REVIEW

Immunomodulatory biomaterials against bacterial infections: Progress, challenges, and future perspectives

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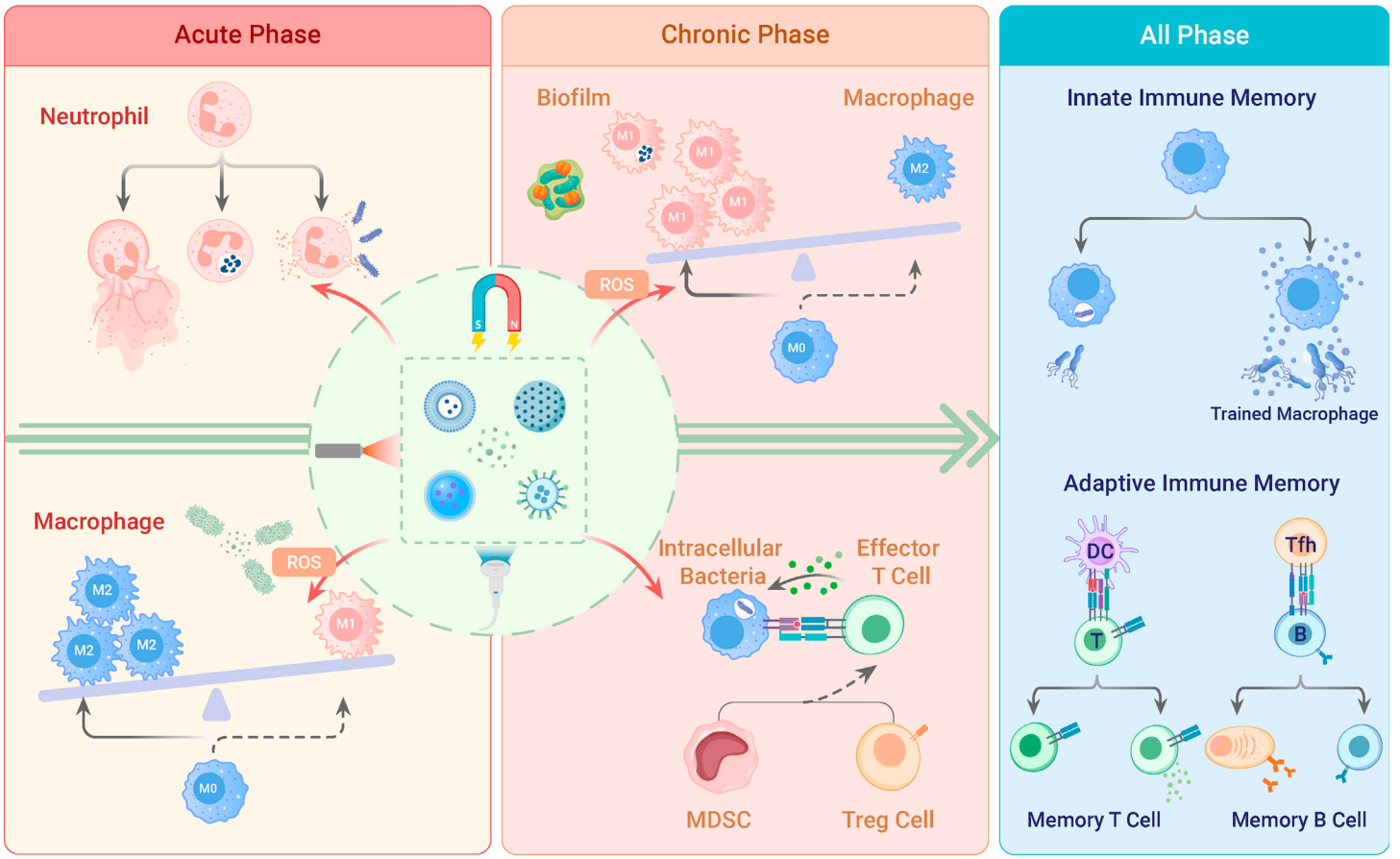
Received: May 12, 2023; Accepted: August 24, 2023; Published Online: August 28, 2023; https://doi.org/10.1016/j.xinn.2023.100503

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Insights into the intricate facets of the immune microenvironment hold the key to pioneering clinical strategies in combatting bacterial infections.
- The design principles for antimicrobial biomaterials vary depending on the immune microenvironment at different stages of infection.
- Immunomodulatory biomaterials display robust antimicrobial efficacy and vaccine attributes in animals and clinical trials, promising for intractable infections.

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Received: May 12, 2023; Accepted: August 24, 2023; Published Online: August 28, 2023; https://doi.org/10.1016/j.xinn.2023.100503

Citation: Zhang S., Yang H., Wang M., et al., (2023). Immunomodulatory biomaterials against bacterial infections: Progress, challenges, and future perspectives. The Innovation **4(6)**, 100503.

Bacterial infectious diseases are one of the leading causes of death worldwide. Even with the use of multiple antibiotic treatment strategies, 4.95 million people died from drug-resistant bacterial infections in 2019. By 2050, the number of deaths will reach 10 million annually. The increasing mortality may be partly due to bacterial heterogeneity in the infection microenvironment, such as drug-resistant bacteria, biofilms, persister cells, intracellular bacteria, and small colony variants. In addition, the complexity of the immune microenvironment at different stages of infection makes biomaterials with direct antimicrobial activity unsatisfactory for the long-term treatment of chronic bacterial infections. The increasing mortality may be partly attributed to the biomaterials failing to modulate the active antimicrobial action of immune cells. Therefore, there is an urgent need for effective alternatives to treat bacterial infections. Accordingly, the development of immunomodulatory antimicrobial biomaterials has recently received considerable interest; however, a comprehensive review of their research progress is lacking. In this review, we focus mainly on the research progress and future perspectives of immunomodulatory antimicrobial biomaterials used at different stages of infection. First, we describe the characteristics of the immune microenvironment in the acute and chronic phases of bacterial infections. Then, we highlight the immunomodulatory strategies for antimicrobial biomaterials at different stages of infection and their corresponding advantages and disadvantages. Moreover, we discuss biomaterial-mediated bacterial vaccines' potential applications and challenges for activating innate and adaptive immune memory. This review will serve as a reference for future studies to develop next-generation immunomodulatory biomaterials and accelerate their translation into clinical practice.

INTRODUCTION

Infectious diseases cause increased mortality in the global population, particularly in low-income countries.[1–3] Despite various clinical treatments, including antibiotic therapy, the number of deaths associated with bacterial infections continues to increase yearly.[4] In 2019, approximately 4.95 million deaths were related to drug-resistant bacterial infections.[5] Furthermore, by 2050, this number is predicted to reach 10 million annually, thus surpassing that of all cancer-related deaths.[6,7] Therefore, antibiotic regimens to treat bacterial infections are no longer sufficient. This is partly attributed to bacterial heterogeneity in the infection microenvironment, including intracellular bacteria, small colony variants (SCVs), biofilms, and persister cells.[8] Biofilms can resist 10–1,000 times the minimal inhibitory concentration (MIC) of antibiotics that kill their planktonic counterparts.[9] In addition, increasing prevalence of multidrug-resistant bacteria worldwide and the decline in the development of novel antibiotics makes treating drug-resistant bacterial infections more challenging.[10] In the last two decades, only a few novel antibiotics have been approved for treating clinical infections, possibly due to the decades-long development time, high cost of funding, and low success rate.[11] Nevertheless, their use for treating multidrug-resistant bacterial infections is also associated with a high frequency of bacterial drug-resistant mutations. Therefore, there is an urgent need to develop novel regimens that overcome the shortcomings of conventional antibiotics.[12–14]

With the development of advanced materials technology, researchers have recently focused on various biomaterials with direct antimicrobial functions.[15,16] These materials can act as carriers to deliver a wide range of antibacterial compounds, including antibiotics, and alter metabolic dynamics and tissue distribution *in vivo*, while allowing surface modification and specific accumulation around the pathogen, thereby reducing side effects in humans.[17,18] In addition, modifying the surface topography of biomaterials, such as pattern, hardness, and moisture, to resist bacterial adhesion is considered an excellent antimicrobial strategy.[19] However, owing to the lack of understanding and modulation of the immune microenvironment during different infection phases, these direct antimicrobial biomaterials have shown disappointing results in the long-term treatment of infections.[20] Moreover, some biomaterials may overemphasize their direct bactericidal function while neglecting their damage to the active defense function of immune cells, which further contributes to the persistence of chronic infections.[21] Therefore, relying on conventional antibiotics or bactericidal biomaterials alone is no longer sufficient to treat multidrug-resistant bacterial infections. Therapy with a direct antimicrobial and synergistic effect on immune cells is required.

Over the past decade, the use of immunomodulatory agents in advanced tumors and complicated drug-resistant bacterial infections has shown many benefits.[22] However, some immunomodulatory agents have shown inconsistent results when used alone in clinical trials.[23] For example, an immune checkpoint inhibitor PD-1 antibody may improve immunosuppression in patients with sepsis to increase survival;[24] however, in patients with *Mycobacterium tuberculosis* infection, PD-1 blockade was associated with disease exacerbation and increased mortality.[25] This contradiction may be partly attributed to non-selective organ distribution when immunomodulatory agents are used alone. Therefore, combining immunomodulatory substances with targeted and sustained-release biomaterials is necessary to achieve better antimicrobial and immunomodulatory action while reducing side effects.[26] Based on their benefits, immunomodulatory antibacterial biomaterials are considered potentially powerful tools for treating recalcitrant bacterial infections in the post-antibiotic era.[27]

In this review, we discuss the recent research progress and future perspectives of immunomodulatory antimicrobial biomaterials while focusing on four main areas: (1) the different characteristics of the immune microenvironment in the acute and chronic phases of bacterial infection, (2) the applications and opportunities of immunomodulatory antimicrobial biomaterials in the acute phase of infection, (3) the applications and challenges of immunomodulatory antimicrobial biomaterials in the chronic phase of infection, and (4) the potential and limitations for biomaterial-mediated bacterial vaccines to enhance innate and adaptive immune memory. This review presents potential therapeutic concepts and research directions to expedite the clinical translation of novel immunomodulatory antimicrobial biomaterials.

