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Advanced Antibacterial Strategies for Combatting Biomaterial-Associated Infections: A Comprehensive Review

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Keywords: antifouling coatings | antimicrobial-eluting coatings | biomaterial-associated infections | contact killing coatings | multifunctional antimicrobial coatings

ABSTRACT

Biomaterial-associated infections (BAIs) pose significant challenges in modern medical technologies, being a major postoperative complication and leading cause of implant failure. These infections significantly risk patient health, resulting in prolonged hospitalization, increased morbidity and mortality rates, and elevated treatment expenses. This comprehensive review examines the mechanisms driving bacterial adhesion and biofilm formation on biomaterial surfaces, offering an in-depth analysis of current antimicrobial strategies for preventing BAIs. We explore antimicrobial-eluting biomaterials, contact-killing surfaces, and antifouling coatings, emphasizing the application of antifouling polymer brushes on medical devices. Recent advancements in multifunctional antimicrobial biomaterials, which integrate multiple mechanisms for superior protection against BAIs, are also discussed. By evaluating the advantages and limitations of these strategies, this review aims to guide the design and development of highly efficient and biocompatible antimicrobial biomaterials. We highlight potential design routes that facilitate the transition from laboratory research to clinical applications. Additionally, we provide insights into the potential of synthetic biology as a novel approach to combat antimicrobial resistance. This review aspires to inspire future research and innovation, ultimately improving patient outcomes and advancing medical device technology.

Esra Kasapgil and Manuela Garay-Sarmiento contributed equally to this study.

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1 | Biomaterial-Associated Infections: The Nightmare of Modern Medical Technologies

Advances in medicine, medical engineering and technology in the past decades have revolutionized modern healthcare practice, opening new possibilities for improving patient outcomes, safety, and quality of life. The development of innovative biomaterials and medical devices plays an indispensable role in these advancements. They are designed to be biologically active and biocompatible, enabling them to maintain their functionality within the body without triggering adverse host responses (Williams 2022). However, despite the substantial advances in biomaterial technology and surgical sterile techniques, biomaterial-associated infections (BAIs), also known as device-associated infections, remain a persistent challenge in modern healthcare (Garvey 2023). BAIs occur when bacteria adhere to the biomaterial surface. This adhesion, usually irreversible, can lead to the formation of biofilms, which are communities of bacteria encased in a protective matrix of extracellular polymeric substances (EPSs). These biofilms are highly resistant to innate immune system and conventional antibiotic treatment, making them difficult to eradicate and contributing to the persistence of infections (Blanco-Cabra et al. 2024; Hodges, Sussman, and Stegemann 2021). BAIs are a major postoperative complication and a leading cause of implant failure (Figure 1) (Ding et al. 2020; Hodges, Sussman, and Stegemann 2021). Furthermore, they represent a significant risk factor for patients, leading to prolonged hospitalization, increased morbidity, higher mortality rates, and elevated treatment expenses (Assefa and Amare 2022). In the United States alone, BAIs account for approximately 25% of all healthcare-related infections (HAIs), with an estimated total of around one million cases and over 100,000 deaths annually (Cao et al. 2022). In the European Union, about 4.3 million cases of HAIs were diagnosed during the 2022–2023 period. Notably, 31.5% of healthcare-associated pneumonia cases, 61.9% of healthcare-associated urinary tract infections, and 36.7% of healthcare-associated bloodstream infections were identified as device-associated (Suetens, Kärki, and Plachouras 2024). Furthermore, BAIs impact specific demographics more than others, with age, underlying health conditions, and immunocompromised states contributing to this selectivity. Among critically ill patients, catheter-associated infections and vascular graft-associated infections have mortality rates ranging from 12% to 26% (Zhong et al. 2021) and 15% to 75% (Sixt et al. 2022), respectively. These alarming statistics highlight the urgent need for effective prevention and management strategies for BAIs.

In this review, we provide a detailed description of the underlying mechanism driving bacterial adhesion and subsequent biofilm formation on biomaterial surfaces. Furthermore, we provide a comprehensive overview of the status quo of antimicrobial strategies for the prevention of BAIs, addressing both advantages and limitations for clinical care. These strategies encompass the use of antimicrobial-eluting biomaterials, contact-killing surfaces, and antifouling surfaces. In particular, among the latter strategy, our focus lies on surface coatings based on antifouling polymer brushes and the intricacies associated to their application onto biomedical devices. In this context, we present recent research efforts toward the clinical translation of polymer brush-like coatings. Additionally, we discuss the latest advancements in multifunctional antimicrobial biomaterials, which combine different mechanisms at once, providing superior protection against BAIs. The objective of this review is to provide guidance and ideas for future studies on the design and development of highly efficient and biocompatible antimicrobial biomaterials. In particular, we discuss potential design routes that facilitate the translation from laboratory settings to real clinical applications. Finally, we provide our perspective on the potential of synthetic biology as a novel avenue for combating antimicrobial resistance (AMR).

2 | Biofilm Formation and Infection Development on Biomaterials

One major concern with biomaterials is that they can create an entry point for bacteria, thereby facilitating their access to the human body and increasing the risk of infection and potentially leading to serious complications (Dong et al. 2022). Bacterial transmission through catheters can occur, for instance, through the main channel or by ascending up the catheter's exterior surface. In this manner, bacteria can gain access to the bloodstream, heart, and other vital organs, where they can cause life-threatening infections. Moreover, biomaterials establish an interface that is distinct from the host's natural environment. Once inserted into the body, macromolecules, which are ubiquitous in interstitial and bodily fluids, rapidly adsorb onto the biomaterial surface, forming a conditioning film. The conditioning film consists of adsorbed proteins, which act as anchorage points for the attachment of bacterial cells (Arciola, Campoccia, and Montanaro 2018; Gasik 2017). This stable adhesion to the surface signals some bacteria to secret EPSs that promotes further colonization and the formation of a biofilm (Figure 1a). Notably, the EPSs creates a robust chemical and physical barrier that complicates the treatment of bacterial infections by 10–1000 times compared to planktonic bacteria (Ding et al. 2020; Mah and O'Toole 2001). Furthermore, the development of resistance is exacerbated by genetic activation within the biofilm, which results in altered surface structures and molecular targets that reduce susceptibility to antimicrobials. It was suggested, that these phenotypic alterations are of greater consequence with regard to AMR than external factors such as the biofilm matrix or glycocalyx (Tenke et al. 2004). Furthermore, bacteria from mature biofilms can be continuously released into neighboring tissues, and the bloodstream, which may result in life-threatening conditions such as bacteremia and sepsis (Di Domenico, Oliva, and Guembe 2022).

