REVIEW ARTICLE

Sepsis diagnosis and treatment using nanomaterials

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Abstract

Sepsis is a life-threatening reaction that occurs when the body's severe response to an infection damages the host's own tissues. Sepsis has been globally recognized as a fatal disease. Rapid treatment of sepsis requires prompt identification, administering antibiotics, careful hemodynamic support, and treating the cause of the infection. Clinical outcomes of sepsis depend on early diagnosis and appropriate treatment. Unfortunately, current sepsis diagnosis and treatment, such as polymerase chain reaction-based assay, blood culture assay, and antibiotic therapy, are ineffective; consequently, sepsis-related mortality remains high and increases antimicrobial resistance. To overcome this challenge, nanotechnology, which involves engineering at a nanoscale, is used for diagnosing and treating sepsis. Preclinical models have shown protective effects and potential utility in managing septic shock. Furthermore, nanotechnology treatments based on diverse materials result in the effective treatment of sepsis, improving the survival rate. In this review, we present an overview of the recent research advancements in nanotechnology to diagnose and treat sepsis with a brief introduction to sepsis.

Keywords Sepsis · Infection · Nanotechnology · Diagnosis · Treatment

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1 Introduction

Sepsis is defined as a condition in which the body's dramatic response to an infection from bacteria, viruses, parasites, or fungi results in damage to healthy tissues. Sepsis is a clinical syndrome leading to organ dysfunction caused by a dysregulated host immune response to infection (2016) [1]. If left unchecked, it can progress to septic shock, a severe condition that occurs when blood pressure drops and organs shut down [2]. Sepsis is a major global health priority contributing to high mortality. It often triggers various symptoms, including high fever, elevated heart rate, and fast breathing, leading to severe organ problems and even death [3]. Every year, approximately 31.5 million sepsis cases are reported worldwide, of which about 5.3 million die annually due to a mortality rate as high as 30% [4]. Consequently, sepsis remains a considerably severe problem. Recently, coronavirus SARS-CoV-2, the cause of COVID-19, has been closely related to sepsis. Most SARS-CoV-2-infected patients show immune dysregulation, hyperinflammatory response, and alterations in coagulation that further contribute to sepsis [5]. SARS-CoV-2 related sepsis has potential crosstalk with neutrophil extracellular traps (NETs), which comprise extracellular DNA decorated with histones and antimicrobial proteins. NETs are released due to inflammation. The process

of NET formation by a neutrophil is called NETosis. The process plays a role in controlling pathogens but has a detrimental effect on cardiovascular and pulmonary health [6]. Intravascular NETosis in COVID-19 infection could play a role in vasculature complications, where thrombotic disease can drive organ damage. This phenomenon is known to cause complications leading to sepsis. Severe sepsis patients are associated with devastating complications to acute respiratory distress syndrome (ARDS) with an increased risk of vascular hyperpermeability, pneumonia, sepsis, and ultimately death [7].

Sepsis occurs through various mechanisms. It is a clinical disease with biological, biochemical, and physiological abnormalities caused by an immune system dysfunction (Fig. 1). Sepsis is characterized by systemic inflammatory response syndrome (SIRS), microcirculatory derangements, and multiple organ dysfunction [8]. Infection is initiated by immune cells recognizing pathogen or damage-associated molecular patterns (PAMPs/DAMPs) [9, 10]. When pathogens are invaded, the complement system, an innate immune system, is activated [11]. Neutrophils migrate to the infection site, and the endothelial cells present at the site of inflammation are expressed as adherent molecules on their surface. Other immature immune cells such as monocytes are differentiated into macrophages in situ, releasing pro-inflammatory cytokines [12]. These pro-inflammatory cytokines were strictly regulated, and homeostasis is restored

after recovering tissue injuries [12–14]. Tissues far from the initial infection show symptoms of inflammation, including vasodilation, increased microvascular permeability, and leukocyte accumulation [15]. Although inflammation is an essential host response, the onset and progression centers of sepsis upon a "dysregulation" of the typical response, usually with an increase in both pro-inflammatory and anti-inflammatory mediators called a cytokine storm, initiating a chain of events that leads to widespread tissue injury [8, 16]. According to a recent study, the body's response to the endotoxin is characterized by releasing cytokines and other inflammatory mediators, leading to a generalized inflammatory response. Mononuclear and endothelial cells activated by the endotoxin induce platelet-activating factors, and coagulation proteases induce additional pro-inflammatory stimuli [17]. The mutual reinforcement of inflammatory and coagulation cascades leads to tissue damage and eventual septic shock [18]. Another study described that the SIRS is characterized by excessive production of pro-inflammatory mediators [19]. The compensatory anti-inflammatory response (hyperinflammatory status) syndrome (CARS) progressively suppresses this early response [20].

Conventional diagnosis of sepsis requires microbiological cultures from blood or urine for the detection of sepsis markers. Microbiological cultures offer helpful information; however, there is a limit for long incubation times, making them unsuitable for rapid diagnostics.
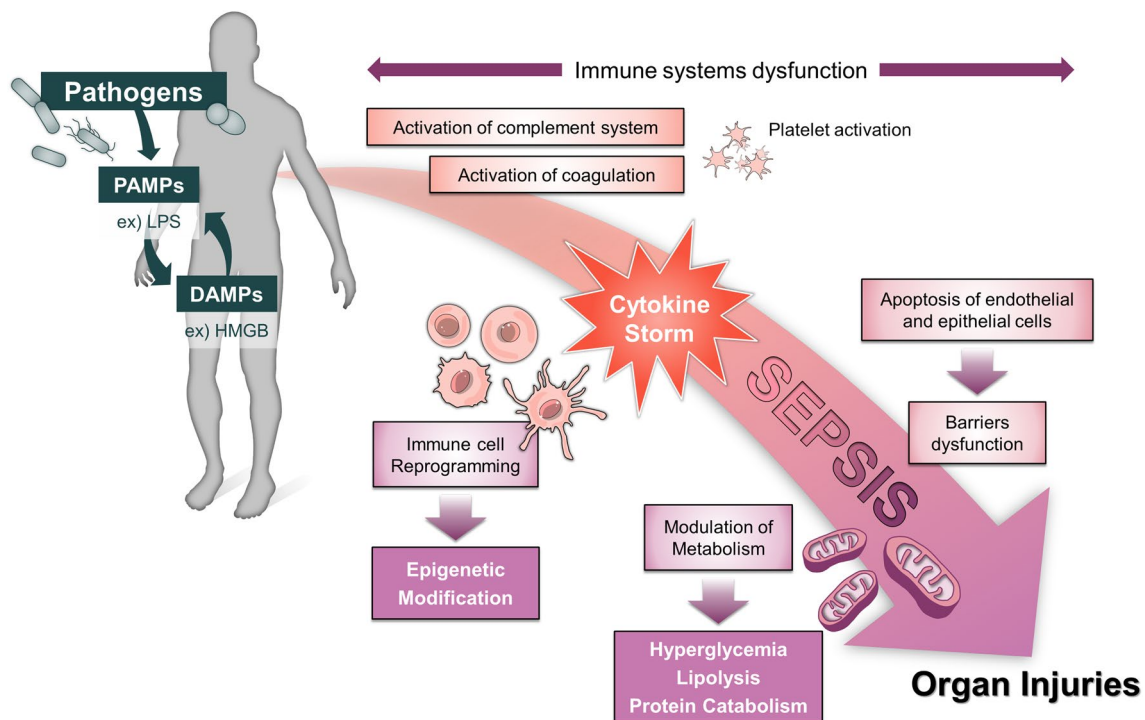

Fig. 1 Schematic illustration of the sepsis players and pathophysiological events occurring in sepsis. Copyright 2020 EMBO Molecular Medicine. Reproduced with permission ref. 10

The polymerase chain reaction (PCR) system is an established technique that offers high sensitivity, reproducibility and multiplies DNA sequences found within biofluids by several orders of magnitude to allow detection of target pathogen DNA sequences. However, there are technical limitations to using PCR. The potential for high laboratory analytical sensitivity and high risk of sample contamination could produce false-positive results due to amplifying contaminant DNA. Commonly available contrast agents and biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) may be used to facilitate the detection of proteins and nucleic acids. However, CRP and PCT have low specificity for diagnosing sepsis in patients with co-developing sepsis episodes and are not a reliable indicator of prognosis and systemic inflammation [21, 22].