IMMUNE IMBALANCE IN BACTERIAL INFECTION MICROENVIRONMENT

Trauma and medical implants are often associated with early postoperative tissue damage and the release of large amounts of damage-associated molecular patterns (DAMPs), which recruit various immune cells and shift the immune balance toward a pro-inflammatory phenotype.[28] Despite the release of numerous pro-inflammatory factors that rapidly inhibit pathogen proliferation, specific opportunistic pathogens can employ complex strategies to evade or disrupt the normal bactericidal function of immune cells, further causing a homeostatic imbalance in the infectious microenvironment.[29] Invasive planktonic bacteria change their growth status by biofilm formation, persister cells, intracellular

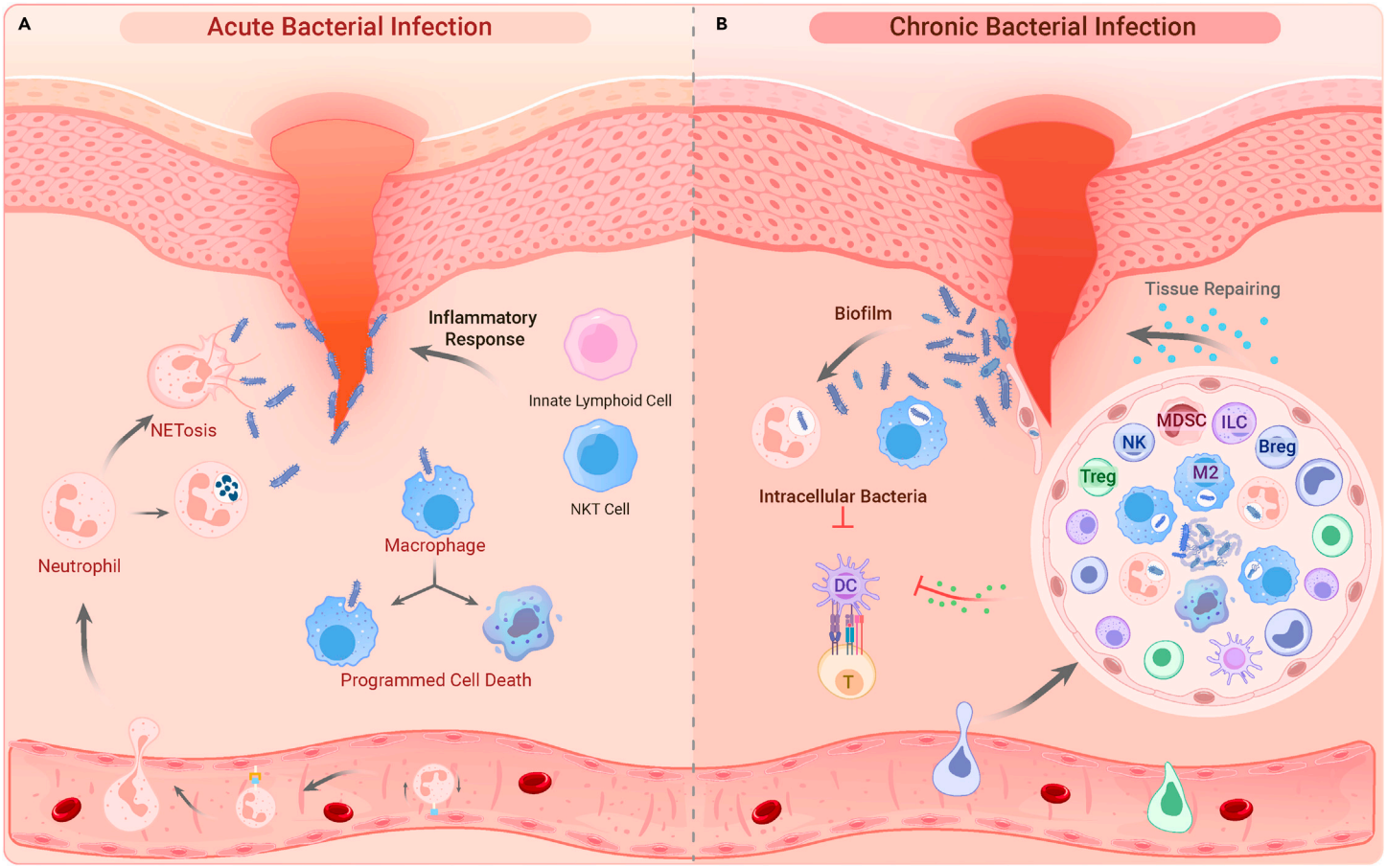

Figure 1. Illustrations show changes in the immune microenvironment during the acute and chronic phases of bacterial infection (A) The release of multiple toxins from bacteria in the acute phase of infection and the activation of innate immune cells lead to an increase in pro-inflammatory cytokines in the immune microenvironment. (B) In the chronic phase of infection, bacteria evade recognition and killing by immune cells through altered survival patterns, which also promote proliferation of multiple immunosuppressive cells, exhaustion of immune cells, and increased release of anti-inflammatory cytokines.

bacteria, and SCVs during the chronic phase of infection, contributing to prolonged and recurrent disease.[30] Thus, the immune microenvironment undergoes corresponding dynamic changes at different stages of infection (Figure 1). Therefore, elucidating the immune profile at each stage could improve understanding of bacterial infections and the characteristics of immunomodulatory antimicrobial biomaterials.

Pro-inflammatory phase of acute bacterial infections

In the early stages of infection, the pathogen usually invades the body as planktonic bacteria. Here, the synergistic action of multiple immune cells in the tissues helps reduce the pathogen load and improve the survival rate of the infected patient.[31] Among the immune cells, neutrophils and macrophages, as the main force of bactericidal activity in the acute phase, have become the focus of studies on various infectious diseases (Figure 2). Typically, there are different pattern recognition receptors (PRRs), such as the Toll-like and NOD-like receptors, on the intracellular space or cytosol of these cells.[32] Once these PRRs detect bacterial pathogen-associated molecular patterns (PAMPs) or DAMPs, these cells can rapidly induce the production of large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS) to directly kill pathogenic bacteria by altering their metabolism.[33] Meanwhile, neutrophils can undergo suicidal death by releasing chromatin and granule proteins to form neutrophil extracellular traps (NETs) that trap and kill bacteria.[34] The released NETs can also transfer neutrophil-specific antimicrobial peptides (AMPs) to macrophages to enhance their bactericidal potency.[35] In addition, direct stimulation of bacterial products can promote the M1 polarization of macrophages, enhancing their bacterial phagocytic and killing activities.[36] M1-polarized macrophages can also enhance the presentation of antigenic peptides after bacterial lysis by upregulating the expression of the major histocompatibility complex class II (MHC class II) and co-stimulatory molecules, which subsequently activate adaptive immune responses.[37] Thus, the synergistic interaction of neutrophils and macrophages in the acute phase allows for more rapid control of bacterial infections.[38] In addition, various tissue-resident immune cells, such as tissue-resident macrophages, tissue-resident memory T cells, mucosa-associated invariant T cells, γδ T cells, natural killer (NK) T cells, and innate lymphoid cells (ILCs), are involved in the rapid clearance of pathogens.[39] For example, ILC3, which has a similar function to that of T helper (Th)17 cells, produces cytokines, such as IL-17 and IL-22, to promote the proliferation of intestinal epithelial cells and secrete AMPs (RegIIIγ, RegIIIβ, and calprotectin subunits S100A8 and S100A9) to fight *Salmonella* species.[40] Some non-immune cells, such as endothelial and epithelial cells, also play an important role in pathogen clearance. For example, certain tissue-specific endothelial cells induce adaptive immunity by recruiting multiple immune cells and presenting phagocytic antigens, thereby regulating immune homeostasis.[41]

In the microenvironment of the acute phase of infection, M1 macrophage polarization can induce the release of pro-inflammatory cytokines to fight bacteria; however, the high level of local inflammatory agents also damages tissues.[42] Furthermore, the abnormal activation of various immune cells and the formation of a cytokine storm that usually accompanies the early onset of sepsis are associated with a higher risk of death.[43] In addition, the hyperinflammatory environment tends to induce bacterial mutations and the formation of persister cells with lower metabolic levels, which help bacteria overcome antibiotic attacks.[44] Moreover, excessive inflammatory stimulation can accelerate the onset of neutrophil senescence, which impairs bacterial phagocytosis and promotes apoptosis,[45] further increasing the risk of bacterial reinfection.

However, in response to the attack of host cells in the immune microenvironment during the acute phase of infection, planktonic bacteria have evolved various sophisticated evasion strategies that move the infection into the chronic phase.[46] Based on whether bacteria lyse immune cells, their evasion schemes can usually be divided into active attack strategies and passive defense strategies. Active attack strategies involve bacteria releasing multiple virulence factors in response to host defenses to lyse immune cells and inhibit their bactericidal