Conventional methods, such as antibiotic treatment, are frequently unable to eradicate biofilms and may even contribute to increased AMR (P. Li et al. 2023). In recent years, the overuse and misuse of antibiotics have increased the spread of antibiotic-resistant bacteria, leading to approximately 700,000 deaths worldwide each year. The World Health Organization predicts that this number could rise to 10 million by 2050 if no alternative strategies are developed (Peng et al 2023). Understanding the driving forces for bacteria to attach to surfaces, enter the body, develop biofilms, and cause infections is of paramount importance. This knowledge is crucial for devising effective antimicrobial strategies that mitigate the development of infection. In addition, introducing new types of multifunctional coatings

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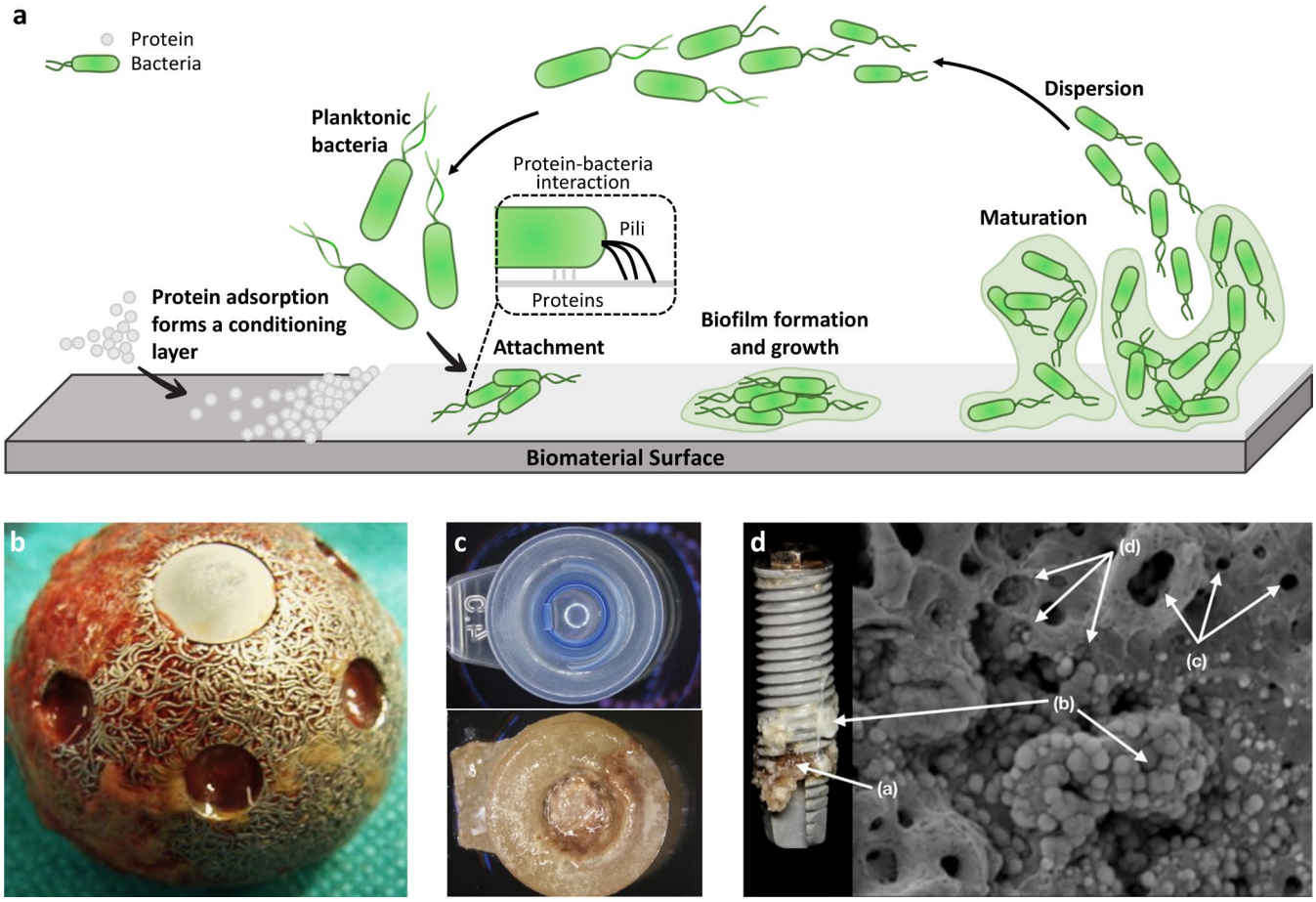

FIGURE 1 | Biofilm formation on medical devices. (a) Schematic illustration of the different stages in biofilm progression. The process begins with the adsorption of proteins onto the device surface, forming a conditioning layer that serves as an anchorage for bacterial adhesion. After first adhesion to the surface, the production of EPS is initiated. The biofilm starts to growth, forming microcolonies where bacterial cells aggregate and accumulate in multiple layers. Ultimately, the mature biofilm disperses and releases planktonic bacterial cells, initiating a new cycle of biofilm formation. (b) Biofilm visible on the titanium surface of an extracted hip acetabular implant (Romanò et al. 2017). Copyright 2016, Springer International Publishing Switzerland. (c) Comparison of a new and an extracted voice prosthesis after 5 months in vivo. The extracted prosthesis is extensively covered with microbial biofilm (Leonhard and Schneider-Stickler 2015). Copyright 2015, Springer International Publishing Switzerland. (d) Extracted screw implant with attached necrotic bone (a) and biofilm (b). SEM images depicts biofilm formation also inside micropores (d) (Viljoen 2019). Copyright 2019, Andre J. Viljoen.

that combine several functions at once holds great promise for addressing the limitations of conventional strategies and assisting in cases of antibiotic failure.

3 | Strategies to Prevent Bais

The prevention of bacterial colonization of biomaterials and their associated infections has followed two approaches: the use of bactericidal or antifouling coatings. Bactericidal coatings are designed to either kill microbial pathogens at the surface by immobilizing bactericidal compounds or by killing them in close proximity by eluting these compounds. The bactericidal compounds employed in such coatings include antibiotics, cationic surfactants, metal nanoparticles, antimicrobial peptides (AMPs) and polymer analogs, antimicrobial enzymes, and bacteriophages. On the other hand, antifouling coatings are based on physical approaches that aim at reducing the attractive interactions between bacteria and the surface or even introducing kinetic barriers to adhesion. This approach includes the use of hydrophilic coatings, superhydrophobic coatings, and slippery liquid-infused porous surfaces (SLIPS). A more recent idea is to integrate both bactericidal and antifouling concepts into a single coating to benefit from synergistic effects (Uneputty et al. 2022). In this section, these four antimicrobial strategies are overviewed: antimicrobial-eluting materials, contact-killing surfaces, antifouling surfaces, and multifunctional coating strategies. Each of these mechanisms offers distinct advantages and shortcomings in combatting BAIs, which is discussed below. Additionally, the potential of bottom-up synthetic biology as an innovative strategy for combating BAIs and AMR is discussed.