Sepsis therapies focus on early recognition, treatment of infection, fluid and metabolic resuscitation, and end-organ support, including mechanical ventilation and stabilization of hemodynamics [23, 24]. Sepsis is a condition caused by bacterial infections. Therefore, it is treated with antibiotics [25]. Information about the type of bacteria that caused sepsis and the progression of the condition can significantly affect the patient's survival. Various treatments such as infection control, immune modulation, and metabolic support are performed [26, 27]. However, due to the complicated sepsis pathology, the successful delivery of antibiotics to the target site is generally not achieved; consequently, the drug's pharmacokinetics change to an extent lower than that before sepsis [28]. In addition, because of the toxicity of the antibiotic, the blood vessels are damaged, and intestinal microorganisms are destroyed [29, 30]. Although the prognosis of sepsis treatment is achieved through antibiotic treatment, antibiotic-resistant sepsis might occur due to other types of bacteria or specific groups of microorganisms [31]. Hence, advanced sepsis diagnostic platforms and therapeutic strategies are urgently required for improving clinical outcomes and reducing mortality. Nanotechnology has been widely used in the biomedical field, especially as a means of diagnosis and treatment of various diseases such as sepsis [22]. Nanotechnology has been also widely used and developed as a drug delivery technology that increases the treatment efficiency of various diseases in the body because it can be injected via a intravenous injection [28]. These applications may suggest promising solutions for more accurate diagnosis and treatment tools for sepsis. Significant studies in the last three years have raised the potential of powerful nanotechnology for the efficient diagnosis and treatment of sepsis (Fig. 2). In this review, we summarized the cases of applying nanotechnology to the diagnosis and treatment of sepsis.
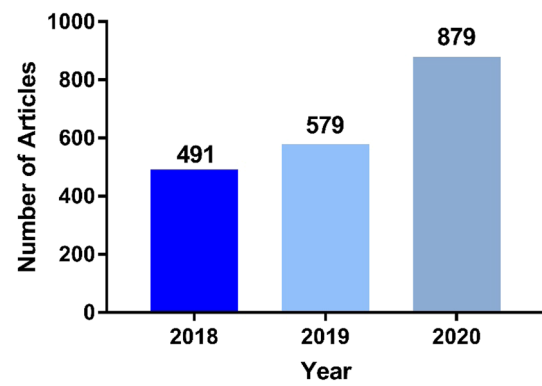

Fig. 2 Distribution of published articles for sepsis-related nanotechnology (2018–2020)

2 Nanotechnology for sepsis diagnosis

Diagnosing sepsis in early-stage patients is challenging because the onset of clinical signs and symptoms is not specific. In addition, proteins for diagnosis have low concentrations in body fluids and have long incubation periods, making it difficult to detect blood probes. Thus, diagnosis depends on clinical manifestations and blood tests for detecting inflammation response-related blood biomarkers such as CRP and PCT. A progressive decline in CRP or PCT concentrations can be used to inform decisions on the early discontinuation of antibiotic therapy without significant risks. However, increasing CRP concentration in the first two days of therapy suggests that antibiotic therapy may be ineffective and needs reevaluation. Using PCT concentration in an antibiotic escalation strategy is not sufficient because it results in worse outcomes. Thus, clinical decisions should not be based on the concentration of a single biomarker [22].

Conventional methods require medically trained personnel and a multi-step analysis, making them time-consuming and costly. Instrumentation of such methods is not compliant with minimization, and such methods are laboratory-based. Several nanoscale platforms have been proposed as a potential carrier to improve sepsis recognition (Fig. 3).

The employment of nanoparticles (NPs) for diagnostic and therapeutic purposes offers excellent potential due to their regulatory properties (e.g., size, shape, surface chemistry, charge, and composition) and their capacity for surface functionalization (with ligands, antibodies, and targeting molecules), allowing targeted and selective binding [32]. To improve the biodistribution of existing therapeutics, nanotechnology drug delivery systems can be engineered by improving the drug's bioavailability, efficacy, and stability at the target site [33]. Research on nanoscale strategies for addressing the prominent disruption associated with sepsis has been conducted according to these possibilities. Several NPs have been investigated to allow the diagnosis
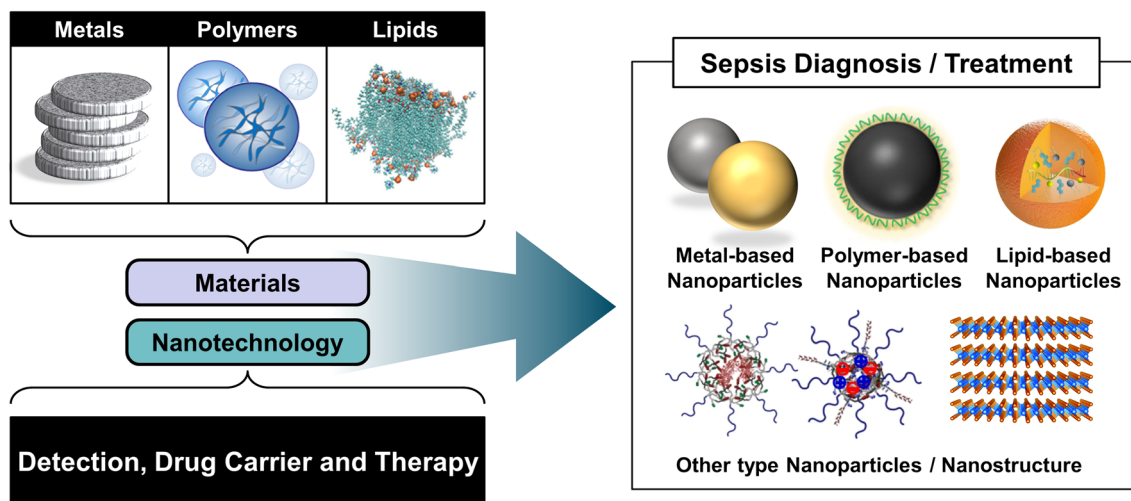
Fig. 3 Several biomaterial-based nanotechnologies for sepsis diagnosis and treatment. Reproduced with permission ref. 56. Copyright 2020 Advanced Science. Reproduced with permission ref. 59. Copyright 2020 Nature Communication. Reproduced with permission ref. 68. Copyright 2020 International Journal of Molecular Sciences

of sepsis-related microbial infections such as magnetic NPs (MNPs), gold NPs (AuNPs), fluorescent NPs (silica and quantum dots QDs), and lipid-based NPs in addition to technologies such as lab on a chip, point of care (POC), biosensor in the development of accurate, fast and sensitive methods for sepsis detection [34]. Portable biosensors comprise an electrical detection system, and a disposable kit for blood processing can take IL-3 on magnetic beads and label it for the electrochemical reaction [35]. Detectors have been developed to measure electrical currents for IL-3 quantification. Biosensors applying NPs or other beads for diagnosing sepsis have been widely published.