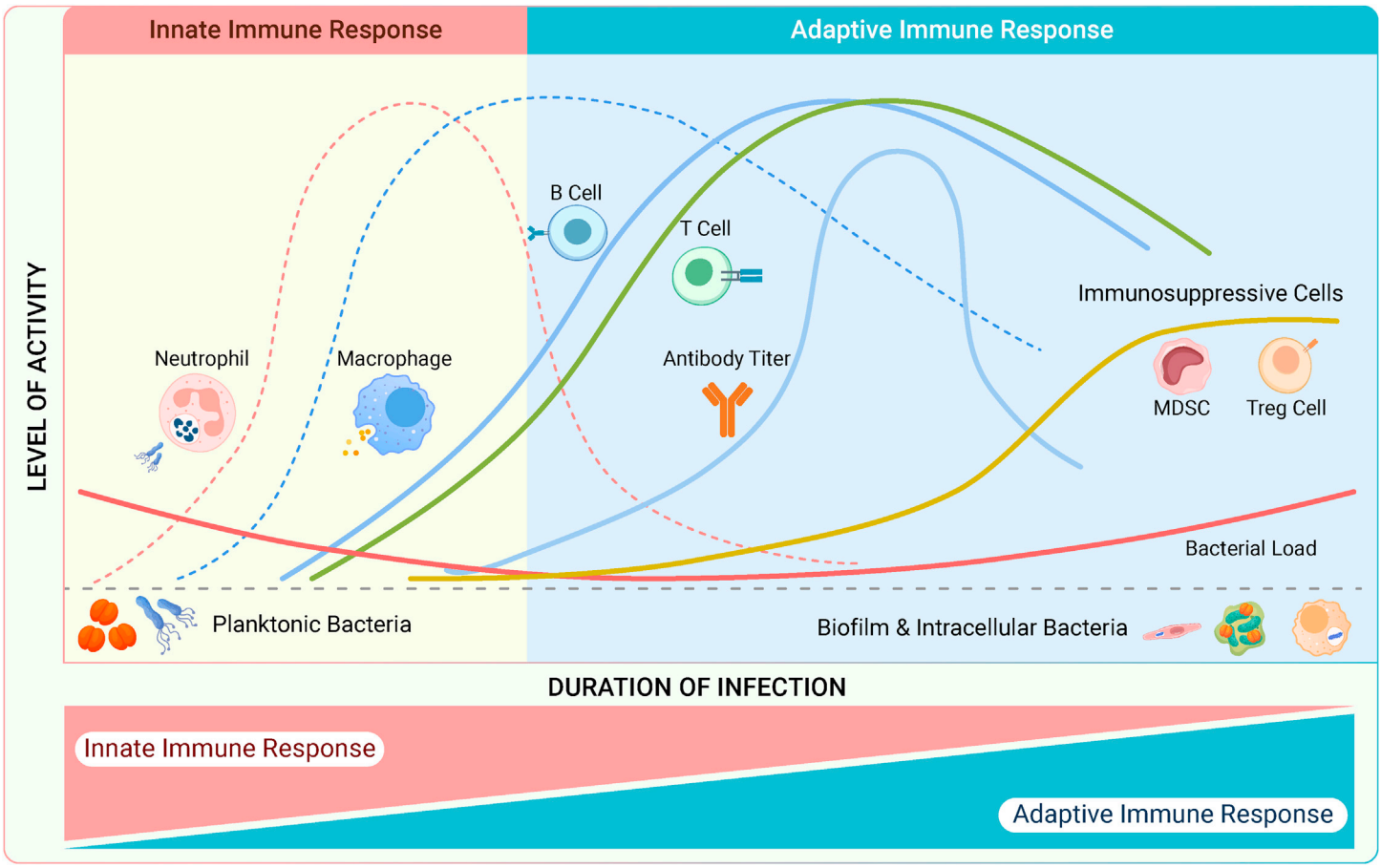

Figure 2. Dynamics of innate and adaptive immunity against bacterial infections over time

function.[47] For example, *Staphylococcus aureus*, the most common opportunistic pathogen in various infectious diseases, can release several pore-forming toxins, including leukotoxins, α-toxins, and phenol-soluble modulators (PSMs).[48] Among these toxins, PSMs are not only involved in bacterial biofilm formation and dispersal but also induce neutrophil chemotaxis and activation by activating formyl peptide receptor 2 (FPR2/FPRL1), which can lyse both erythrocytes and leukocytes.[49] In addition, *S. aureus* can evade killing by secreting extracellular vesicles that upregulate the expression of the pro-apoptotic DNA damage-inducible transcript 4 gene and downregulate the expression of the anti-apoptotic B cell lymphoma 2 gene in macrophages, thereby promoting their apoptosis.[50] In contrast, to active attack strategies, the passive defense strategy of bacteria involves their reliance on the properties of their structural components to evade recognition by immune cells, allowing them to remain hidden in the infected tissue.[51] For example, the capsules of many Gram-positive and Gram-negative bacteria contain sialic acid residues that effectively inhibit the activation of the alternative complement pathway in innate immunity, thereby avoiding the formation of the membrane attack complex.[52] In addition, *S. aureus* can reduce neutrophil chemotaxis while resisting daptomycin-induced killing by increasing cardiolipin and decreasing phosphatidylglycerol levels within the bacterial membrane.[53] Modulating the interaction between immune cells and bacteria during acute infections is important to mitigate tissue damage from the anti-bacterial inflammatory storm.

Anti-inflammatory phase of chronic bacterial infections

If cytokines from the various immune cells do not eliminate the bacteria in the acute phase, the infection progresses to the chronic phase. Bacteria can use two strategies to prolong infection during the chronic stage.[54] The first involves the formation of bacterial biofilms around the implant and the presence of associated persister cells,[55] whereas the other consists in invading tissue cells to form intracellular bacteria and SCVs.[56] According to the National Institute of Health, biofilms are found in more than 80% of patients with microbial infections,[57] making them an important target for treating chronic infections. Neutrophils and macrophages are the primary immune cells involved in biofilm clearance *in vivo*. Mediated by chemokines, these activated specialized phagocytes secrete various pro-inflammatory factors and engulf biofilm debris to reduce bacterial accumulation within biofilms and disseminate to distant sites.[58] The complex formed by binding biofilm-associated antigens to antibodies secreted by plasma cells may also promote phagocytosis by macrophages. However, compared with biofilm clearance, the fight against intracellular bacterial infections involves other immune cells, such as NK cells and cytotoxic T lymphocytes (CTLs).[59]

Usually, bacteria are eliminated via lysis by multiple bactericidal substances within the cytosol after recognition and phagocytosis by specialized phagocytes.[60] In addition, pathogen-invaded cells can initiate multiple programmed cell death pathways, such as apoptosis, pyroptosis, necroptosis, autophagy, and PANoptosis. Moreover, the released cytokines can recruit other immune cells to synergistically eradicate bacteria.[61] For example, macrophages can undergo apoptosis after invasion by *M. tuberculosis*, and the cellular debris containing the pathogen are further removed by uninfected macrophages in the surrounding area through efferocytosis. ILC3 can rapidly initiate caspase-1-mediated cellular pyroptosis upon invasion by *S. typhimurium*, thus reducing IL-22 production and facilitating intracellular bacterial clearance.[62] However, NK cells and CTLs are often required to release intracellular bacteria within specific non-specialized phagocytic cells, such as osteoblasts and epithelial cells. These infected cells can activate CTLs and NK cells to release perforin and granzyme to lyse infected cells through the MHC class I molecular pathway for bacterial antigen processing and presentation and upregulation of NK cell activation ligand expression, respectively.[63]

Compared with planktonic bacteria in the acute phase, biofilms are formed by massive aggregation of bacteria through adhesion and autolysis, conferring them with more escape strategies.[64] For example, the dense physical barrier of the biofilm effectively prevents the penetration of the activated complement, thereby protecting bacteria within the biofilm from being killed by the membrane attack complex. The biofilm matrix of *Pseudomonas aeruginosa* contains high levels of

exopolysaccharides Psl and alginate, which can effectively attenuate complement activation and help the bacteria evade killing by macrophages.[65] Similarly, lactate accumulation within the biofilm can inhibit histone deacetylase 11 to regulate the epigenetic reprogramming of host immune cells to secrete high levels of the anti-inflammatory cytokine IL-10, preventing the activation of adaptive immunity.[66] In addition, the low-oxygen, nutrient-deficient environment within the biofilm can cause bacteria to switch to a low metabolic state, forming persister cells.[67] As this process does not involve genetic mutations, bacteria can respond quickly to harmful factors and resist antibiotics attacks (1,000× MIC).[12] Once the harmful factors are reduced, persister cells can quickly return to a normal metabolic state, leading to the recurrence of infection.[68] Some intracellular bacteria can interfere with the normal bactericidal process described above by releasing several regulatory substances, resulting in bacterial persistence. This condition resembles a "Trojan horse" that can cause recurrent infections and bacterial spread.[69] For example, *M. tuberculosis* can produce a natural phagolysosome disruptor, 1-tuberculosinyladenosine, which can disrupt the normal structure of the lysosome while neutralizing its acidic environment.[70] *M. tuberculosis* can also use the protein tyrosine phosphatase B to inhibit the ubiquitination of host cells, subsequently preventing cell pyroptosis and escape from immune attack.[71] Similarly, enterohemorrhagic *E. coli* can secrete Shiga toxins to block the activation of the caspase-11-dependent classical inflammasome by cytosolic lipopolysaccharide, thereby inhibiting the onset of pyroptosis and release of the pro-inflammatory cytokine IL-1.[72] In addition to invading specialized phagocytes, bacteria can invade non-phagocytic cells, such as osteoblasts, endothelial cells, and fibroblasts. After invading cells using deformation or ligand-receptor binding strategies, they can convert into SCVs for persistent survival.[73] For example, *S. aureus* can invade osteoblasts through the surface adhesion protein fibronectin, which binds to the α5β1 integrin of osteoblasts, inhibiting early osteogenic differentiation.[74] Similarly, uropathogenic *E. coli* can invade urothelial cells and compete for intracytoplasmic oxygen via respiratory quinol oxidase cytochrome bd to maintain bacterial proliferation, thus altering energy metabolism in urothelial cells and antagonizing their apoptotic shedding, ultimately resulting in persistent infection.[75]

In the microenvironment of chronic infection, multiple immune evasion strategies by pathogens not only facilitate their persistence in infected tissues but also lead to the formation of immunosuppressive networks through the regulation of various immune cells.[76] For example, the depletion of glucose and oxygen within bacterial biofilms and the accumulation of lactate can lead to M2 polarization of macrophages, increased differentiation of regulatory T (Treg) cells, and depletion of CD8 T cells, which reduces the secretion of pro-inflammatory factors and is detrimental to biofilm clearance by immune cells.[77] Furthermore, the intracellular bacterium *S. typhimurium* can secrete effector SteE to promote macrophages toward an anti-inflammatory state after granulocytic macrophage invasion.[78] Similarly, *S. aureus* and its exotoxins can interfere with the normal differentiation of hematopoietic stem cells in the bone marrow from an early stage and induce the production of large numbers of immature neutrophils and macrophages, namely the myeloid-derived suppressor cells (MDSCs).[79] Moreover, several regulatory cells, including Tregs, regulatory B cells, regulatory NK cells, and regulatory dendritic cells, have been implicated in the immunosuppressive network.[80] A significant increase in Treg cells and secretion of several anti-inflammatory and inhibitory enzymes, such as arginase 1 and indoleamine 2,3-dioxygenase, has been reported in patients with chronic *M. tuberculosis* infection.[81] The surface of Treg cells contains abundant membrane molecules, such as PD-L1 and PD-L2, which can induce cytotoxic T cell exhaustion and weaken the bactericidal effect of adaptive immunity upon direct binding of inhibitory receptors (e.g., PD-1, CTLA-4, TIM-3, and TIGIT).[82] Thus, in contrast to the acute phase, characterized by excessive activation of immune cells, the chronic phase of infection is typically characterized by immune cell exhaustion, increased anti-inflammatory cytokine release, and bacterial persistence.[83] Overall, reducing the differentiation of immunosuppressive cells, reversing the immunosuppressive microenvironment, and restoring the bactericidal function of exhausted T cells during chronic infection may be an important challenge.