3.1 | Antimicrobial-Eluting Materials

Antimicrobial eluting coatings consist of a matrix, usually inert, in which one or more antimicrobial agents are encapsulated for sustained release. The matrix usually consists of polymers (amorphous, above Tg), hydrogels and porous ceramics, among others, which are designed to be as biocompatible as possible

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to avoid the occurrence of adverse reactions (Bhattacharjee et al. 2022; Olmo et al. 2020). The two main functions of the matrix are to contain the antimicrobial compound and to limit its release to ensure continuous delivery over a period of time relevant to the application. In this way, only small concentrations of the active agent are released at a given time, reducing potential toxicity issues and ensuring prolonged protection. At the same time, the matrix protects the active component from degradation under physiological conditions (Bhattacharjee et al. 2022). Several mechanisms have been developed for drug release, including passive diffusion, pore formation, stimuli-responsive erosion/degradation of the coating, or desolvation and shrinkage of hydrogels to expel the active agent, as well as its enzymatic production. Ideally these mechanisms should avoid burst release but be rather constant in time, which is usually achieved by designing the matrix to have predictable degradation kinetics (Campoccia, Montanaro, and Arciola 2013; Mu et al. 2023). The most commonly utilized class of antimicrobial in drug-eluting materials is antibiotics. It encompasses a range of broad-spectrum antibiotics, including gentamicin (Lazic et al. 2022; Sharma et al. 2024), vancomycin (Cai et al. 2021; Y. Li et al. 2020; Yuan et al. 2018), rifampicin (Qayoom et al. 2024; Sung et al. 2021), linezolid (Eren Boncu, Ozdemir, and Uskudar Guclu 2020; Kaur, Harjai, and Chhibber 2014), and amoxicillin (Qu et al. 2019). However, antibiotic-based strategies carry several risks, including systemic toxicity, water insolubility, and the potential for drug resistance stemming from inappropriate and excessive use of antibiotics (H. Wei et al. 2022). As a result, there is a strong movement toward developing alternative coatings that do not rely on antibiotics. These alternatives incorporate metal nanoparticles, cationic molecules and polymers, HDPs, antimicrobial enzymes, bacteriophages, and the in situ production of nitric oxide (Figure 2a).

Among the most commonly used metal compounds are silver (Ag), copper (Cu), zinc (Zn), and gold (Au). These compounds generate metal ions that induce bacterial death by creating oxidative stress or by chelating with DNA and proteins within bacterial cells (Frei et al. 2023). Ag has garnered considerable attention for its long-lasting antimicrobial properties and low toxicity. At present, numerous commercially available biomedical products contain Ag, including bandages, ointments, catheters, and bone implants (Sim et al. 2018). The biocidal mode of action of Ag involves the permeabilization of the cell membrane, the binding to and inhibition of enzymes and proteins that are essential for cell survival, the interruption of DNA replication, and the generation of reactive oxygen species (ROS) (Takac et al. 2023). Its toxicity toward host cells is reduced by limiting their availability away from the coating. The solubility of Ag^+ in the presence of Cl^- is extremely low ($K_{sp} = 1.8 \cdot 10^{-10}$); thus, these ions are only present next to the coating but rapidly reduced their concentration away from it. Nonetheless, several research groups have highlighted concerns regarding the extensive use of Ag and potential hazards to the environment, human health, and safety (Bondarenko et al. 2013; Liao, Li, and Tjong 2019). Additionally, there have been multiple reports of metal-resistant bacterial isolates, highlighting the necessity for cautious use of these metals (Hosny et al. 2019; Vats, Kaur, and Rishi 2022).

The cytoplasmic membrane of bacteria is composed of lipopolysaccharides and phospholipids, including phosphatidylglycerol and cardiolipin, which feature negatively charged groups (Talapko et al. 2022). These negatively charged components strongly attract positively charged molecules, AMPs, polymers and quaternary ammonium compounds (QACs) making them promising candidates as antimicrobial agents. Cationic molecules disrupt the integrity of the negatively charged bacterial membrane causing cell death (Alfei and Schito 2020; Carmona-Ribeiro and de Melo Carrasco 2013; Talapko et al. 2022). Chlorhexidine is a potent cationic antimicrobial agent that exhibits bacteriostatic properties at low concentrations and bactericidal activity at higher ones (Shahid et al. 2021; Zussman, Giladi, and Zilberman 2022). It has been used to formulate antimicrobial coatings for dental (Wood et al. 2015) and titanium (Ryu et al. 2015) implants as well as catheters (Gefter Shenderovich et al. 2018). Despite its efficacy, chlorhexidine presents challenges related to the emergence of resistance, as well as the difficulty in ensuring a safe dosage range that effectively targets bacteria while avoiding toxicity to human cells, especially at higher concentrations (George, Klika, and Higuera 2017).

HDPs, produced by nearly all organisms, are short, positively charged peptides. Since the 1980s, HDPs have been recognized as effective antimicrobial agents against AMR strains. Upon contact with biological membranes, most HDPs adopt a facially amphiphilic conformation enabling the hydrophobic regions to insert into the hydrophobic domains of the microbial membrane thereby disrupting the membrane and leading to cell death (Figure 3a). The cationic domains facilitate interaction with the more negatively charged membranes of microbes, providing a degree of specificity for HDPs toward microbial cells rather than mammalian cells. The antimicrobial activity of HDPs extents to both Gram-positive and Gram-negative bacteria as well as fungi and viruses (Gupta et al. 2018). Moreover, the likelihood of resistance development is low as mutations are unlikely to result in large changes in the physical properties of the membrane thus bacteria cannot evade their action (Bertelsen et al. 2023; Etayash and Hancock 2021; Song et al. 2020). Over the past years, scientists have developed a wide range of surface coatings that elute natural and synthetic HDPs aimed at preventing bacterial infections at implant sites (Dong et al. 2024; Duque-Sanchez et al. 2024; Kazemzadeh-Narbat et al. 2013; Lin et al. 2021; Y. Zhang et al. 2017; L. Zhang et al. 2021). In particular, the usage of the synthetic analogues has helped overcome shortcomings such as stability and proteolysis under physiological conditions (Mookherjee et al. 2020). Nevertheless, their chemical synthesis is a time-consuming, costly, and challenging process, which is difficult to translate into large-scale production. Toward overcoming these limitations and make clinical translation more feasible, HDPs-mimicking oligomers/polymers were introduced. These molecules are engineered to mimic the amphiphilic structure of HDPs (Figure 3b), while being easier and more cost-effective to synthesize. Moreover, they can be designed to exert excellent stability and resist proteolysis. By analogy, these molecules comprise cationic and hydrophobic moieties which are conjugated in various ways, such as block, random, or alternating sequences (Kuroki et al. 2017). Among some examples are arylamide (Scott, DeGrado, and Tew 2008), phenylene–ethynylene (Arnt and Tew 2002), poly(-methacrylate) (Kuroda, Caputo, and DeGrado 2009), nylon-3, poly(norbornene) (Ilker et al. 2004), poly(4-vinylpyridine) (Tiller et al. 2001), and poly(2-oxazoline)–based (M. Zhou