NPs, defined as a particle of having a size range from 1 and 100 nm in diameter, have been proposed as carriers of sepsis diagnostics and treatments. Small-molecule drugs possess undesirable side effects and undergo rapid renal clearance and reduce residence time due to the spread throughout the body. NPs adjusting size and surface characterization have a longer circulation half-life and differential biodistribution profile than their free drug [36]. Nanotechnology has shown that high sensitivity, specificity, and complex diagnosis can meet these demands. However, the unique characteristics of NPs vary depending on what material it is made of. Currently, metal-based NPs such as gold or magnetic NPs are widely used for diagnosing sepsis (Fig. 4-1). They show promising results by being grafted into biosensors and POC technology (Table 1). In particular, AuNPs and AgNPs have unique optical and biochemical characteristics depending on the size and concentration of the NPs.

The AuNPs have been widely used as nanotechnology for theranostic application because of their biochemical advantages that offer precise control over physicochemical and optical properties. It showed multifunctional characterization in imaging, surface modification, and therapeutics and is biocompatible. AuNPs can be combined with liposomes or polymeric NPs that deliver a drug or large construct for high and efficient delivery and enhanced targeting properties [37]. Because of the gold NPs' optical, physical, and chemical properties, selective and specific identification of DNA/RNA sequences related to pathogens are possible. One example is that the bio-barcode assay is developed to detect protein and nucleic acid targets more sensitively. Bio-barcode detection technology using AuNPs is fast and straightforward in detecting small molecules; it is also cost-effective [38]. The surface of AuNPs and the convenience and synthesis of DNA/RNA molecules, proteins, and other biomolecules serve as an optimal tool for testing target molecules. A study showed that gold NPs can help detect sepsis diagnostic markers, owing to the NP's higher sensitivity and quicker detection time [39]. Imaging-based plasmonic biosensing technology, which uses AuNPs, can be enhanced using gold nanohole arrays (Au-NHAs), which leads to a high sensitivity for protein detection and enhancement in single analyte resolution. The proposed method was implemented using a sandwich immunoassay measurement to detect clinical biomarkers of acute inflammatory diseases. This biosensing NP approach enables detecting 10 pg/mL of biotinylated bovine serum albumin (bBSA) and 27 pg/mL CRP [40]. This result was at least four orders of magnitude lower than the clinically relevant concentrations, making it a critical and fast approach paired with the large-area plasmonic sensor chips [40].

Another study demonstrated sensitive and rapid detection of pathogenic bacteria with POC microbial sensing based

on AuNPs modified with azide and alkyne functional molecules. Exogenous Cu^{2+} was first captured and reduced to Cu^+ by pathogenic bacteria from detected samples, where Cu^+ subsequently acts as a catalyst to trigger the click reaction between the azide- and alkyne-AuNPs. These results in the NPs were aggregating, causing the solution to change color from red to blue. Based on this color change of the AuNP solution, POC detection of pathogenic bacteria can be obtained easily and quickly by simple observation, i.e., the color changing of the AuNPs solution [41]. This result showed outstanding potential for the early diagnosis of bacterial infections.

MNPs are also common in diagnostic medicine because they can be used in various ways through surface modification and separation by magnets. They suggested a nanosystem based on iron oxide MNPs functionalized with chlorin e6 molecules and bacterial species-identifiable aptamers (Fe_3O_4-Ce6-Apt), reported for early diagnosis of sepsis. It has a comparable detection sensitivity; however, it significantly reduces the time required for diagnosis, revealing a significant potential for early sepsis diagnosis in clinical settings. In sepsis diagnosis, species identification and bacterial enrichment are two critical works because of the co-existence of giant blood cells and proteins in the early stages of sepsis and the low concentration of bacteria (about 10–100 cells per mL) bloodstream. Fe_3O_4-Ce6-Apt nanosystem, a novel strategy, can simultaneously achieve blood bacterial species identification and magnetic enrichment in a single step. Furthermore, Fe_3O_4-Ce6-Apt nanosystem could easily detect enriched bacteria with the assistance of fluorescence microscopic determination [42].

Diagnostic technology using nanobead demonstrates impressive results. Markers for diagnosing sepsis include CRP, PCT, and IL-6. A recent study generally demonstrated that the PCT levels in healthy human serum are shallow and undetectable via standard methods; however, serum PCT concentration increases rapidly (> 100 ng/mL) in response to pro-inflammatory stimulation severe infections like sepsis. They proposed an efficient homogeneous immunoassay for precisely detecting PCT for the early diagnosis of sepsis based on luminescent oxygen channeling assay technology, called AlphaLISA technology. They demonstrated that the novel PCT detection technique had developed a high sensitivity and yielded accurate results within a short period. It will be helpful for the prognosis and early screening of diagnosis for sepsis patients [43].

3 Nanotechnology for sepsis treatment

Recently, several NP systems have demonstrated excellent treating effects against sepsis in preclinical models, suggesting their potential efficacy in managing sepsis and septic shock. As antibacterial agents, NP systems can provide platforms to immobilize endotoxin adsorbents, interact with inflammatory cells to restore homeostasis, and detect sepsis biomarkers promptly [45]. However, even simply administering the drug tends to distribute it throughout the body, causing undesirable systemic effects or reducing the drug's circulation time. In limited conditions, the kidneys or macrophages (renal clearance, phagocytosis) rapidly remove the drugs from the body [46]. Several NP platforms have been proposed as potential carriers of anti-sepsis therapies owing to the unique properties of NPs, such as their small size, surface functionalization, and pharmacokinetic/biodistribution profiles [47]. NP systems can be easily surface-modified and conjugate with various molecules to their surface. This increased the circulation time in the body by preventing it from being removed by other immune cells, enabling the release of the drug-loaded inside using substances to target specific cells, inflammatory sites, and proteins [48, 49].

The progress of novel therapy of sepsis critically depends on the understanding of sepsis-related physiological mechanisms. Sepsis pathology comprises highly complicated and integrated responses, including activation of multiple cell types, inflammatory agents, and hemostatic systems [14]. During sepsis, lipopolysaccharide (LPS) was engaged with endothelium's toll-like receptor 4 (TLR4) or several inflammatory mediators (IL-6, TNF-α, IL-1, kinins, and C5a) interact with their receptors. Therefore, the endothelium was activated, and later the sepsis cascade may be conditioned by other surrounding factors (hypoxia, low blood flow, temperature change, homeostasis imbalance, and hyperglycemia). The interaction of extracellular mediators with their receptors leads to the activation of downstream signaling pathways like mitogen-activated protein kinase (MAPK) and protein kinase C (PKC), which can promote posttranscriptional changes in cell function or alter gene expression profiles through several transcription factors, including NF-κB [50].