Opportunities and challenges

Although the characteristics of the immune microenvironment at different stages of bacterial infection have been studied, an extensive mechanistic study of the infection microenvironment is necessary. A comprehensive understanding of the immune microenvironment dynamics at different bacterial infection stages is essential to guide the development of novel immunomodulatory antibacterial biomaterials. Recently, cancer-associated fibroblasts have been revealed to stimulate immune activation, contrary to their previously thought role in immunosuppression and promotion of tumor metastasis.[84] Recent advances in high-throughput sequencing technologies have identified the presence of specific cell subpopulations at different microenvironment stages, such as infection-associated macrophages and fibroblasts, thereby expanding the focus beyond classical innate immune cells. Several cell subsets that could serve as early diagnostic markers of sepsis and thus contribute to improved clinical outcomes, such as HLA-DR^{lo}IL1R2^{hi}CD14^{+} monocytes, CD10^{-}CD64^{+}PD-L1^{+} neutrophils, and CD10^{-}CD64^{+}CD16$^{low/-}$CD123^{+} immature neutrophils, were identified.[85,86] Although the role of tumor-infiltrating B cells and tertiary lymphoid structures in oncology has been extensively studied,[87] few experiments have investigated the cellular composition and function of tertiary lymphoid structures in bacterial infectious diseases. Therefore, it is necessary to explore their heterogeneity in different bacterial infection microenvironments using advanced technologies to improve the treatment outcomes of multidrug-resistant bacterial infections. The continuous stimulation of inflammatory factors in the infectious microenvironment accelerates immune cell senescence, and senescent cells exhibit several characteristic changes, such as loss of circadian genes and disruption of energy metabolism, leading to impaired antimicrobial function.[88] Therefore, further investigations are needed to elucidate the mechanisms underlying the onset of immune cell senescence during different periods of bacterial infection to guide the development of novel targeted therapeutic strategies. Finally, owing to their ability to self-renew and generate heterogeneous tumor cells, cancer stem cells are believed to play an important role in tumor survival, proliferation, metastasis, and recurrence.[89] However, whether a unique subpopulation of cancer stem-like cells exists also during intracellular bacterial infection to maintain the continuous dissemination and recurrence of the pathogen within normal cells remains unknown. Therefore, in future studies, we can further explore the molecular mechanisms of intracellular bacteria to identify specific surface markers.

MODULATION OF INFECTION MICROENVIRONMENT USING IMMUNOMODULATORY ANTIMICROBIAL BIOMATERIALS

Acute infection microenvironment regulation

Immunomodulatory biomaterials capable of eradicating pathogens and promoting tissue healing are necessary to modulate the immune microenvironment at different stages of bacterial infection. In the acute phase of infection, rapid activation of neutrophils and macrophages promotes resistance to bacterial invasion and releases several pro-inflammatory cytokines and bactericidal ROS.[90] However, excessive accumulation of inflammatory cytokines could induce tissue necrosis or exacerbate the onset of autoimmune diseases.[91] Therefore, identifying the correct strategy to employ immunomodulatory materials to rapidly eliminate bacteria while reducing inflammatory damage to tissues and promoting healing is an important challenge. These strategies are discussed below (Figure 3; Table S1).

Enhancing neutrophil bactericidal function for early bacterial clearance. As one of the first immune cells mobilized after infection, neutrophils are critical in killing bacteria in the acute phase and preventing infection from progressing to the chronic phase.[32] Neutrophils can exert effective bactericidal effects through phagocytosis, the release of ROS and RNS,[92] and the production of an extracellular trapping network comprising depolymerized chromatin and intracellular granule proteins through a specific mode of cell death called NETosis.[35] Therefore, using biomaterials to enhance the bactericidal activity of neutrophils during the acute phase of infection is an important strategy for rapidly eradicating pathogens. Next, we discuss the regulation of neutrophils based on the physicochemical properties of biomaterials and their role as delivery vehicles.

The physicochemical properties of biomaterials typically include size, shape, composition, charge, roughness, and hardness.[93] It has been shown that neutrophils secrete higher levels of pro-inflammatory cytokines and enzymes on smooth or rough hydrophobic surfaces.[94] Moreover, these surfaces promote the formation of neutrophil NETs more than rough hydrophilic surfaces.[95] In addition, the degradability of the biomaterial is important for regulating neutrophil function. For example, Zn and its alloys have unique advantages over traditional inert medical materials, such as titanium alloy.[96] Zn not only has a direct bactericidal effect but can also enhance the phagocytic bactericidal function of

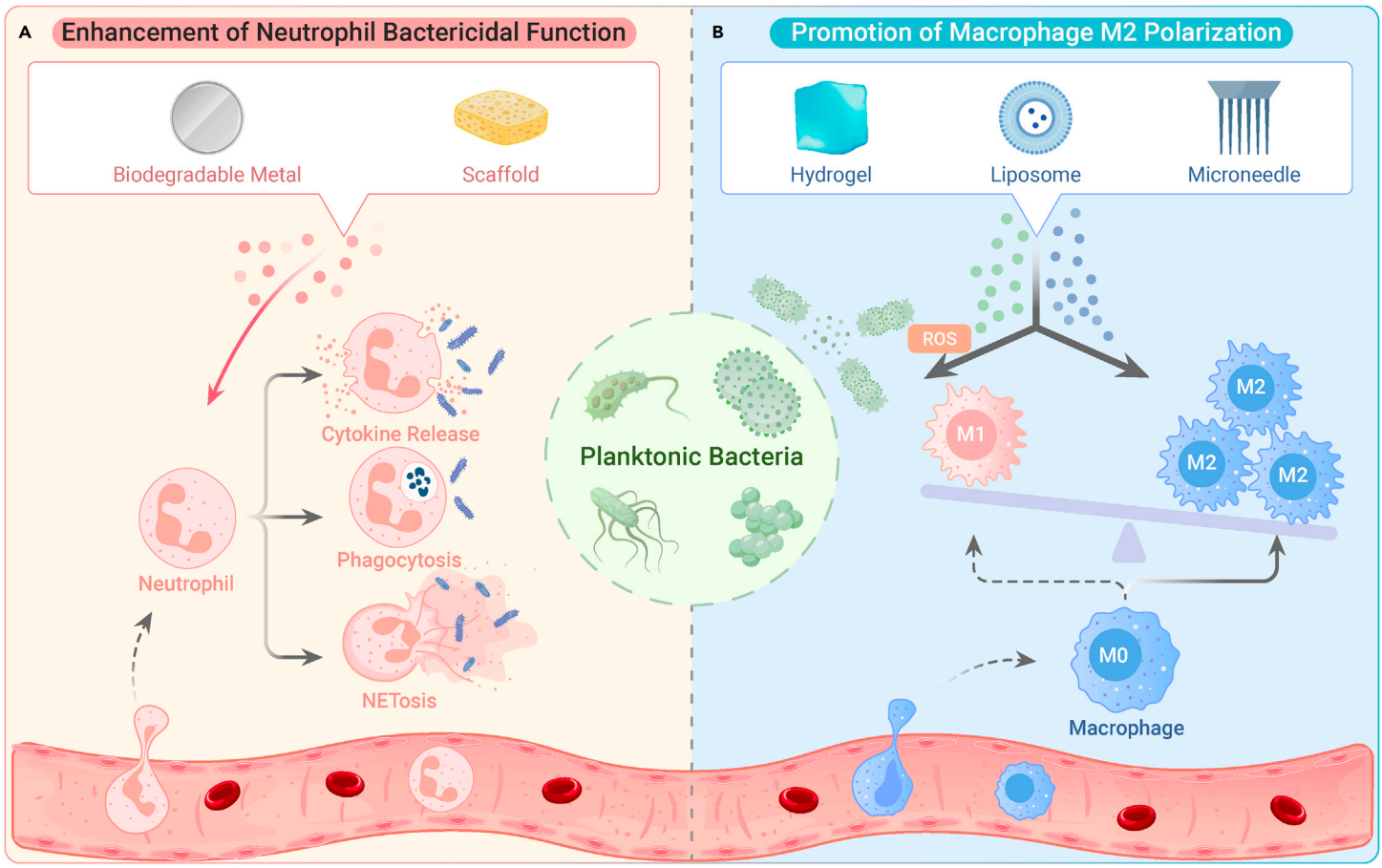

Figure 3. During the acute phase of infection, immunomodulatory antimicrobial biomaterials modulate the immune microenvironment (A) Biomaterials promote early neutrophil recruitment, and activation and phagocytosis of bacteria through the release of pro-inflammatory agents or their own physicochemical properties. Biomaterials also stimulate neutrophils to release ROS, RNS, and NETs to rapidly kill bacteria. (B) Biomaterials promote M2 polarization of macrophages through direct bactericidal action and release of anti-inflammatory agents that accelerate the healing of infected tissue while removing bacteria.

neutrophils by releasing Zn ions.[97] Studies have shown that Zn promotes the formation of NETs by neutrophils to clear pathogens and promote osseointegration at the site of infection in a ROS-dependent manner.[98,99] Furthermore, biomaterial surface modification is also an excellent strategy for neutrophil regulation. For example, magnetron-sputtered tantalum nanofilms showed no significant antibacterial effect in *in vitro* tests; however, *in vivo*, studies unexpectedly found that it enhanced the phagocytic activity of polymorphonuclear neutrophils and reduced neutrophil lysis. In addition, tantalum nanofilms enhanced the release of pro-inflammatory cytokines from macrophages to synergistically clear bacteria, thereby alleviating infectious osteolysis,[100] consistent with previous clinical reports describing that tantalum reduced the failure rate after revision for bone infection.[101]

In addition, to using their physicochemical properties to modulate the antimicrobial function of neutrophils, biomaterials can also act as delivery vehicles for various pro-inflammatory substances to synergistically enhance antimicrobial immunity. For example, Ag/Ag@AgCl nanostructures and ZnO nanoparticles were assembled into hydrogels using ultraviolet light chemical reduction and NaOH precipitation methods in a way that continuously released Ag, Zn ions, and ROS under visible light excitation.[102] This nanomaterial system provides rapid pathogen eradication and increases neutrophil recruitment and phagocytosis to synergistically accelerate wound healing. Compared with traditional single antimicrobial therapies, it shows potential for treating a wide range of clinical drug-resistant bacterial infections.