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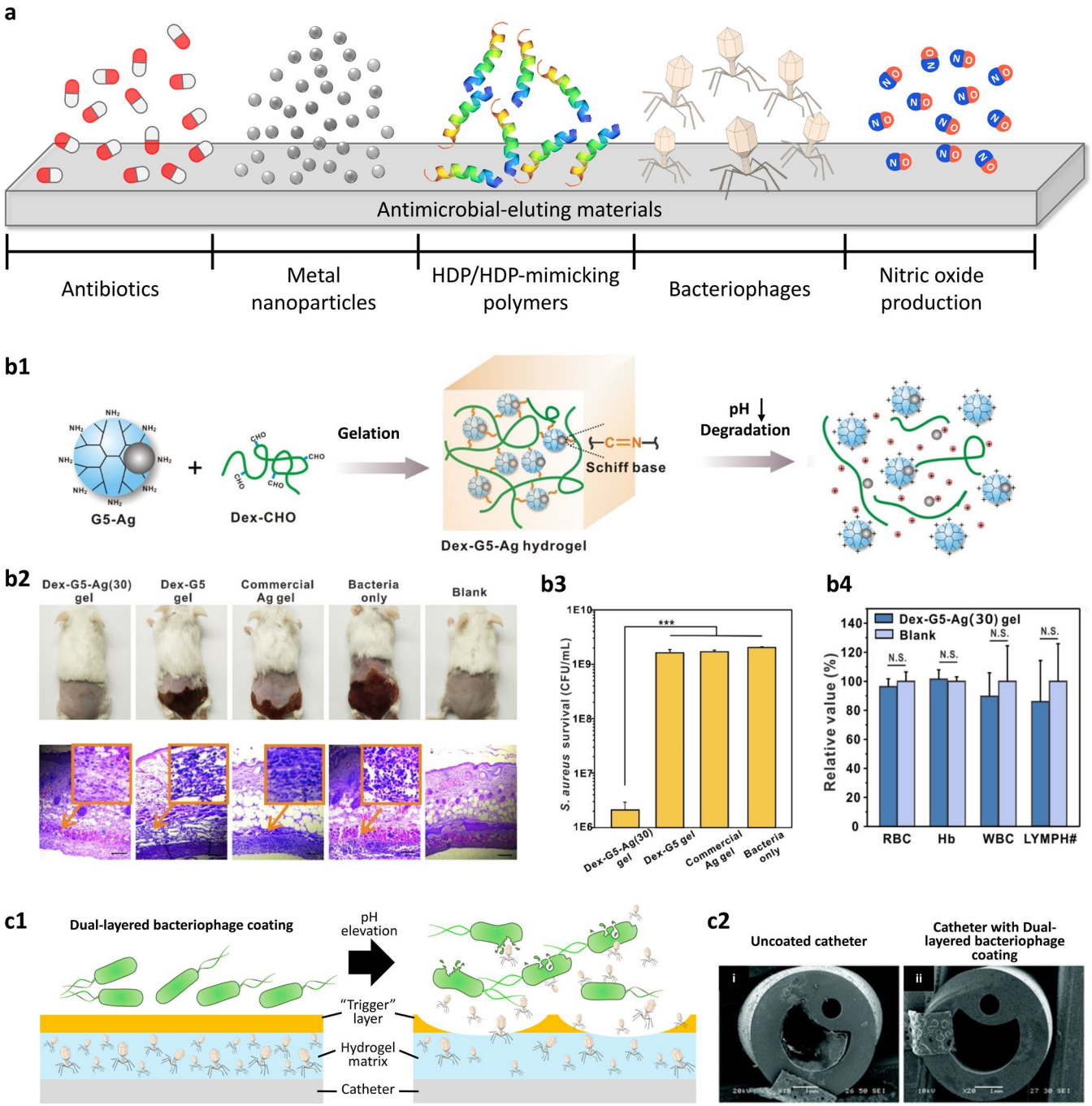

FIGURE 2 | (a) Drug-eluting materials employ a range of antimicrobial agents, including antibiotics, metal nanoparticles, HDP, synthetic antimicrobial peptides, and polymer analogues as well as bacteriophages and the in situ production of nitric oxide. (b) The pH-responsive Dex-G5–Ag nanocomposite hydrogel was formed via a Schiff-base linkage between oxidized polysaccharides and cationic dendrimers, which encapsulate Ag nanoparticles. The release of both the cationic dendrimers (G5) and Ag is initiated upon the degradation of the Schiff base linkage, which is caused by the acidity generated by the growth of bacteria in the vicinity (b1). Comparison images and histological examination of mice treated with *S. aureus* (10^8 CFU mL^{-1}) and the Dex-G5–Ag (30) hydrogel, the Dex-G5 gel, bacteria only and without any treatment. The blue color indicates *S. aureus* infection (b2). Scale bars are 200 μm. Quantification of *S. aureus* survival (CFU mL^{-1}) at the infected site (b3). Hematological parameters of mice that were injected with the Dex-G5–Ag (30) hydrogel or PBS (control) for a period of 2 weeks (b4). Adapted with permission from Dai et al. (2018). Copyright 2018, American Chemical Society. (c) An in situ infection detection sensor coating for urinary catheters. The coating employs a dual-layered system consisting of a lower hydrogel "reservoir" layer that contains bacteriophages and a second "trigger" layer that degrades in response to increased urinary pH. Adapted with permission from Milo et al. (2016). Copyright 2016, The Authors. Published by Elsevier B.V (c1). SEM images depicting cross-sections of (i) uncoated and (ii) coated (dual-layer bacteriophage) urinary catheter, comparing levels of encrustation and blockage by *P. mirabilis* (c2). Reproduced with permission from Milo et al. (2017). Copyright 2017, The Royal Society of Chemistry.

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et al. 2020) derivates. Notably, it was demonstrated that an appropriate balance of hydrophilic/hydrophobic moieties, as well as charge and facial amphiphilicity are key aspects determining the antimicrobial activity of these molecules as well as their specificity toward microbial membrane rather than host cells (Figure 3c). Following these principles, the arylamide-based HDP-mimicking oligomer Brilacidin (Hu et al. 2022), has successfully completed Phase II clinical trials. The growing development of more HDP-mimicking molecules and their success so far holds promise for the development of novel antimicrobial formulations for biomaterial-coatings aimed at effectively preventing BAIs.

Overall, antimicrobial-eluting materials are designed to combat BAIs by ensuring a controlled and sustained release of antimicrobial compounds directly at the site of medical device implantation, thereby constraining initial colonization and preventing biofilm formation on implanted surfaces (Shahid et al. 2021). A short overview of these materials is provided in Table 1. It is important to note that the effectiveness of antimicrobial-eluting systems depends not only on the type of antimicrobial used but also on the manner and rate of release. The primary drawback of antimicrobial-releasing coatings is their limited effective lifetime; once the antibacterial agents are completely released, the coatings become ineffective, raising the risk of infection. Therefore, achieving controlled release and long-term stability is a significant challenge in antimicrobial-eluting systems. Specifically, combating AMR and BAIs requires antimicrobial strategies with sustained inhibition of biofilm formation.