The overexpression of cell adhesion molecules in endothelium surfaces, such as E-selectin, P-selectin, Intracellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1), can elevate the adhesion, rolling, and transmigration of circulating leukocytes. Leukocyte-endothelial interactions further modulate the phenotype of these cells. During the activation process, nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) may induce the formation of reactive oxygen species (ROS), releasing nitric oxide (NO), and increase the cell permeability. Based on this fact, it is possible to treat sepsis through various strategies such as targeting the inflammatory region using TNF-α and ICAM-1 or controlling the body's ROS level with NP manufacturing technology [51]. The NPs that proved effective for sepsis treatment are sorted by their physicochemical properties and size (Table 2).
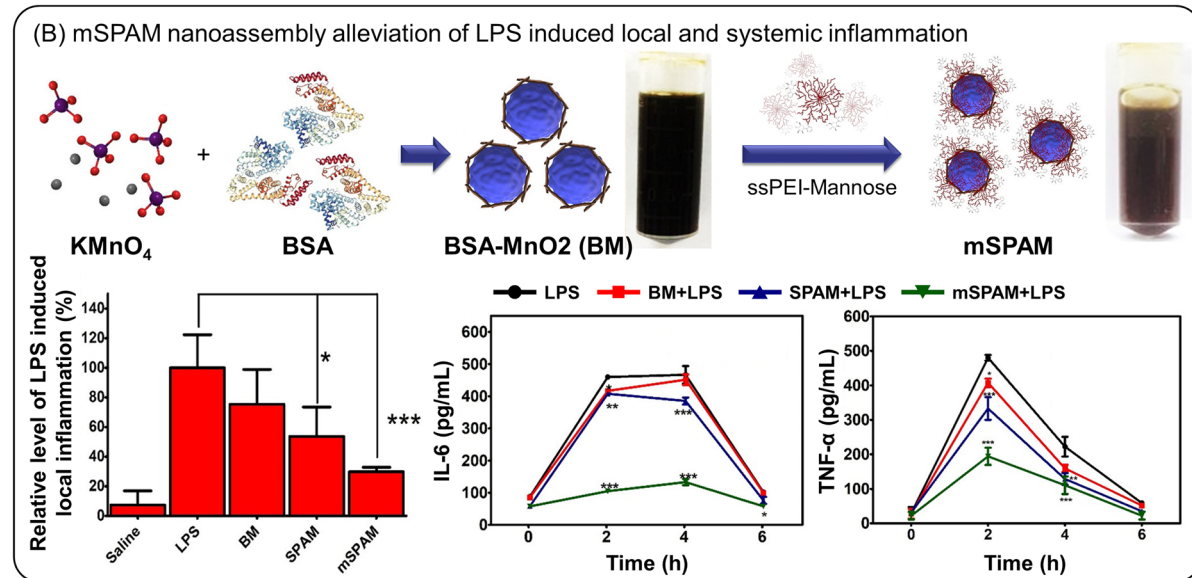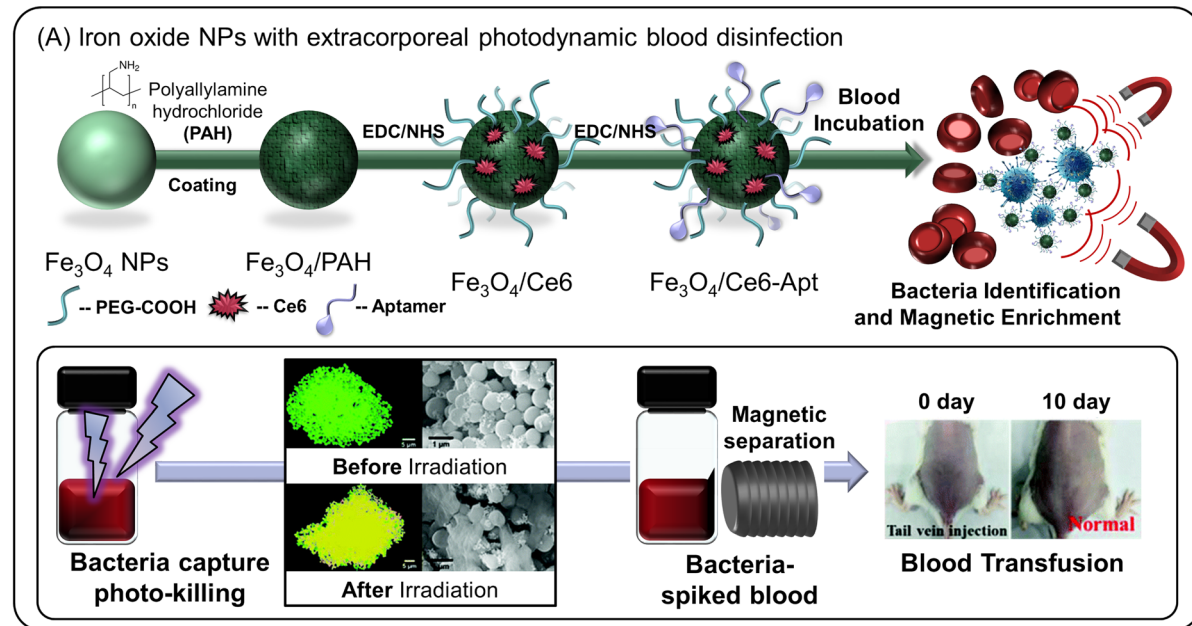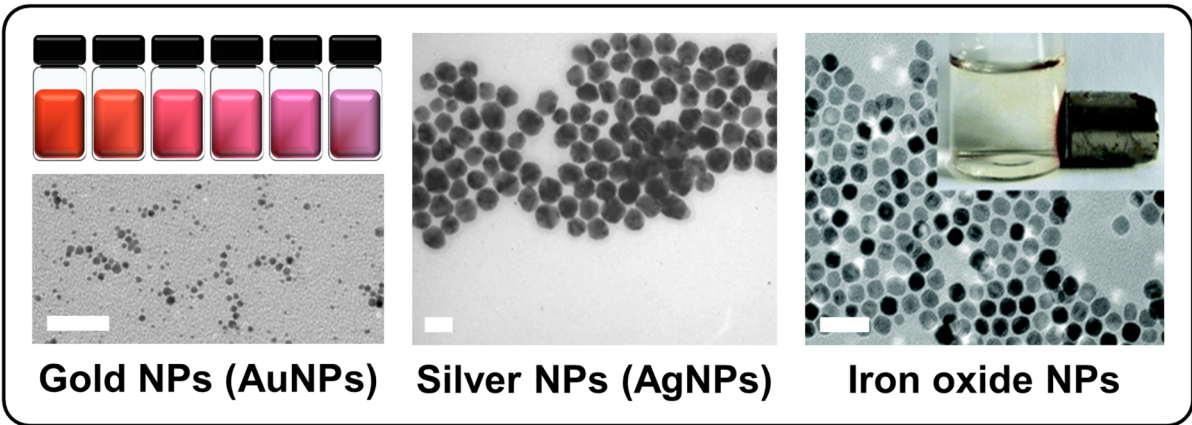
Gold NPs (AuNPs)   **Silver NPs (AgNPs)**   **Iron oxide NPs**

(A) Iron oxide NPs with extracorporeal photodynamic blood disinfection

Polyallylamine hydrochloride (PAH)

Coating   EDC/NHS   EDC/NHS   Blood Incubation

Fe_3O_4 NPs Fe_3O_4/PAH Fe_3O_4/Ce6 Fe_3O_4/Ce6-Apt

-- PEG-COOH   -- Ce6   -- Aptamer

Bacteria Identification and Magnetic Enrichment

Before Irradiation

After Irradiation

Bacteria capture photo-killing

Magnetic separation

Bacteria-spiked blood

0 day   10 day

Tail vein injection   Normal

Blood Transfusion

(B) mSPAM nanoassembly alleviation of LPS induced local and systemic inflammation

$KMnO_4$ +   BSA   BSA-MnO2 (BM)   ssPEI-Mannose   mSPAM

Relative level of LPS induced local inflammation (%): Saline, LPS, BM, SPAM, mSPAM (*, ***)

IL-6 (pg/mL) vs Time (h); TNF-α (pg/mL) vs Time (h)

Legend: LPS, BM+LPS, SPAM+LPS, mSPAM+LPS

◄**Fig. 4** 1 Several types of metal-based NPs. Gold NPs (AuNPs), silver NPs (AgNPs), iron oxide NPs (Fe_3O_4), and SPIONs. (scale bar: 50 nm). 2 Metal-based NP with sepsis treatment. **A** Fe_3O_4/Ce6-Apt nanosystem identifies the sepsis-induced bacteria capable of early sepsis diagnosis. Bacteria-infected blood was treated with photoirradiation, and bacteria capturing NPs were separated by magnetic force. **B** mSPAM nanoassembly system synthesized by BSA-MnO_2 complex could reduce inflammation in the LPS-induced sepsis model. It was reproduced with permission from ref. 54. Copyright 2018 American Chemical Society

3.1 Metal-based nanoparticle

In recent years, metallic NPs in different medical applications, such as bioimaging, biosensors, target/sustained drug delivery, hyperthermia, and photoablation therapy, have received significant interest. Metal NPs are prepared from metal-based precursors; they can be synthesized by chemical, electrochemical, or photochemical methods. In chemical methods, the metal NPs are obtained by reducing the metal-ion precursors in the solution by chemical reducing agents [34]. These can adsorb small molecules and have high surface energy. In particular, AuNP/AgNPs were known to have antimicrobial effects. Several approaches incorporated these advantageous features of NP systems for preventing and treating sepsis [61].