Promoting M2 polarization of macrophages to accelerate tissue repair. In the acute phase of infection, appropriate activation of immune cells facilitates rapid clearance of pathogens. However, the continuous release of numerous pro-inflammatory cytokines disrupts the homeostasis of the immune microenvironment in local tissues, leading to cellular inflammatory damage and impaired bacterial clearance.[103] Therefore, developing biomaterials capable of regulating immune cells to the anti-inflammatory state in the acute phase of infection to avoid the formation of a cytokine storm and accelerate the healing of infected tissues is a critical challenge in treating bacterial diseases. Macrophages are one of the most abundant immune cells in the infection microenvironment, have excellent plasticity, and can switch between a pro-inflammatory M1 state and an anti-inflammatory M2 state under the influence of multiple microenvironmental factors. Therefore, they have attracted the attention of researchers developing immunomodulatory antibacterial biomaterials.[104]

The effect of the physicochemical properties of the biomaterial on the antimicrobial function of macrophages has been reported previously.[105,106] Surface hydrophilicity or wettability is the most potent factor influencing the transition of macrophages to an anti-inflammatory state.[107] Although increased material roughness promotes macrophage M1 polarization, the combination of material roughness and hydrophilicity inhibits the expression of pro-inflammatory markers and increases macrophage M2 polymerization.[108] In addition, the nanoenzyme effect of the biomaterial itself has been shown to be excellent for rapid bacterial killing and tissue healing. Some biomaterials cannot only rapidly kill pathogens by photothermal, photodynamic, chemodynamic, or magnetothermal action but also rely on the action of their nanoenzymes to remove excess ROS from infected tissues and modulate macrophages toward M2 polarization;[109] for example, the excitation of the CeO2@Ce6 nanocomposite with photodynamic function under red light-induced ROS production to kill bacteria. In addition, the nanoenzyme system showed superoxide dismutase-like action to scavenge excess ROS via redox cycling reactions between Ce^{3+} and Ce^{4+}, thus reducing the M1 polarization of macrophages and avoiding the destruction of normal tissues.[110]

In addition, biomaterials can be used as delivery vehicles for various substances (anti-inflammatory drugs or anti-inflammatory factors) that synergistically regulate the immune response of macrophages. For example, near-infrared (NIR) light-induced excitation of the FDA-approved herbal medicine baicalein (BA) loaded in a mesoporous Prussian blue (MPB) nanoenzyme platform caused

hyperthermia and large amounts of ROS, synergistically killing bacteria. Subsequently, the MPB-BA nanosystem can remove unwanted ROS from tissues to regulate macrophage switching to M2 polarization and mitigate the bone loss caused by excessive accumulation of inflammatory cytokines.[111] Besides, biomaterials loaded with exosomes can stimulate macrophage M2 polarization. Exosomes are usually derived from mammalian cells. Their non-reproducibility and inclusion of multiple immunomodulatory substances confer a higher safety profile and greater anti-inflammatory effects than traditional drugs.[112] For example, an engineered exosome was successfully prepared by loading cationic antimicrobial carbon dots inside TNF-α-stimulated mesenchymal stem cell-derived exosomes, and the exosomes showed a direct bactericidal effect and promoted neovascularization and M2 macrophage polarization, which significantly improved the hypoxic environment of infected tissues. In addition, engineered exosomes were loaded onto reductive 2D covalent organic frameworks to attenuate normal cell necrosis due to excessive ROS accumulation in infected tissues, which showed superior tissue healing in a diabetic foot infection model.[113]

Recently, the successful application of gene therapy in several genetic diseases has encouraged its use in drug-resistant bacterial infections.[114] Indeed, incorporating nucleic acids into biomaterials for targeted delivery to immune cells to enhance their antimicrobial capacity is an effective alternative therapy. For example, the targeted delivery of fusogenic lipid-coated porous silicon nanoparticles containing small interfering RNA to activated M1-type macrophages can specifically silence their interferon regulatory factor 5 (*IRF5*) gene to preserve the bactericidal capacity of the cells, effectively block the production of pro-inflammatory cytokines, and reduce inflammatory tissue damage.[115] This strategy not only avoids the development of drug-resistant bacteria and reduces dependence on traditional antibiotics but also effectively alleviates wound non-healing caused by excessive inflammatory factors.[116]

Opportunities and challenges. Regarding regulating the immune microenvironment in acute infections, several biomaterials can enhance bactericidal effects and promote the repair of infected tissues through their physicochemical properties or as drug delivery vehicles. Still, some shortcomings need to be addressed in the future. First, the effects of the physicochemical properties of biomaterials on multiple immune cell functions have not been fully elucidated. It remains unclear how macrophages sense the physicochemical properties of biomaterials and which signaling pathways may be involved. Previous studies have mainly focused on materials' direct antimicrobial effects, neglecting their degradation products' effects on multiple immune cell targets. For example, silver ions were once incorporated into various medical dressings because of their potent direct bactericidal activity *in vitro*.[117] However, recent *in vivo* studies have shown that silver ions can also inhibit neutrophil phagocytosis, which is detrimental to bacterial clearance.[118] Therefore, it is necessary to consider the effects of the intrinsic physicochemical properties of biomaterials, such as size, shape, and topology, on immune cell functions in the future development of immunomodulatory antimicrobial materials. Second, strategies to prevent cytokine storms associated with the use of biomaterials need to be developed. Although releasing numerous pro-inflammatory factors in the acute phase of infection contributes to bacterial clearance, excessive inflammation accelerates bacterial mutation and the development of an immunosuppressive state, which can exacerbate tissue necrosis. Therefore, an important research direction could be an antimicrobial biomaterial with a specific chemical composition that can precisely respond to the inflammatory level of the infected microenvironment and correct the immune imbalance. Third, biomaterial-induced regulation of macrophage M2 polarization is associated with the recurrence of residual bacteria, which requires further investigation. Although the increased M2 polarization of macrophages helps to reduce inflammation and accelerate tissue repair, the high secretion of anti-inflammatory cytokines by macrophages also hinders the clearance of recalcitrant bacteria. Therefore, to reduce the risk of infection recurrence, further studies are needed to optimize the chemical structures of biomaterials to achieve complete clearance of bacteria before promoting M2 macrophage polarization.

Chronic infection microenvironment regulation

Unlike in the acute phase of bacterial infections, biofilms, persister cells, intracellular bacteria, and SCVs in the chronic infection microenvironment typically result in the proliferation of multiple immunosuppressive cells, accumulation of anti-inflammatory agents, and exhaustion of immune cells.[119] Therefore, developing immunomodulatory antimicrobial biomaterials capable of directly removing biofilms and intracellular bacteria, restoring exhausted immune cell function, and reversing the immunosuppressive microenvironment is critical. The mechanisms and advantages of such biomaterials are discussed below (Figure 4; Table S2).

Regulating macrophage M1 polarization to eliminate recalcitrant bacteria. In the chronic infection microenvironment, bacteria typically exist in multiple forms to evade recognition and killing by immune cells. For example, they can form biofilms and persister cells on the surface of implants or enter normal cells to transform into intracellular bacteria and SCVs.[120] Forming biofilms and intracellular bacteria protects bacteria from antibiotic killing, regulates macrophage M2 polarization, and attenuates their bactericidal efficacy, leading to the persistence and recurrence of bacterial infections.[78] Therefore, using biomaterials for direct bactericidal activity while promoting macrophage M1 polarization and secretion of pro-inflammatory factors to enhance biofilm and intracellular bacterial clearance is one of the major challenges in the chronic infection phase.