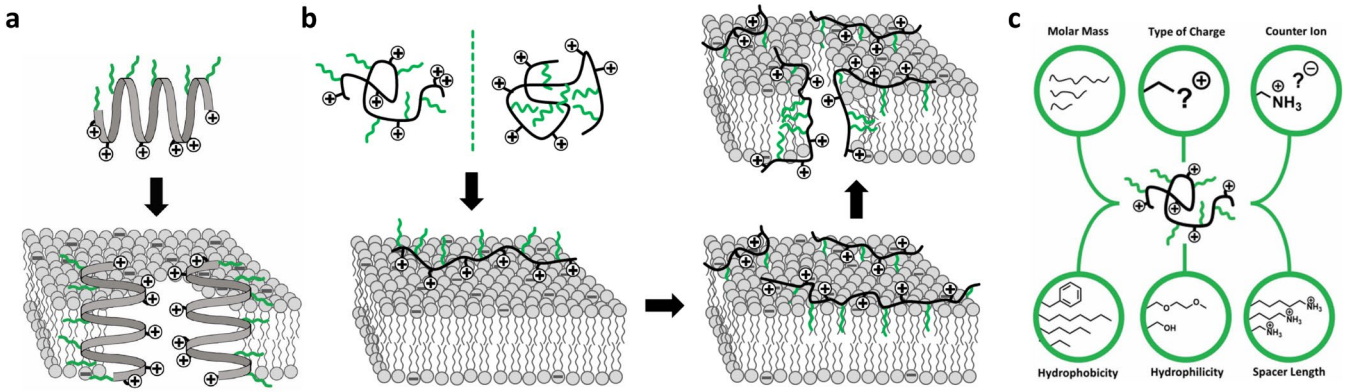

FIGURE 3 | (a) Schematic illustration of the mode of action of HDPs. (b) Schematic illustration of the mode of action of HDP-mimicking polymers. In solution the polymer has either a random coil or partially segregated conformation. At the bacterial membrane, the polymer adopts a facially amphiphilic conformation enabling the hydrophobic regions to insert into the hydrophobic domains of the microbial membrane thereby disrupting the membrane and leading to cell death. (c) Parameters that have been shown to affect the antimicrobial properties of the HDF-mimicking polymers. Reprinted with permission from Hartlieb et al. (2017). Copyright University of Warwick.

TABLE 1 | Summary of the discussed antimicrobial eluting coating systems for combatting BAIs.

Antimicrobial agent	Matrix	Tested pathogens	References
Silver–cationic polymer	pH-responsive hydrogel	*S. aureus* *E. coli*	(Dai et al. 2018)
Chlorhexidine	Chlorhexidine–hexametaphosphate nanocoating on Ti substrates	*Streptococcus gordonii (S. gordonii)*	(Wood et al. 2015)
	Varnishes based on ethylcellulose or ammonio methacrylate copolymer on Foley catheters	*P. aeruginosa*	(Gefter Shenderovich et al. 2018)
HDPs	Mesoporous silica nanoparticle-functionalized titanium implants	*S. aureus* *E. coli* *P. aeruginosa* MRSA	(Dong et al. 2024)
	Multilayered calcium phosphate coatings and a phospholipid layer on Ti substrates including nanotubes	*S. aureus* *P. aeruginosa*	(Kazemzadeh-Narbat et al. 2013)
	Poly(ethylene glycol)-poly(caprolactone) polymer coating on urinary catheters	*E. coli*	(Lin et al. 2021)
	Collagen coating around Ca- and Si-based ceramic nanorods on Ti implants	*S. aureus*	(L. Zhang et al. 2021)

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3.2 | Contact-Killing Surfaces

Contact-killing surface modifications are engineered to kill bacteria upon contact. These strategies include surface nanostructuring and the application of coatings based on metal ions, cationic polymers, AMPs, and antimicrobial enzymes (Figure 4a and Table 2) (Yao et al. 2023). Surface nanostructuring involves creating sharp submicrometer structures that mechanically stretch, and rupture the bacterial cell envelope, inducing cell death through extensional deformation and stress concentration (Figure 4b) (Oopath et al. 2022; Tripathy et al. 2017; Wu, Liu, and Chu 2024). The height, diameter, spacing, stiffness, and arrangement of the nanostructures are key parameters that control their bactericidal efficacy (Figure 4c,d). Fabrication technologies include different mechanical and chemical methods such as nanoimprinting lithography, electron beam lithography, laser-based lithography, anodization, and hydrothermal synthesis (Kumara

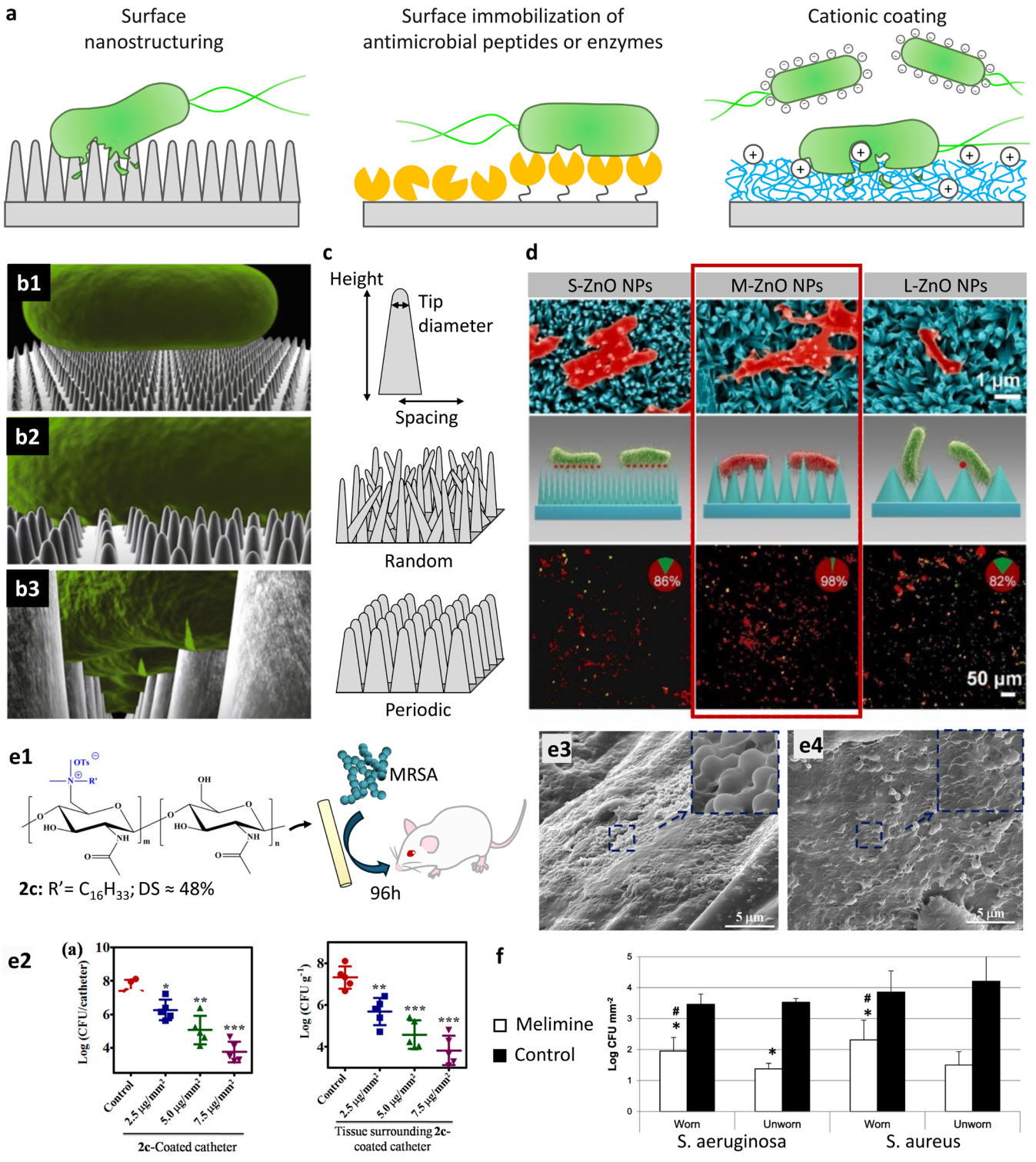

FIGURE 4 | Legend on next page.