AuNPs were demonstrated as an adjuvant therapeutic agent in one of the studies, with a proper antibiotic, attenuated cecal ligation, and puncture (CLP)-induced bacterial sepsis in mice [52]. AuNPs have a potential antibiotic effect and elicit the macrophage function toward the anti-inflammatory responses. In this study, the weak antibiotic effect of AuNP results of *Escherichia coli* (*E. coli)* colony reduction was demonstrated. In addition, AuNP increased M2 macrophages (CD206$^+$F4/80$^+$ cells) with IL-10 and decreased inflammatory cytokines (TNF-α, IL-6, IL-1β) in vivo sepsis model [52]. Another study employed 4,6-diamino-2-pyrimidinethiol (DAPT) with AuNPs (D-Au NPs) to treat a bacterial infection induced by *E. coli* in gut. D-Au NPs recovered the gut intestinal microflora more effectively than levofloxacin without side effects from bacterial infections in mice models. D-Au NPs elevated the relative abundance of specific probiotics and protected the gut microbiome; thus, they were non-toxicity in the liver and kidney [62]. Furthermore, the AgNPs were utilized as antimicrobial materials to a gram-positive and negative bacterial infected model. It explained the clinical effect of combining with ultrasound that does not elicit systemic toxic effect [63].

MNPs, along with AuNPs and AgNPs were applied to a sepsis treatment model through various surface functionalization to evaluate their efficacy. As shown in Fig. 4-2A, surface-modified iron-oxide NPs, which are suggested as a nanosystem for early sepsis diagnosis and complete extracorporeal blood disinfection, conjugate with chlorin

e6 molecules and bacterial species-identifiable aptamers (Fe_3O_4-Ce6-Apt). The Fe_3O_4-Ce6-Apt nanosystem-based strategy has high sensitivity and requires a short diagnosis turnaround time; thus, it has great potential for early sepsis diagnosis in clinical settings. Moreover, it benefitted from the strong bacteria capture effect of the Fe_3O_4-Ce6-Apt nanosystem, achieving complete extracorporeal blood disinfection without transfusion adverse reactions.

Another type of MNPs, superparamagnetic iron oxide NPs (SPIONs), were known as tiny size (~ under 20 nm), capable of controllable and biocompatible iron oxide NPs. It has led to their numerous biomedical applications: magnetic resonance imaging (MRI) and imaging, hyperthermia for cancer treatment, drug delivery, biosensor systems, magnetic separation immunoassays, parasite diagnostic assays, nano bridges substances for surgery, wound healing, and cell labeling [64, 65]. SPIONs provided higher magnetic liability to the surrounding magnetic field than other paramagnetic materials. SPIONs have attracted attention in recent years as a nanomedicine, owing to their antibacterial properties. In this context, SPION was reported to activate anti-tumor therapeutic potential by inducing pro-inflammatory macrophage polarization [66]. This idea was further investigated, and a mechanism that promotes the production of IL-10 in macrophages, leading to inhibition of inflammation in LPS-induced sepsis and liver injury, was proposed [53].

In other work, a mannosylated disulfide cross-linked polyethyleneimine (ssPEI-Mannose)-coated bovine serum albumin-reduced MnO_2 (BSA-MnO_2) was developed (mSPAM), and a nano-assembly was formed to control the H_2O_2 levels, an extremely toxic ROS, in LPS-induced systemic and local inflammation mice model [54]. As shown in Fig. 4-2B, the LPS induced inflammation signal was lower in the mSPAM group than in other groups except for the saline group. mSPAM nano-assembly demonstrated efficient anti-inflammatory activities to treat LPS-induced endotoxemia; compared to other groups, the level of IL-6 and TNF-α reduced until 4 h and 2 h, respectively [54].

3.2 Polymer-based nanoparticle

Polymeric NP drug delivery systems are highly biodegradable and biocompatible. The polymeric NPs can specific targeting, protection of drug molecules, ability to combine therapy and imaging, controlled release, and surface functionalization through diverse precursors [67, 68]. The encapsulation of cytotoxic chemotherapeutic agents in biodegradable PLGA NPs may offer advantages over other delivery systems. The addition of poly(ethylene glycol) to NP surfaces (PEGylation) was known as a strategy to increase circulation time by opsonization, inhibiting nonspecific protein adsorption and subsequent clearance [69].

Table 1 Nanotechnology for sepsis diagnosis

Agents	Target molecules	Technique	Results	Refs.
AuNPs, MNPs	Target DNA	Colorimetric detection	Detection by naked eyes and metabolic activity assessment of pathogens	[38]
AuNPs	CRP	Sandwich Immunoassay	27 pg/ml of CRP detection within 2 h	[40]
AuNPs	Cu^{2+}/NDH-2	Colorimetric detection	*E. coli* detection with high sensitivity (40 CFU/mL)	[41]
MNPs	Lipopolysaccharide (LPS), Endotoxin	Magnetic separation	Rapid, high accuracy of *E. coli* / *S. aureus* (6–12 CFU) without blood culture	[42]
Nanobead	PCT	AlphaLISA	Hypersensitive (18.6 pg/ml)	[43]
AgNPs	LPS	Colorimetric method	5 nM of LPS detection from urine sample within 5 min	[44]
Magnetic bead	IL-3 in the blood fluid	Electrochemical reaction	Sensitivity < 10 pg/ml (10 times more sensitive)	[35]

Table 2 Nanotechnology for sepsis treatment

	Agents	Size (nm)	Target	Technique	Refs.
Metal-based	AuNPs	21	M2 macrophages	AuNPs own antibiotics effect (only in vitro test)	[52]
	Fe_3O_4-Ce6-Apt	17	Bacterial colony (live/death)	Magnetic enrichment for capturing blood disinfection	[42]
	SPION	6.5	Liver-resident macrophages	Increasing IL-10 and attenuate organ damage by autophagy	[53]
	mSPAM	97	Intracellular levels of H_2O_2	Suppression of HIF-1α-mediated NF-κB activation	[54]
Polymer-based	Atv/PTP-TCeria NPs	8	ROS level in kidney	ROS downregulation drug delivery (atorvastatin)	[48]
	CIP-NPs-Abs	120	Infectious microenvironments (I-CAM1)	Co-delivery of antibiotics and anti-inflammatory cytokine	[55]
	DNase-I pMNSs	170	NETosis by Neutrophils	Delivery of DNase-I	[56]
Lipid-based	V_CLNPs	127–174	AMP-Cathepsin B macrophage	Delivery of AMP with CatB mRNA	[47]
	M-Lipo	200	LPS in the blood fluid	Absorption of LPS and endotoxin	[57]
	Leukosome	94	Macrophages	Cytokine control: reduce the pro-inflammatory genes (IL-6, IL-1b, and TNF-α) regulation and increase anti-inflammatory ones (IL-10 and TGF-β)	[58]
Others	TMD	–	ROS and RNS	Scavenging activity and sustainability for H_2O_2, $O_2\cdot-$, OH·	[59]
	TD-NT	–	Pro-inflammatory cytokine, DAMP and PAMP	Charge-dependent (negative) size exclusive (~ 50 kDa)	[60]