An immunomodulatory antimicrobial biomaterial that could respond to the biofilm microenvironment would have unique advantages in chronic infections. Generally, biofilms have low pH and a high concentration of H_2O_2 inside, whereas the outside is characterized by opposite conditions.[121] Thus, $CuFe_5O_8$ nanocubes with chemodynamic effects can generate high concentrations of hydroxyl radicals (·OH) inside the biofilm to destroy eDNA, an important structural component of the biofilm. In contrast, $CuFe_5O_8$ nanocubes catalyze the production of low concentrations of hydroxyl radicals outside the biofilm, which then synergize with Cu and Fe ions to regulate M1 macrophage polarization and enhance their bactericidal activity.[122]

In addition, to better prevent the spread of lysed biofilm fragments to non-infected tissues, it is necessary to promote macrophage M1 polarization by synergistically delivering immunomodulatory substances based on the physicochemical properties of the biomaterial.[123] This combination could enhance their bactericidal effect and reduce infection recurrence.[124] For example, NIR-induced excitation of modified red phosphorus nanomembranes containing S-nitro succinic acid (NO donor) on the surface of biologically inert titanium implants induced the release of large amounts of NO gas and superoxide ion, which effectively disrupted bacterial biofilm structure. Moreover, generating ROS and NO at low levels stimulated macrophage M1 polarization and the release of TNF-α, which enhanced the clearance of residual bacteria.[125] Similarly, co-encapsulation of chemodynamic Fe_3O_4 nanoparticles with photothermal graphene oxide nanosheets in hydrogel microneedle patches not only produced synergistic anti-biofilm effects to induce bacterial ferroptosis but also restored the function of neutrophils and enhanced the bactericidal activity of macrophages by releasing large amounts of Fe ions.[126]

Regarding insidious intracellular bacteria, although biomaterials have been developed to increase the accumulation of antibiotics in infected cells,[127] antibiotic killing alone cannot overcome the problem of immune escape and reactivation of intracellular bacteria. Therefore, it is necessary to use multiple means (drug delivery, genetic engineering) to kill bacteria while activating the bactericidal capacity of infected immune cells and reversing their immunosuppressed state. For example, poly(amino acid) nanoparticles loaded with the antibiotic rifampicin were modified with a targeting peptide to enter macrophages specifically in the infected microenvironment. The modified nanoparticles were cleaved in the acidic environment of phagosomes and escaped into the cytoplasm to bind intracellular bacteria, releasing large doses of rifampicin *in situ* for direct bactericidal action. In addition, this cascade-targeting drug delivery system can stimulate the M1 polarization of macrophages and reduce the secretion of the inflammatory factor IL-10, thus preventing intracellular bacterial escape.[128] Apart from the delivery of classical antibiotics, the delivery of other types of antimicrobial compounds also shows unique advantages and can prevent drug-resistant bacterial mutations. For example, the delivery of the traditional Chinese medicine cinnamaldehyde into intracellular bacteria-infected macrophages using PCA nanoparticles directly disrupted the bacterial wall and induced the generation of low levels of ROS to promote macrophage M1 polarization, which enhanced its bactericidal effect.[129] In addition, with the advancement of genetic engineering, using biomaterials for targeted modification of macrophages *in vitro* and subsequent transfusion back into patients has also proven to be an excellent antibacterial strategy. For example, the use of vitamin C lipid nanoparticles to deliver AMP and cathepsin B (AMP-CatB) mRNA into macrophages specifically increased AMP-CatB protein levels in

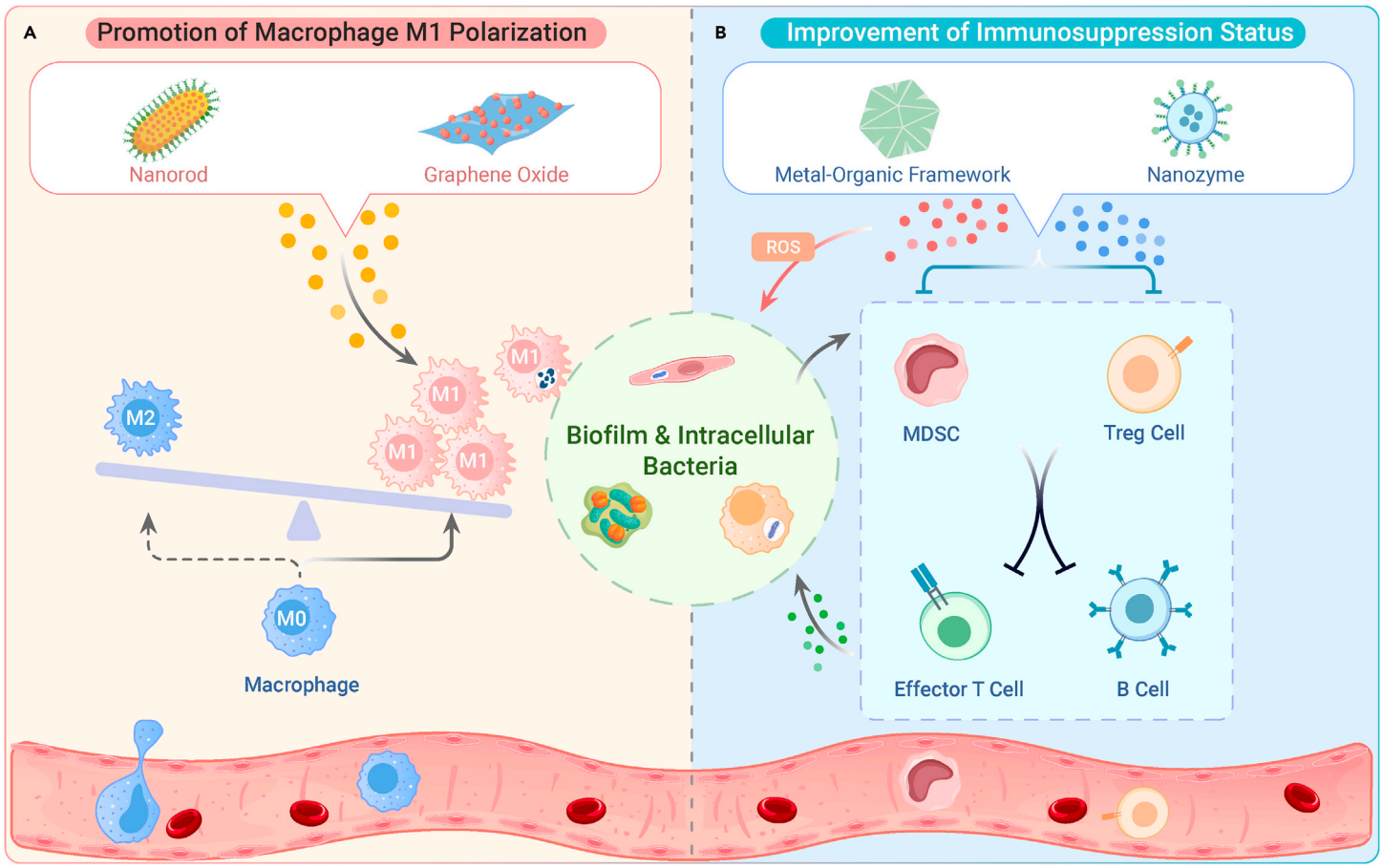

Figure 4. During the chronic phase of infection, immunomodulatory antimicrobial biomaterials modulate the immune microenvironment (A) Biomaterials promote M1 macrophage polarization and reduce infection recurrence through direct lysis of biofilms and intracellular bacteria and release of pro-inflammatory agents. (B) Biomaterials enhance the killing of intracellular bacteria and biofilms through direct bactericidal activity and by releasing immunomodulatory substances that reduce the number of immunosuppressive cells and restore the function of exhausted cells.

macrophage lysosomes, thereby enhancing the bactericidal effect of lysosomes and reducing the escape of drug-resistant bacteria and the formation of intracellular bacteria.[130]

Reducing MDSC proliferation to improve immunosuppression status. Similar to that in the tumor microenvironment, the continuous stimulation of bacteria and their metabolites in the chronic infection microenvironment can lead to the exhaustion of normal immune cells and the accumulation of multiple immunosuppressive cells.[131] Among these, MDSCs have been found to have a suppressive effect on several infectious diseases.[132] MDSCs can inhibit T cell proliferation and normal bactericidal function by releasing the anti-inflammatory cytokine IL-10 and altering arginine metabolism.[133] Therefore, using biomaterials to reduce MDSC proliferation in the chronic infection microenvironment would be beneficial to reverse the immunosuppressive state and increase bacterial clearance.

Although this treatment strategy has been used for several years in the field of oncology with remarkable results,[134] its efficacy against bacterial infections has not been extensively studied. However, Yue and colleagues recently showed that zeolitic imidazolate framework-8 material grafted and encapsulated with the natural antimicrobial peptide LL-37 and its plasmids exerted high bactericidal effects against planktonic and intracellular bacteria.[135] Further animal studies have demonstrated that this system transfected infected cells to produce the antimicrobial peptide LL-37 not only consistently but also significantly reduced the number of MDSCs and reversed the immunosuppressive microenvironment around the infected area. This immunomodulatory biomaterial is the first attempt to enhance intracellular bacterial killing by reducing the number of MDSCs.

Tregs are also key in forming immunosuppressive networks in the chronic infection microenvironment. Tregs effectively inhibit the normal antimicrobial function of effector T cells and DCs in the following ways to result in persistent bacterial infection: CTLA-4-mediated intercellular suppression, secretion of suppressive cytokines (IL-10, TGF-β, and IL-35), release of perforin and granzyme to lyse cells, and metabolic interference with other cells.[136] In addition to regulating the progression of infectious diseases, Tregs are associated with neovascularization and tumor-distant metastasis.[137] Therefore, in response to the above immunosuppressive functions of Tregs, several strategies have been developed to improve the survival of tumor patients, such as the use of targeted biomaterials to deliver immunomodulatory drugs, cytokines, and monoclonal antibodies to reduce Treg infiltration and promote their apoptosis.[138] However, in the therapeutic area of bacterial infections, few biomaterials are currently available that modulate Tregs in the chronic infection microenvironment to enhance bacterial clearance. Similarly, prolonged stimulation by antigens in the infected microenvironment also leads to the exhaustion of CD8 T cells.[139] Typically, T cell exhaustion is associated with multiple changes such as impaired proliferative capacity, decreased cytokine production, unique epigenetic modifications, and persistently high expression of multiple inhibitory receptors (PD-1, TIM-3, LAG-3, CTLA-4, and TIGIT).[140] Therefore, to rapidly restore normal T cell function and reduce the risk of disease recurrence, current oncology strategies include biomaterial-directed delivery of immune checkpoint inhibitors and adoptive T cell therapies.[141] As mentioned, although the above therapeutic approaches have achieved significant efficacy in various advanced tumors, only a few biomaterials with similar functions have been developed to restore the antimicrobial function of exhausted T cells in the chronic infection microenvironment. In the future, these strategies may become important research directions for developing immunomodulatory antimicrobial biomaterials.