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et al. 2023). However, most of these fabrication techniques require multiple time-consuming steps, and the original substrate must be flat, making this bactericidal strategy less viable for commercial-scale biomedical applications. Moreover, its performance can be rapidly impaired in complex biological media where fouling can alter the adhesion to the structures. Biocidal coatings, on the other hand, can be applied to the various intricate shapes of implants, covering both internal and external features. Coatings consisting of the AMP melimine have demonstrated the ability to reduce biofilm formation on titanium implants in in vivo rodent studies (R. Chen et al. 2016) and to decrease the incidence of microbial keratitis when applied to contact lenses in human clinical trials (Figure 4e) (Dutta, Ozkan, and Willcox 2014). Despite the

TABLE 2 | Summary of the discussed contact killing coating systems for combatting BAIs.

Antimicrobial Component	Substrate	Tested Pathogens	References	Shortcomings
Nanostructured surfaces				
ZnO nanopillars	Silicone	*P. aeruginosa*	(Yi et al. 2022)	Time-consuming fabrication Limited to flat substrates Reduced effectiveness due to fouling
AMP				
Melimine	Titanium	*S. aureus* *P. aeruginosa*	(R. Chen et al. 2016)	High production costs Toxicity Susceptibility to biodegradation Decrease in activity after immobilization
Melimine	Contact Lenses	*S. aureus* *P. aeruginosa*	(Dutta, Ozkan, and Willcox 2014)	
Antimicrobial enzymes				
Endolysin, Clyf	Siliconized glass, silicone-coated latex catheter, and silicone catheter	*S. aureus*	(W. Yang et al. 2021)	Lack of studies on the efficacy of enzymes on solid surfaces
Endolysin, PlyGBS94	Polycaprolactone (PCL) meshes	*S. agalactiae*	(Garay-Sarmiento et al. 2022)	
Cationic polymers				
Chitin	Polystyrene plates, glass	*S. aureus* *E. coli* *P. aeruginosa*	(Hoque et al. 2016)	Nonselective toxicity to mammalian cells Prone to debris deposition and reducing effectiveness

FIGURE 4 | Antimicrobial contact-killing strategies. (a) Strategies are based on the modification of the surface with submicron, sharp structures, the non-oriented and oriented immobilization of AMP and antimicrobial enzymes as well as the decoration of the surface with cationic polymers. (b) The bactericidal action of the surface nanostructuring approach is attributable to the direct contact between the bacterial membrane and the surface protrusions, which results in significant membrane stretching at regions between nanopillars and subsequent cell lysis. Reprinted with permission from Pogodin et al. (2013). Copyright 2013, The Biophysical Society. (c) The bactericidal effectiveness depends on different parameters such as the features geometry and organization. The surface features can exhibit a variety of aspect ratios, heights, tip diameters, base widths, and spacings (densities), and they can be either periodic or randomly organized. (d) Schematic illustration, SEM, and CLSM images of *P. aeruginosa* incubated on flat silicon and surfaces of varying sizes of ZnO nanopillars. Reprinted with permission from Yi et al. (2022). Copyright 2022, Elsevier B.V. All rights reserved. (e) Biodegradable antimicrobial paint coating based on quaternary chitin polymers tested in vivo for 96 h in rodent animal studies (1). In vivo antimicrobial effect of coated catheters on MRSA. Cell count on harvested catheters and in the surrounding tissue samples (2). SEM images visualizing MRSA cells on uncoated and coated catheters (3). Adapted and reprinted with permission from Hoque et al. (2016). Copyright 2016, American Chemical Society. (f) Quantification of *S. aeruginosa* and *S. aureus* adhesion on melimine-coated and uncoated (control) contact lenses tested in human clinical trial. Asterisk (*) represents significant difference between coated and uncoated samples, while dagger (#) represents significant difference between worn and unworn samples. Reprinted with permission from Dutta, Ozkan, and Willcox (2014). Copyright 2014, American Academy of Optometry.

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promise shown by AMPs as alternatives to antibiotics, their widespread use has been hindered by high production costs, toxicity, and susceptibility to biodegradation. Moreover, immobilizing AMPs onto surfaces often results in a decrease in their bactericidal activity (Rapsch et al. 2014). Recently, the immobilization of antimicrobial enzymes has garnered significant attention due to their advantages including high-specificity, cost-effective production, and rapid mode of action against biofilms (Liao, Li, and Tjong 2019). Moreover, it has been demonstrated that their physical and chemical immobilization on surfaces not only renders them more resistant to environmental changes and improves bench stability, but also enhances their bactericidal efficiency. Consequently, immobilized amylase, cellobiohydrolase, pectinase, subtilisin A, and β-*N*-acetyl-glucosaminidase (DspB) demonstrated enhanced efficacy in inhibiting biofilm formation and removing matured biofilms compared to their free forms (Lahiri et al. 2022; Villa et al. 2015). In particular, endolysins, which are a family of phage-encoded enzymes that have a novel mode of action based on peptidoglycan degradation, are rapidly developing enzybiotics with some candidates already in late stages of clinical development or commercially available (Shah et al. 2023). However, the efficacy of lysins on solid surfaces has been sparsely investigated. Some of the few studies on the subject include the utilization of the endolysins, ClyF, on silica surfaces (W. Yang et al. 2021) and PlyGBS94 on poly(-caprolactone) wound dressings (Garay-Sarmiento et al. 2022). Both coatings demonstrated effective prevention of bacterial contamination in in vitro studies, while exhibiting no toxicity to mammalian cells. These studies indicate the promising potential and safety of endolysins for combating BAIs.

The utilization of cationic polymers is one most widely used strategies to prepare contact-killing surfaces in scientific research. Cationic polymers have a broad antimicrobial activity based on the attraction of the negatively charged bacterium to the surface, where the polymers are able to disrupt the bacterial cell envelope causing leakage and concomitant bacterial death. Most cationic polymer coatings include chitin-derivates, monomers bearing QACs or poly(ethylenimine) (Y. Qiu et al. 2007; Yao et al. 2023). For example, medical grade catheters have been coated with a chitin-based paint significantly reducing biofilm formation and bacterial infection in mice (Figure 4f) (Hoque et al. 2016). Nevertheless, most cationic polymer coatings lack selective toxicity, which also results in the varying grades of toxicity to mammalian cells (H. Qiu et al. 2020; Song et al. 2020). Furthermore, cationic surfaces are more vulnerable to the deposition of cell debris due to electrostatic interaction, which in turn masks and blocks the active surface reducing its bactericidal effectiveness.

In general, the usage of contact-killing strategies offers significant advantages, as it reduces the likelihood of generating AMR. Furthermore, its non-leaching nature might accelerate approval by regulatory agencies. However, current systems also exert great limitations due to the susceptibility of the modified surface to cell and cell debris accumulation. The build-up of debris blocks the active surface, reducing its bactericidal effectiveness and providing anchoring points for further bacterial attachment. Because of this, the antimicrobial activity of these coatings last only for a short period which may not always be sufficient to achieve complete clearance of infections in vivo, highlighting the need for further advancements and complementary approaches to enhance their long-term efficacy. To maintain long-term antibacterial activity, it is therefore desirable to combine this strategy with a nonadhesive or cleaning mechanism that either prevents or removes buildup on the surface. The development of such multifunctional modification strategies will be further discussed in Section 3.4.

