokinase, its clinical usage has thus far been limited to diagnosing sepsis and predicting prognosis based on blood level elevations of its receptor, soluble urokinase plasminogen activator receptor, correlating to disease severity (Sharma et al., 2020; Efat

FIGURE 3
Common strategies for targeting thromboinflammation. Currently, efforts to inhibit thromboinflammation focus on **(A)** disrupting signaling pathways to reduce neutrophil and platelet activation, thrombus formation, and inflammatory cytokine release; **(B)** inhibiting cell-cell interactions, such as leukocyte-endothelial and leukocyte-platelet interactions; and **(C)** developing biomaterials with physical properties that enhance endothelial margination. Created with Biorender.

et al., 2021; Ma et al., 2023). Urokinase is not widely used as a thrombolytic due to its markedly reduced specificity for fibrin and increased bleeding risk in comparison to tPA (Adivitiya and Khasa, 2017; Kadir and Bayraktutan, 2020).

3.4 Challenges for biomaterials targeting coagulopathies

Special considerations are necessary for biomaterials administered intravenously to ensure compatibility with blood. The complement system plays a role in immune surveillance and recognizes foreign materials and pathogens (Figure 2). It can be activated through three different pathways: the classical, the lectin, and the alternative pathways. Each of these pathways result in the production of anaphylatoxins C3a and C5a (Maisha et al., 2020; Maisha et al., 2021). Once generated, these anaphylatoxins can trigger allergic reactions, including histamine release and vasodilation. When trying to improve clotting, vasodilation is counter-effective by increasing blood flow and minimizing platelet interactions with the endothelium. In severe sepsis, anaphylatoxins are already generated (Landsem et al., 2022) and administering therapeutic biomaterials may actually worsen a patient's condition. It is crucial to conduct *in vitro* testing for cell lysis of blood cells, platelet

activation, plasma clotting, and C3a levels. Additionally, *in vivo* testing in an animal model with complement activation similar to that in humans is essential for anticipating adverse effects and advancing biomaterials (Harm et al., 2019; Maisha et al., 2020).

4 Biomaterials for thromboinflammation

As sepsis worsens, it can progress to thromboinflammation, which involves the inappropriate and unregulated formation of blood clots due to an extreme immune response (Banka et al., 2023). In more detail, inflammation activates the complement system and induces thrombosis (Vagionas et al., 2022). For example, activated neutrophils form neutrophil extracellular traps (NETs), which both activate platelets and entrap platelets, amplifying clot formation. Activated neutrophils also enhance platelet release from the bone marrow, contributing to thrombi formation (Petzold et al., 2022). In turn, activated platelets release pro-inflammatory signals, further increasing inflammation and injuring tissues in a pathologic cycle (Jackson et al., 2019; Senchenkova et al., 2019; Perrella et al., 2021). Thromboinflammation is a commonality in cardiovascular diseases, including atherosclerosis, COVID-19, and disseminated intravascular coagulation (DIC). In

TABLE 3 Biomaterials for Thromboinflammation. The composition, preparation methods, sizes, and investigated anti-thromboinflammatory properties of biomaterials. PEMA: poly(ethylene-co-maleic acid); PVA: polyvinyl alcohol.

Material composition	Preparation method	Size	Model	Investigated properties	Reference
PLGA-PEMA microparticles with E-selectin binding ligands	Emulsion-solvent evaporation	200 nm–4.5 μm	C57BL/6 mice; LPS i.p.	Interfere with leukocyte binding to platelets and endothelium: Leukocyte and platelet binding specificity Impaired cell binding to endothelium Biodistribution Neutrophil infiltration in LPS-induced sepsis model Liver toxicity	Banka et al. (2023)
tPA-loaded pNIPAm nanogels with fibrin antibody fragments	Precipitation polymerization, EDC/Sulfo-NHS chemistry	225 nm–275 nm	Sprague Dawley rats; LPS i.v. Sprague Dawley rats; LPS i.v. and liver laceration	Enhance clot maturation and promote existing clot lysis: Clot targeting Fibrinolysis Biodistribution Platelet count, fibrinogen and D-dimer concentration Clot formation and density Blood loss Clearance Toxicity via hematology and blood chemistry	Mihalko et al. (2021), (2022)
PLGA microspheres with E-selectin binding ligands and ICAM-1 antibodies	Co-solvent method	5.8 μm	In vitro assays	Leukocyte mimicking particles: Enhanced selectivity for inflamed endothelium Rolling and adhesion mimicry of leukocytes	Eniola and Hammer (2005)
PVA hydrogels with VCAM-1 and E-selectin antibodies	Precipitation polymerization, carbodiimide chemistry		Human umbilical vein endothelial cells	Greater binding retention to inflamed endothelium: Enhanced binding strength to activated endothelial cells	Rafat et al. (2012)