Opportunities and challenges. Although specific biomaterials could act as drug carriers to reverse the immunosuppressive state and restore the function of exhausted immune cells, the effect of the physicochemical properties of biomaterials on the function of MDSCs, Tregs, and exhausted T cells in the infected microenvironment have not been well studied. Therefore, to provide a reference for the development of biomaterials, it is necessary to investigate the effects of the physicochemical properties of biomaterials on the molecular mechanisms of cells in the immune microenvironment of chronic infections. Moreover, breaking

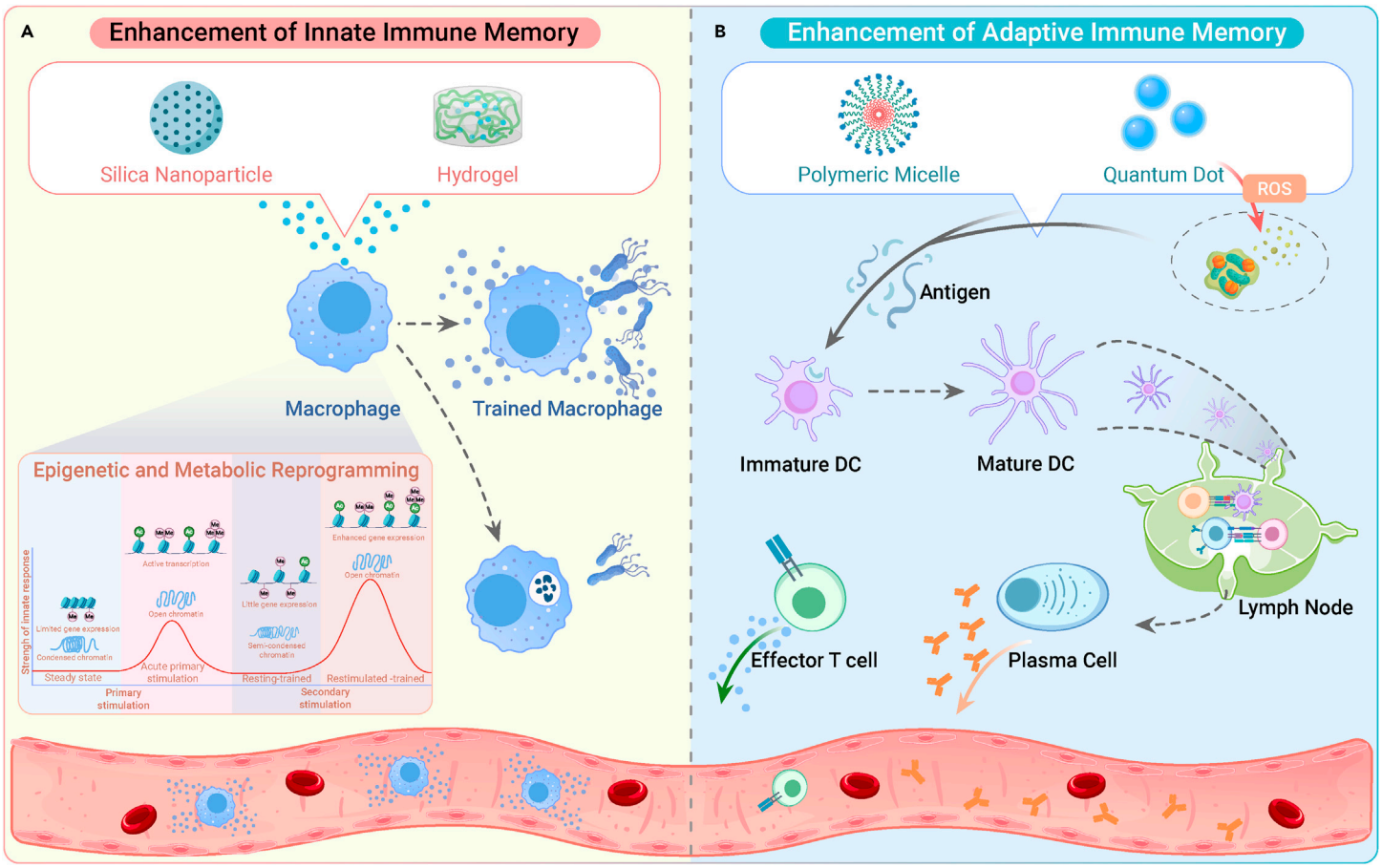

Figure 5. Immunomodulatory antimicrobial biomaterials induce the formation of innate and adaptive immune memory (A) Biomaterials enhance the long-term bactericidal capacity of macrophages by releasing trained immunity inducers that promote metabolic reprogramming. (B) Biomaterials enhance the function of antigen-presenting cells and induce the production of adaptive immune memory by exogenously introducing bacterial antigens or releasing antigens by *in situ* lysis of bacteria from infected tissues.

through the tightly interconnected immunosuppressive networks in the chronic infection microenvironment to enhance the antimicrobial function of immune cells is a major challenge for biomaterials. Recent studies on biomaterials have mainly focused on regulating macrophage M1 polarization, ignoring the presence of multiple suppressor cells, such as MDSCs, Tregs, and DCregs, in the chronic infection microenvironment.[142] In other words, reversing the persistent immunosuppression during chronic infections may increase the number of immune cells, thereby addressing this problem at its source. Therefore, it is necessary to optimize biomaterial properties to penetrate the immunosuppressive network by acting on the molecular targets of several immune cells to improve the treatment of chronic infections. In addition, previous studies have mainly focused on evaluating the efficacy of biofilm and intracellular bacterial clearance, neglecting the presence of insidious persister cells and SCVs. Thus, further studies are needed to evaluate the effectiveness of immunomodulatory antimicrobial biomaterials against persister cells and SCVs *in vitro* and *in vivo*, which could facilitate their clinical translation. Finally, improving the cell specificity of biomaterials targeting intracellular bacteria is important. Although several ligands have been developed to bind macrophages specifically, almost no specific ligands can accurately distinguish between intracellular bacteria-infected and non-infected macrophages, which increases the risk of side effects and reduces the antimicrobial efficacy of biomaterials. Currently, intracellular bacteria are removed by binding the biological material to planktonic bacteria, which then gets delivered into the macrophage.[143] Therefore, further studies using multi-omics and biomaterial technologies are needed to improve the cell specificity of biomaterials for the targeted removal of intracellular bacteria.

BIOMATERIALS FOR BACTERIAL VACCINE DEVELOPMENT

In addition to immunomodulatory antimicrobial agents that can be administered during the acute and chronic phases of infection, bacterial vaccines can enhance the innate or adaptive immune memory before infections occur.[144,145] However, in clinical practice, only symptomatic treatment can be used once an infection has occurred, which is rarely effective in eliminating the pathogen.[146,147] Therefore, using biomaterials to induce *in situ* immune memory in infected tissues has become a popular topic in bacterial vaccine research.[148] Compared with conventional bacterial vaccines, this strategy avoids the complex process of *in vitro* antigen manufacturing, accelerates clinical use during infectious epidemics, and mitigates bacterial damage.[149] Next, we will discuss the characteristics of different biomaterials based on how they enhance innate immune and adaptive immune memory (Figure 5; Table S3).

Enhancing innate immune memory

Innate immune memory, also termed "trained immunity," refers to the epigenetic and metabolic reprogramming changes in monocytes and macrophages after stimulation by certain exogenous factors, including BCG and β-glucan.[150] Subsequently, the immune system can rapidly induce a protective immune response whenever it encounters a different or the same pathogen by secreting high levels of pro-inflammatory factors to fight bacterial invasion.[151] In addition, combinations of multiple cytokines (IL-12, IL-15, and IL-18) have also been shown to induce trained immunity in NK cells.[152] Apart from classical immune cells, several non-immune cells, including endothelial cells and fibroblasts, have been shown to undergo trained immunity.[153] For example, IL-17-dependent fibroblastic reticular cells can promote the secretion of protective antibodies and the anti-inflammatory cytokine IL-10 by B cells after the induction of trained immunity, which improves the clearance of pathogens and reduces inflammatory tissue destruction.[154] Therefore, innate immune memory has unique advantages over adaptive immune memory, such as ease of induction and broad antimicrobial effects.

BCG and β-glucans, two of the most classic inducers of trained immunity, have a good safety profile and are used as adjuvant therapy for several clinical diseases, such as cancer and COVID-19.[155] However, when used alone *in vivo*, β-glucan has some disadvantages, such as a short half-life and several side effects that make it difficult to induce long-lasting trained immunity.[156] Thus, a

Table 1. Clinical trials of immunomodulatory antimicrobial biomaterials

Material type	Active agent	Indications	Status	Clinical trial number
Liposome	heat-inactivated *M. tuberculosis* bacilli	tuberculosis	phase 2	NCT05136833
Liposome	ID93 recombinant protein	tuberculosis	phase 1	NCT02508376
Patch	detoxified pertussis toxin	whooping cough	phase 1	NCT03035370
Aluminum adjuvant	iron surface determinant B	staphylococcal infections	phase 1	NCT01324440
Aluminum adjuvant	recombinant Als3 protein	staphylococcal infections	phase 2	NCT03455309
Alhydrogel adjuvant	recombinant staphylococcal enterotoxin B	toxic shock syndrome staphylococcal	phase 1	NCT00974935

biomaterial capable of improving the metabolism of β-glucan *in vivo* could induce higher levels of innate immune memory. For example, β-glucan coupled with FDA-approved superparamagnetic iron oxide promoted targeted phagocytosis by macrophages in treating sepsis, effectively reprogramming the metabolism of macrophages and inducing the release of markers for training immunity. Compared with the control group, the induction of trained immunity by the nanoparticle significantly enhanced bacteria phagocytosis by macrophages, improving the survival rate of patients with sepsis and enhancing the secondary antibacterial capacity of macrophages.[157]

Enhancing adaptive immune memory

Adaptive immune memory refers to the gene recombination in T and B lymphocytes after infection with a particular pathogen, resulting in an adaptive immune response against that particular pathogen.[158] Enhancing adaptive immunity improves the clearance of residual bacteria from infected tissues and effectively protects the host against repeated attacks by specific pathogens.[159] Therefore, developing biomaterial-based bacterial vaccines capable of efficiently inducing the generation of adaptive immune memory and reducing the reliance on complex conventional vaccines is a critical challenge. The characteristics of two classes of biomaterials for bacterial vaccine production are discussed below based on the location of the bacterial antigen source.