3.3 | Antifouling Surfaces

Antifouling surfaces prevent the initial colonization of bacteria and can be categorized into two main strategies: minimizing surface energy to reduce wetting and introducing kinetic barriers. Fluorinecarbone- and silicon-based coatings, omniphobic coatings, superhydrophobic coatings, and SLIPS are examples of low surface energy materials, whereas hydrophilic polymer coatings exemplify those with kinetic barriers (Figure 5a) (DeFlorio et al. 2021).

The first category consists of surfaces that avoid wetting, thereby reducing soiling. This category includes hydrophobic, superhydrophobic, and SLIPS surfaces. A key requirement for these surfaces is that they must be non-wettable. The wetting behavior of a surface by a fluid is characterized by the spreading parameter (S), as shown in Equation (1). Here, α_S and α_L represent the polarizabilities of the solid and liquid, respectively, and k is a proportionality constant. When $S<0$, the liquid is repelled by the surface, indicating that $\alpha_S<\alpha_L$. In other words, surfaces with very low polarizability are not wetted by either hydrophilic or hydrophobic liquids (Gennes 1985; Israelachvili 2011). Common examples include fluorocarbons with zero net dipole moments (CF_3), carbonaceous materials, silicones, and highly organized aliphatic chains with exposed CH_3 groups.

$$S = k \cdot \left(\alpha_S - \alpha_L\right) \cdot \alpha_L \tag{1}$$

Superhydrophobic surfaces are a subclass characterized by water contact angles greater than 150° and very low contact angle hysteresis between advancing and receding angles (Erbil 2020). However, achieving superhydrophobicity on flat surfaces is impossible. Increasing surface roughness raises the contact angle, but superhydrophobicity is only attained upon entering the Cassie–Baxter regime. In this regime, superhydrophobic surfaces exhibit heterogeneous wetting, where the liquid rests on top of microstructures and nanostructures, trapping air in the spaces between these structures beneath the droplet (Figure 5a1) (Bayer 2020; X. Zhang, Wang, and Levänen 2013). Techniques such as lithography, templating, electrospinning, sol-gel method, etching, and chemical vapor deposition are used to achieve the desired surface textures, while low surface energy is typically attained by modifying the surface with fluorocarbons, organosilanes, long-chain alkylamines, and similar compounds (L. Wang, Guo, et al. 2022; Zaman Khan et al. 2022). The nonadhesive properties of superhydrophobic surfaces, characterized by low surface energy and air entrapment within hierarchical structures, prevent direct contact between bacteria and the surface, thereby

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inhibiting bacterial adhesion and biofilm formation (Z. Li, Liu, et al. 2022; Zhan et al. 2021). Various studies have demonstrated that superhydrophobic coatings can prevent the adhesion and biofilm formation of bacteria such as *Staphylococcus aureus (S. aureus)* (Hizal et al. 2017), *Escherichia coli (E. coli)* (Ladouceur et al. 2022) and *Pseudomonas aeruginosa (P. aeruginosa)* (Bartlet et al. 2018; L. Wang, Guo, et al. 2022), however, the mechanical durability of these coatings has not been sufficiently investigated. Despite their promising antifouling properties, superhydrophobic surfaces face significant challenges in biomedical applications due to their inherent fragility and low abrasion resistance, which can lead to

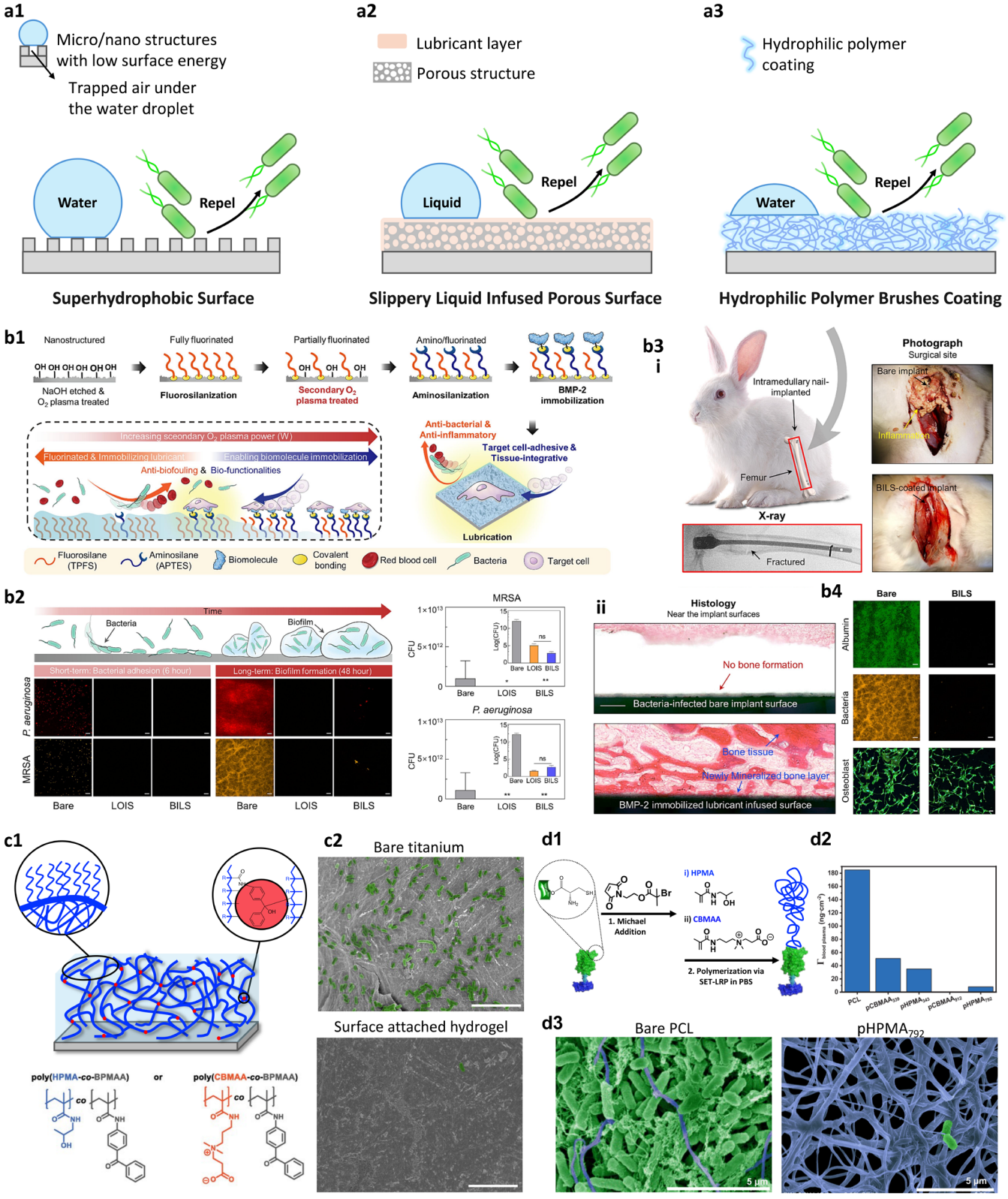

FIGURE 5 | Legend on next page.