DIC, coagulation factors, platelets, and fibrinogen are consumed leading to the inappropriate formation of microthrombi and subsequent activation of fibrinolysis. Excessive platelet activation has been hypothesized to lead to platelet dysfunction and impaired response (Sloos et al., 2022). Clinically, this can present with prothrombotic and/or hemorrhagic phenotypes, resulting in contradictory treatment strategies. The concurrent ischemia, hemorrhage, and pro-inflammatory cytokines potentiate inflammation and injury, leading to multiple organ dysfunction syndrome (MODS). As expected, MODS is associated with a significantly worse prognosis (Helms et al., 2023). Therefore, there is an urgent need for the development of a single therapeutic that can simultaneously address inflammation, thrombosis, and hemorrhage.

To reduce thromboinflammation, studies have shown that cargo-free polystyrene microparticles can disrupt leukocyte adhesion to the endothelium in LPS models, emphasizing the importance in biomaterial physical characteristics (Banka et al., 2023) (Figure 3). Specifically, carriers with rod-like shapes and diameters between 2 and 5 microns demonstrate enhanced margination along the endothelium compared to spherical nanoparticles. This increased interaction with endothelial cells improves adhesion and targeting efficiency (Kelley et al., 2016; Van Der Meel et al., 2014; Y. Gao et al., 2020). At this moment, most studies focus on altering platelet signaling pathways involved in thromboinflammation by administering agonists or inhibitors. For example, increased expression of platelet chemokine receptor ACKR3/CXCR7 and administration of ACKR3/CXCR7 agonists reduced neutrophil activation, platelet activation, and thrombosis (Cebo et al., 2022). Another mechanism to reduce platelet-

lymphocyte interactions is to eliminate platelet glycoprotein GPIb binding abilities to neutrophils. This was found to inhibit downstream Sema7a signaling and subsequent thrombus formation (Gauer et al., 2022). Alternatively, inhibition of CLEC-2 signaling by knocking out platelet expression of CLEC-2 or administering antibodies was found to inhibit thrombosis, reduce the release of pro-inflammatory mediators, and limit the severity of sepsis-related symptoms in mice (Meng et al., 2021).

Thrombosis can also lead to acute ischemic stroke, which currently only has one FDA approved therapy: tPA. As previously discussed, tPA presents a significant bleeding risk (Beyer et al., 2022). To address this, our research group has designed fibrin-targeting nanogels that site-specifically deliver anti-clotting drugs while also enhancing fibrin-crosslinking and clot formation. When loaded with tPA, we found that our nanogels accomplished a dual function of targeting and dissolving existing clots while promoting clotting at sites of hemorrhage, eliminating the bleeding risk posed by tPA (Mihalko et al., 2021; Mihalko et al., 2022). Other investigations using fibrin-specific systems have been similar in loading anti-fibrin antibody nanoparticles with fibrinolytics (Marsh et al., 2011), while more others target thrombi by decorating liposomes with anti-fibrin protein binders (Petroková et al., 2019) and conjugating anti-fibrin antibodies directly to fibrinolytics (Peter et al., 2000; El-Sherbiny et al., 2014). Recognizing the complexity of thromboinflammation, other strategies involve targeting different cell types. Some research groups have explored multitargeting by using nanoparticles with

multiple ligands to interact with multiple cell types and receptors. This approach enhances the specificity of nanoparticle interactions, drug release sites, and reduces systemic side effects (Eniola and Hammer, 2005; Rafat et al., 2012; Anselmo et al., 2014) (Table 3).

5 Discussion

Sepsis continues to be associated with high mortality, despite decades of research. Until recently, treatments for sepsis focused solely on reducing inflammation. Now, researchers understand that the pathophysiology of sepsis is driven by a close interplay between inflammation and hemostasis, termed "thromboinflammation" – a term first introduced only 25 years ago. As more information about thromboinflammation emerges, biomaterials continue to be the most promising solution for addressing thromboinflammation and treating sepsis. However, challenges remain in developing a single biomaterial that can effectively control inflammation, endothelial damage, and coagulopathy. Further examination and identification of the advantages of synthetic biomaterials and cell-derived biomaterials is necessary. Incorporating elements from each type of biomaterial appears effective in developing biomaterials that have improved blood circulation times and endothelial margination. Moreover, biomaterials have thus far been largely designed to target specific cell interactions, either reducing pro-inflammatory cytokines or preventing inappropriate thrombus formation separately. Recognizing the complexity of sepsis pathology and developing a multifunctional biomaterial is required to produce an effective therapy for this deadly disease.

Author contributions

HL: Conceptualization, Visualization, Writing–original draft, Writing–review and editing. AB: Funding acquisition, Project administration, Resources, Supervision, Writing–review and editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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