In Fig. 5A, a ROS-responsive nano-drug delivery system was designed by combining mitochondria-targeting ceria NPs with atorvastatin for sepsis-induced acute kidney injury (AKI). mPEG-TK-PLGA (PTP) coating significantly improves the biocompatibility and mono-dispersity while prolonging the half-life in the bloodstream. Moreover, it allows NPs to load and release drugs appropriately. Loading atorvastatin (Atv) could help reduced the dosage of ceria NPs and increased the therapeutic effect. The pro-inflammatory cytokine, IL-6, and TNF-α, demonstrated reduced inflammatory effect and TUNEL assay; the apoptosis cell was lower than AKI groups. TCeria NPs would target mitochondria through triphenylphosphine (TPP)-derived activity to eliminate excessive ROS effectively; the PTP coating and Atv loading demonstrated enhanced anti-inflammatory effect [48].

Other types of polymer-based NPs suggest the co-delivery of an antibiotic and anti-inflammatory agent to the injection site; this may be a novel strategy for sepsis therapy because it may concurrently prevent bacterial dissemination and manage inflammation. It designed a novel micelle-structured NP conjugated with an ICAM-1 antibody to target bacterial infectious sites (Fig. 5B). The NPs are co-loaded with ciprofloxacin (CIP) and the anti-inflammatory agent (2-[(aminocarbonyl)amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide, TPCA-1) proved helpful in managing

sepsis provoked by a lethal dose of *Pseudomonas aeruginosa* in a mouse model of peritonitis. Co-delivery of CIP and TPCA-1 loaded NPs with anti-ICAM-1 groups demonstrated the highest survival rate compared to other groups, showing 90% survival. The IL-6 and TNF-α also decreased in CIP/TPCA-1 NPs with anti-ICAM-1, meaning anti-inflammatory effects in bacteria-induced sepsis [55].

In addition, recent studies reported that COVID-19 is associated with neutrophil-specific plasma membrane burst, which releases immoderate NETs and extracellular DNAs (eDNAs). Advanced stages of COVID-19 have exhibited a hyper-inflammatory state, known as a 'cytokine storm', along with sepsis and acute respiratory distress syndrome (ARDS) [70]. A recently published paper proposed the demonstration of DNase-I-coated melanin-like nanospheres (DNase-I pMNSs) for modulation of sepsis-associated NETosis dysregulation (Fig. 5C). Polydopamine-based DNase-I pMNSs have a structure similar to squid ink and melanin. DNase-I was readily attached to the NPs' surface using the excellent adhesive properties of polydopamine. Therapeutic delivery of a DNase-I pMNSs suppressed the eDNA, thereby alleviating sepsis progression in severe COVID-19 patients. This was also confirmed in a CLP-operated septic mouse model. DNase-I pMNSs demonstrated 40% survival rate for the CLP-operated septic mice for over 132 h leading to the full recovery of these mice. It is a promising bioinspired vehicle and demonstrates a potential new strategy for SARS-CoV-2-induced sepsis therapy [56].

3.3 Lipid-based nanoparticle

Lipid-based nanoformulations exist in various types, such as nano-emulsions, liposomes, and solid lipid NPs (SLNs) frequently applied to transport antibiotics in sepsis. Lipid NPs are advantageous for drug delivery to target cells because they can smoothly merge (endocytosis) with other cell membranes and deliver the loaded antibiotics directly to the target cell cytoplasm. As a carrier, lipid NPs can prolong circulation time and accelerate cellular uptake, countering therapeutic resistance [71]. Lipid nanocarriers, such as nanostructured lipid carriers (NLCs) and nanoemulsions, appear suitable as drug-carrier systems due to their very low cytotoxicity relative to polymeric NPs [72]. As drug carriers, lipid NP releasing mRNA and siRNA have application during sepsis therapy [73].