The first type is the exogenous introduction of bacterial antigens. This requires substances containing bacterial antigenic components to be first loaded onto biological material and then injected into healthy patients before the onset of infection to induce the development of adaptive immune memory.[160] Currently, this strategy is the first choice for developing different types of bacterial vaccines.[161] Loading bacterial subunit vaccines onto biomaterials with immune adjuvant properties prolongs antigen release *in vivo* and selectively targets immune cells to induce high levels of adaptive immune memory.[162–164] For example, chitosan-modified poly(lactic-co-glycolic acid) nanoparticles loaded with the recombinant protein outer membrane protein A from *E. coli* have been reported to effectively activate the Th2-dominant immunoprotective response and stimulate the production of specific antibodies to reduce the incidence of meningitis.[165] Although subunit vaccines with well-defined components have considerable potential for clinical translation, the complex antigen production process would limit their rapid deployment during infectious epidemics.[166] In addition, the simple antigenic composition of bacterial subunit vaccines makes it difficult to overcome bacterial immune escape.[167] Therefore, loading biomaterials with substances with multiple bacterial antigenic components would be beneficial to improve the protective efficacy of vaccines. Based on this concept, bacterial extracellular vesicles, attenuated live bacteria, or whole bacterial lysates have been considered promising alternatives to subunit vaccines recently.[168] Bacterial extracellular vesicles are natural products secreted by bacteria rich in immunostimulatory molecules. In addition, bacterial extracellular vesicles have good safety profiles due to their non-reproducibility.[169] For example, extracellular vesicles have shown remarkable efficacy in preventing *Neisseria meningitidis* infection.[170] Extracellular vesicles can also prolong the activation of adaptive immune responses and enhance the bactericidal capacity of various immune cells when co-delivered with biomaterials. For example, *S. aureus*-derived extracellular vesicles loaded on the surface of magnetic mesoporous silica nanoparticles containing the photosensitizer indocyanine green significantly enhanced DC maturation and the proteasome-dependent antigen presentation pathway. In addition, this material system improved the specific bactericidal potency of CD8 T cells and maintained normal humoral immunity.[171]

The second type of vaccine uses biomaterials for *in situ* bacterial lysis and antigen release in infected tissues. Although bacteria alone can be phagocytosed by immune cells *in vivo*, their low immunogenicity makes it difficult to induce adaptive immune memory with protective efficacy.[172] Therefore, biomaterials with immune adjuvant effects, such as nanomaterials containing manganese, selenium, or phosphorus, are needed at the site of infection to enhance bacterial lysis and the release of their immunogenic substances, which can promote the formation of adaptive immune memory to prevent subsequent infections with the same pathogen.[173] For example, injecting a hybrid cell membrane-coated manganese oxide nanoparticle into the site of osteomyelitis infection increased bacterial lysis via an acoustodynamic effect. In addition, the immune adjuvant effect of this system induced chemotaxis, maturation, and antigen delivery of multiple immune cells, thereby enhancing the adaptive immune memory of the body against subsequent *S. aureus* infections.[174] Compared with traditional bacterial vaccines, this strategy does not require the prophylactic injection of complicated bacterial antigens, making it more suitable for rapid clinical use during drug-resistant bacterial epidemics. Moreover, with the success of the "immunogenic cell death" strategy of tumor cells in the treatment of various cancers,[175,176] the possibility of inducing the immunogenic death of bacteria at the site of infection could be an interesting topic for antimicrobial biomaterials research. Recently, Mooney's team has developed a nanovaccine that can significantly induce the activation of antigen-presenting cells by first isolating and killing bacteria under *in vitro* conditions and then enriching and injecting immunogenic substances into the body.[26] Yue and Qu's team first introduced the concept of immunogenic bacterial death, i.e., enhancing the antigenic presentation of DCs by increasing the immunogenicity of dead bacteria to promote the formation of adaptive immune memory.[177] Moreover, AgB nanodots with photothermal and photodynamic effects can also induce immunogenic bacterial death. The nanosystem releases large amounts of PAMPs and stress response proteins during rapid bacterial killing, thereby increasing the recruitment of macrophages and DCs and promoting the formation of memory B cells. This exciting result also provides an example for the future development of novel immunomodulatory antimicrobial biomaterials.

Opportunities and challenges

The use of biomaterials in the development of bacterial vaccines has achieved significant results in enhancing both innate and adaptive immunity and inducing significant immune effects before and after the onset of bacterial infection. However, the development and clinical translation of biomaterial-assisted bacterial vaccines, such as *S. aureus* and *E. coli*, has been challenging due to difficulties in obtaining regulatory approval, with most studies stopping at phase I or II clinical trials.[178] Overall, it is important to address some of these issues limiting the application of biomaterial-assisted bacterial vaccines in future studies. Specifically, antigenic components with higher immunogenicity, specificity, and safety need to be selected for bacterial vaccine development to improve the success rate of clinical translation. Recent studies of non-canonical bacterial antigens using proteogenomics and mass spectrometry-based immunopeptidomics technologies have shown promising results.[179] Compared with traditional single-component vaccines, vaccines produced using complex bacterial antigens can avoid high-frequency mutations in bacterial surface antigens, significantly reducing the risk of death from infection.[180] Another challenge is that the molecular targets of the immune cells affected by biomaterial-assisted bacterial vaccines remain to be explored. Previous evaluations of bacterial vaccine efficacy have often focused on changes in immune memory cell numbers and levels of effector

molecule release. Therefore, understanding the molecular mechanisms of biomaterials and their interaction with other immune cells is poor. For example, tissue-resident memory T cells are important members of adaptive immunity involved in bacterial clearance.[181] However, their specific functions and mechanisms require further investigation. Furthermore, improving the ability of bacterial vaccines to avoid phagocytosis and lysosomal degradation after entry into the body to enhance the induction of immune memory is a challenge affecting the development and application of biomaterial-assisted bacterial vaccines. Usually, after phagocytosis by macrophages, biomaterials are easily destroyed by multiple acids within the lysosome, resulting in the inactivation of bacterial antigens.[182] Therefore, further studies are needed to optimize the chemical structure of biomaterials to avoid lysosomal destruction and achieve efficient induction of immune memory. Furthermore, immunogenic bacterial death is a useful supplement to enhance adaptive immune memory. Therefore, it is necessary to actively search for compounds that can effectively enhance immunogenic bacterial death during clinical treatment and combine them with biomaterials to enhance such effects.

CONCLUSION AND PERSPECTIVES

The complex nature of the immune microenvironment at different stages of bacterial infection often renders biomaterials with direct bactericidal activity ineffective over time, which may partly be attributed to the multiple immune evasion strategies of bacteria and their increased resistance to biomaterials. Thus, immunomodulatory antimicrobial biomaterials with active and passive bactericidal effects offer unique advantages. In this review, we focused on the research progress and future perspectives of immunomodulatory antimicrobial biomaterials used at different stages of infection. First, we discuss the characteristics of the immune microenvironment in the acute and chronic phases of bacterial infection. Then, the research progress, potential advantages, and challenges of immunomodulatory antimicrobial biomaterials for each phase of bacterial infection are separately summarized. Furthermore, the characteristics of biomaterials for bacterial vaccine development are discussed based on their ability to induce innate and adaptive immune memory. Taken together, this review may provide new strategies and approaches for further research treating recalcitrant bacterial infections.

However, there are some limitations to this review. First, because we mainly focus on the application of immunomodulatory biomaterials in the different stages of bacterial infection, advances in biomaterials for fungal or viral infections have not been included in this review. Several reviews on this topic are available.[183,184] Second, as the chemical synthesis methods and structural design of immunomodulatory biomaterials have been discussed in many reviews in recent years,[185,186] we have not compared and summarized the biomaterials from these perspectives in this review.

Clinical translation is always the ultimate goal in developing immunomodulatory antimicrobial biomaterials. With recent technological advances, some biomaterials have entered clinical trials (Table 1). However, several challenges still need to be addressed in a collaborative and multidisciplinary manner to accelerate the application of these biomaterials for the treatment of clinical infections. First, the characteristics of the immune microenvironment at different stages of infection need to be further explored. For example, elucidating the spatial distribution and cellular interactions of immune cells within infected tissues at different stages of infection will facilitate eliminating immunosuppressive networks. Similarly, the discovery of new immune cell subsets in the infection microenvironment and the detailed decoding of tertiary lymphoid structures will facilitate the early diagnosis of bacterial infections and the assessment of the risk of recurrence. A more precise understanding of the dynamic characteristics of the immune microenvironment induced by different pathogens will allow the proposal of novel therapeutic strategies and the development of immunomodulatory antimicrobial biomaterials. Second, the influence of the biomaterial's physicochemical properties on immune cells' antimicrobial efficacy must be investigated in detail. Biomaterials of different sizes, shapes, charges, hardness, and surface roughness have very different effects on the differentiation and function of immune cells. Therefore, the traditional emphasis on the physicochemical properties of biomaterials for bactericidal activity is no longer sufficient to meet the needs of today's clinical management of chronic infections. Furthermore, the application of artificial intelligence platforms to the structural design and surface modification of immunomodulatory biomaterials will accelerate the exploration of the effects of the physicochemical properties of biomaterials on immune cells. In addition, novel strategies to regulate immune cells against bacteria should be proposed and improved. For example, immunogenic bacterial death and trained immunity are promising strategies for treating infections, and future research should further elucidate the molecular mechanisms behind them. On this basis, novel immunomodulatory antimicrobial biomaterials could be developed to mitigate tissue damage caused by recalcitrant bacteria and reduce the infection recurrence rate.

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ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (grant nos. 32222042, 82225031, 82172464, 82172453, and 81972086), the Shanghai Rising-Star Program (21QA1405500), and the Program of Shanghai Excellent Academic Leader (grant no. 22XD1401900).

AUTHOR CONTRIBUTIONS

S.Z., X.Q., B.Y., and L.T. conceived and organized the review. X.Q. and S.Z. wrote the manuscript. S.Z., H.Y., and M.W. participated in the data collections. X.Q., B.Y., D.M., F.W., L.T., and K.Y. revised the manuscript. All authors approved the submission of the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.1016/j.xinn.2023.100503.

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