In this regard, Hou's work aimed to express two substances in macrophages, the antimicrobial peptide (AMP) and cathepsin-B (CatB), which are lethal to sepsis-induced bacteria (Fig. 6A). Vitamin C lipid NPs (V_CLNPs) loaded AMP-CatB mRNA treated to macrophage, and adoptive transfer macrophages (MACs) can be proved its efficacy for treating multidrug-resistant bacteria-induced sepsis in mice. After screening with MACs, the blood colony-forming unit (CFU) scale was dramatically descended in MACs-RAW264.7 groups with intraperitoneal (i.p.) and intravenous (i.v.) treatment. In addition, the survival rate was shown in i.p. and i.v. injected MACs-RAW264.7, approximately 58%, and mouse body weight also increase in MACs-RAWs (i.p. + i.v.) group. Thus, due to the AMP and CatB in macrophages, V_CLNPs with mRNA delivery reduce the sepsis-induced bacteria and improve the survival rate, which is the primary strategy for curing patients with sepsis [47].
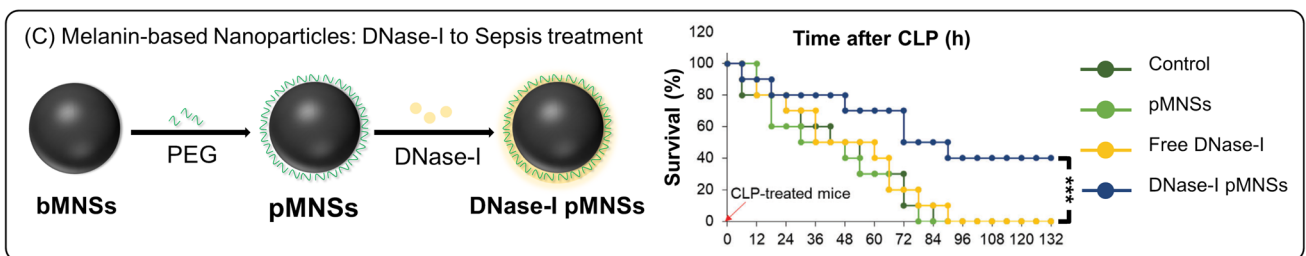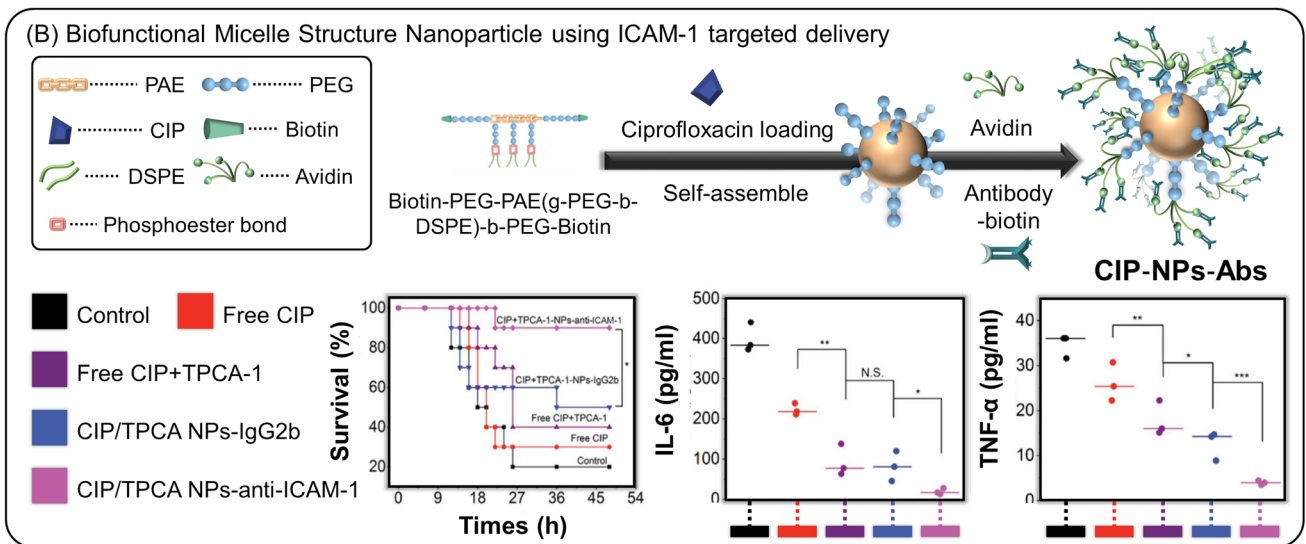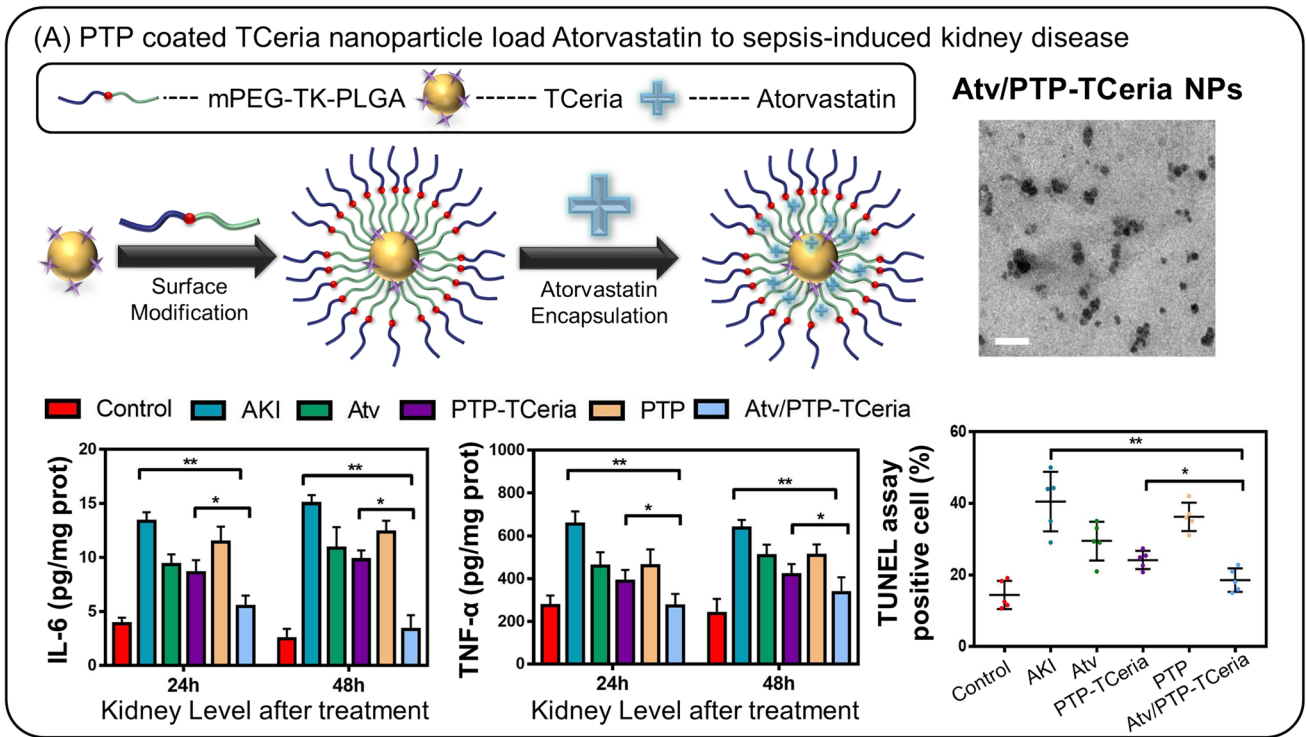
Biomimetic liposome, a macrophage membrane component mixed with an artificial PEGylated lipid, could stabilize the natural membrane and prolong the circulation in the bloodstream. In Fig. 6B, M-Lipo was synthesized by two membranes that could complement one another and extend their bio function as they integrate. M-Lipo had surface proteins similar to those of macrophages and could substantially adsorb LPS. With assistance from the PEGylated lipids, M-Lipo demonstrated much better stability than the only macrophage membrane (M-membrane) vesicle. In addition, the pharmacokinetic results revealed that M-Lipo had longer retention in blood than the natural M-membrane. By combining these properties, the hybrid M-Lipo reduced the toxicity of LPS in vitro and protected the mouse against endotoxic shock in vivo. Post-injection of M-Lipo in sepsis mice demonstrated ~ 44% of survival rate after 24 h. M-Lipo also reduced the inflammatory cytokine level, IL-6, and TNF-α, compared to other LPS injected groups. In the histologic analysis, the hepatocytes of LPS treated groups showed partial necrosis (red arrow), but M-Lipo improved LPS-induced liver damage in mice, similar to the non-LPS treating control group [57].

Another team investigated this idea, which evaluated the role of macrophage-derived biomimetic NPs, named leukosomes, in an LPS-mediated murine sepsis model. They demonstrated the interplay of leukosomes with macrophages induced downregulation of pro-inflammatory genes (IL-6, IL-1β, and TNF-α), expression of anti-inflammatory ones (IL-10 and TGF-β), which indirectly elicit an anti-inflammatory response on the endothelial cells. These results showed that the leukosome-mediated inflammatory response regulation in target cells serves as a bioactive nanotherapeutic [58].

3.4 Other nanomaterials

NPs are widely known as the most-applicable nanotechnology; it was categorized with different types depending on their particle size, morphology, and physical and chemical properties. Those NP systems with sepsis treatment were based on several materials such as carbon, ceramic, or semiconductor instead of metal, polymeric, and lipid-based NPs [32].

Besides the NP systems, other nanotechnologies have also been reported in the literature aimed at sepsis treatment. One

(A) PTP coated TCeria nanoparticle load Atorvastatin to sepsis-induced kidney disease

---- mPEG-TK-PLGA   ------ TCeria   ------ Atorvastatin

Atv/PTP-TCeria NPs

Surface Modification

Atorvastatin Encapsulation

Control   AKI   Atv   PTP-TCeria   PTP   Atv/PTP-TCeria

IL-6 (pg/mg prot)

Kidney Level after treatment

TNF-α (pg/mg prot)

Kidney Level after treatment

TUNEL assay positive cell (%)

(B) Biofunctional Micelle Structure Nanoparticle using ICAM-1 targeted delivery

----- PAE   ----- PEG
----- CIP   ----- Biotin
----- DSPE   ----- Avidin
----- Phosphoester bond

Biotin-PEG-PAE(g-PEG-b-DSPE)-b-PEG-Biotin

Ciprofloxacin loading
Self-assemble

Avidin
Antibody-biotin

CIP-NPs-Abs

Control   Free CIP

Free CIP+TPCA-1

CIP/TPCA NPs-IgG2b

CIP/TPCA NPs-anti-ICAM-1

Survival (%)

Times (h)

IL-6 (pg/ml)

TNF-α (pg/ml)

(C) Melanin-based Nanoparticles: DNase-I to Sepsis treatment

Time after CLP (h)

Survival (%)

bMNSs   PEG   pMNSs   DNase-I   DNase-I pMNSs

Control
pMNSs
Free DNase-I
DNase-I pMNSs

CLP-treated mice

of the studies reports a telodendrimer (TD) nanotrap (NT) to capture cytokines. DAMPs and PAMPs by multivalent, hybrid, and synergistic interactions [59]. The flexible TD

scaffold freely changed its conformation by itself and bound with inflammatory mediators effectively. The broad range of inflammatory mediators was combined through multivalent

◄Fig. 5 Polymer-based NPs with sepsis treatment. **A** ROS-responsive nanodrug delivery system was designed using triphenylphosphine (TPP)-modified Ceria NPs coated with mPEG-TK-PLGA polymer; loading atorvastatin could increase the therapeutic effect of sepsis-induced acute kidney disease. **B** CIP-TPCA NPs coated with ICAM-1 antibody to target infectious microenvironments have clinical potential in infectious disease and reduce systemic inflammation. **C** DNase-I pMNSs have the potential of sepsis treatment suggesting the highest survival rate compared to other groups in CLP-treated sepsis mice. It was reproduced with permission from ref. 56. Copyright 2020 Advanced Science

hydrophobic and electrostatic interaction. This study demonstrated a 100% survival rate of severe in vivo sepsis murine models using optimized TD NT combined with a moderate antibiotic therapy by attenuating hyper inflammation and infection [59].

In a more specific study, the therapeutic efficacy of the 2D shape of transition-metal dichalcogenides (TMD) nanosheets served as an antioxidant through effective scavenging of mitochondrial and intracellular ROS and reactive nitrogen species (RNS) for sepsis treatment. This strategy demonstrated that the therapeutic efficacy of nanosheets significantly reduced the secretion of inflammatory cytokines in the cells, whereas anti-inflammatory cytokine and ROS-producing enzymes were not affected and manifested in severe CLP-induced bacteremia mouse models [60]

4 Conclusion

Sepsis, a dysregulated systemic inflammatory response caused by drug-resistant pathogens, is a major global health issue. Nanotechnology has contributed numerous nanomedicines ever since its inception, including possible treatments for sepsis. In particular, nanotechnology significantly improved the existing challenge of low diagnostic sensitivity, which was considered a disadvantage in diagnosing and treating sepsis. This has significantly contributed to the early diagnosis of sepsis and was directly linked to the improvement of patient survival. In addition, NP technology based on various materials could control the systemic immune response, the most significant challenge in sepsis. Thus, it has established itself as a technology that compensates for the existing shortcomings, such as improving drugs' targetability.

Despite the advancement in nanotechnology, considerable research is required before it can be used in actual treatments. First, nano-based technology requires the utilization of diverse nanomaterials, but most of these nanomaterials have not been approved as pharmaceutically acceptable adjuvants by the FDA. Second, the use of therapeutic and diagnostic nano-based technologies in clinical applications is not yet accepted due to the lack of clinical assessments in terms of long-term safety and biocompatibility. Therefore, clinical evaluation and further optimization of nanotechnologies are imperative. Finally, the detailed mechanisms of sepsis are still unknown. If additional sepsis mechanisms are revealed utilizing advanced nanotechnology, we can expect that the survival rate can increase through early diagnosis and more diverse treatment strategies. Thus, nanotechnology in the diagnosis and therapy of sepsis has ongoing challenges demanding collaborative research with multidisciplinary fields. Furthermore, it is possible to develop an advanced nano-based platform that can be used to treat other infectious diseases.
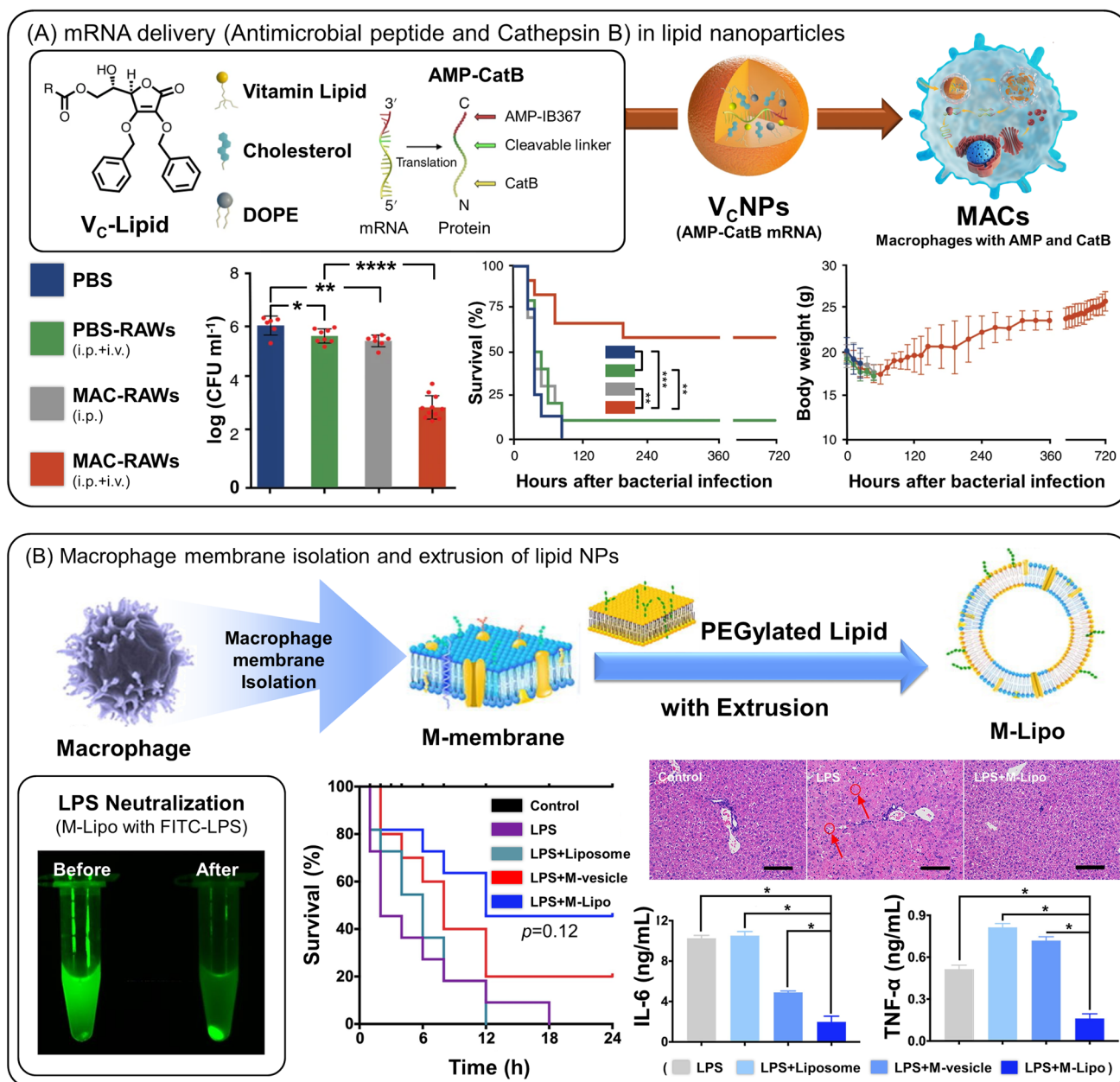
Fig. 6 Lipid-based NPs with sepsis treatment. **A** MACs comprising vitamin C lipid NPs that deliver antimicrobial peptide and cathepsin B (AMP-CatB) mRNA beneficially improved the bacterial-induced sepsis model's survival rate. **B** The hybrid liposome, M-Lipo, devel- oped by fusing M-membrane with PEGylated lipids, has advantages in treating sepsis. (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, ****: $p < 0.0001$)

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

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