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mechanical damage and localized defects (Ashok et al. 2023). These defects can compromise the effectiveness of the coatings by providing nucleation sites for bacterial adhesion. Therefore, additional research is essential to explore options that enhance the stability and longevity of superhydrophobic surfaces for clinical applications.

SLIPS have emerged as a highly effective low-surface-energy antifouling strategy for combating biofouling and BAIs. Inspired by the slippery behavior of Nepenthes pitcher plants, SLIPS consist of a porous substrate embedded with a lubricating liquid (low polarizability) that forms a liquid film on the surface. This significantly lowers the friction and surface energy, creating a highly slippery interface (Figure 5a2). These coatings are omniphobic, repelling both hydrophilic and hydrophobic molecules with extremely low sliding angles (< 5°) (Kasapgil, Erbil, and Anac Sakir 2022; C. Wang and Guo 2020; Wong et al. 2011; Zeng, Guo, and Liu 2021). The construction of SLIPS requires creating interconnected porosity in a material and introducing a liquid that thoroughly wets these pores, forming a stable slippery surface. Ensuring surface-liquid compatibility is essential for a continuous lubricating film, which can self-replenish from the pore reservoir if damaged. This compatibility, achieved through correct matching or surface functionalization, locks the liquid layer in place via van der Waals and/or capillary forces, creating a durable, slippery, and repellent interface. Thus, achieving the right surface energy match between the substrate and liquid is critical (X. Chen, Wen, and Guo 2020; Peppou-Chapman and Neto 2018). Sunny et al. (2014) showed that a porous substrate, created through the layer-by-layer self-assembly of silica nanoparticles and then coated with fluorinated silane, can successfully stabilize a fluorinated liquid. SLIPS have also displayed notable hemocompatibility, and exceptional bacterial repellency and biofilm prevention properties (Howell et al. 2018; J. Luo et al. 2022). The liquid layer on SLIPS forms a low-surface-energy, low-friction barrier that effectively prevents microbial adhesion and biofilm formation by eliminating the driving force for bacterial attachment. Even if bacteria come into contact with the surface, the liquid conceals it, preventing the recognition necessary for colonization. This lack of recognition inhibits the production of EPS, which is essential for bacterial attachment and biofilm development. Without the activation of their mechanical sensors, bacteria are unable to recognize the surface, and therefore, they do not produce the polymers needed to establish a stable attachment. The effectiveness of SLIPS in preventing bacterial attachment and biofilm formation on biomaterials such as catheters (Badv et al. 2017; Hao et al. 2022), nasal splints (Kasapgil et al. 2021), metallic implants (Cheng et al. 2020; Doll et al. 2017), and surgical instruments (Tesler et al. 2015) has been demonstrated in various studies. In medical applications, prioritizing biocompatibility when choosing lubricants is crucial. For instance, fluorinated lubricants such as perfluorodecalin are employed in medical applications, FDA approved but known for their high volatility, limiting their suitability for long-term use (Jia et al. 2024; Kasapgil, Anac, and Erbil 2019; Leslie et al. 2014). Medical-grade silicone oils are favored for their adjustable viscosities and nonvolatile properties (MacCallum et al. 2014; C. Wei et al. 2016). Ionic liquids offer high tunability and are increasingly utilized in SLIPS for medical applications (Wylie et al. 2020). Additionally, food-grade oils like canola, coconut, olive, almond, and sesame oils hold promise for medical applications that require minimal patient contact (Howell et al. 2018). Recent studies reported that while SLIPS have exceptional antibacterial properties, their extreme antifouling nature can prevent the adhesion of essential biomolecules and osteogenic cells needed for bone-implant integration (Park et al. 2024; Villegas et al. 2022). To overcome this, researchers integrated bioactive materials like chitosan or bone morphogenetic protein 2 (BMP-2) into SLIPS to facilitate cell adhesion while preventing biofilm formation. Park et al. developed a BMP-2 immobilized SLIPS that promotes selective osteoblast adhesion while preventing unwanted bio-substance adhesion. Applied to intramedullary nails and tested in a rabbit femoral fracture model, these coatings demonstrated excellent repellency against liquids, proteins, and bacteria, and significantly enhanced osteoblast adhesion and proliferation (Figure 5b) (Park et al. 2024).

FIGURE 5 | Antifouling surface modifications strategies. (a) Antifouling strategies rely on superhydrophobic surfaces (1), SLIPS (2), and hydrophilic polymer-brush coatings (3). (b) Fabrication and characterization of BMP-2 immobilized SLIPS that promotes selective osteoblast adhesion while preventing biofilm formation. (1) Schematic illustration of coating process: The alkali-etched titanium substrates were treated with O_2 plasma to form hydroxyl groups, then coated with trichloro(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)silane (TPFS) via CVD to achieve a fully fluorinated surface. Secondary O_2 plasma partially removed TPFS, forming localized hydroxyl groups. Additional CVD was used to silanize 3-aminopropyltriethoxysilane (APTES), to which BMP-2 was covalently immobilized via EDC/NHS chemistry. Finally, SLIPS was created by infusing the substrate with perfluoropolyether (PFPE) lubricant. (2) Fluorescence microscopy images illustrate bacterial adhesion and biofilm formation on each substrate; LOIS indicates SLIPS without BMP-2, while BILS denotes BMP-2 immobilized SLIPS (scale bars are 50 μm). (3) (i) Photograph and x-ray image of an intramedullary nail implanted in a rabbit femur and optical images of surgical sites 28 days post-surgery; (ii) H&E-stained images illustrating the tissue-implant interfaces for bacterial-infected bare and BILS-coated implants (scale bars are 200 μm). (4) Fluorescence microscopy images showing albumin, bacteria, and osteoblast adhesion on bare and BILS substrates (scale bars are 50 μm). Reprinted with permission from Park et al. (2024). Copyright 2024, Elsevier B.V. All rights reserved. (c1) Concept of surface-attached hydrogel coatings consisting of benzophenone crosslinking groups and carboxybetaine antifouling moieties. Adapted with permission from Witzdam et al. (2022). Copyright 2022, The Authors. Macromolecular Bioscience published by Wiley-VCH GmbH. (c2) Adhesion of *E. coli* bacteria on titanium substrates coated with the surface-attached hydrogels after 24 h of contact *t* time. Scale bars are 10 μm. Reprinted with permission from Witzdam et al. (2024). Copyright 2023, The Authors. Macromolecular Bioscience published by Wiley-VCH GmbH. (d1) Illustration of the synthetic route to polymerize LCI-eGFP-polymer hybrid. (d2) SPR measurement of protein fouling from blood plasma on PCL substrates coated with different LCI-eGFP-polymer hybrids. The results demonstrated that the longer the polymer chain, the more effective the antifouling properties. (d3) SEM micrographs demonstrating the LCI-eGFP-polymer coating successfully prevented the adhesion of *E. coli* bacteria (10^7 CFU) to the substrate. Reprinted and adapted with permission from Garay-Sarmiento et al. (2022). Copyright 2021, The Authors. Advanced Functional Materials published by Wiley-VCH GmbH.

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The lubricating liquid in SLIPS mitigates the drawbacks of superhydrophobic surfaces, such as poor stability and low mechanical strength due to the loss of entrapped air, but SLIPS also face challenges like lubricant evaporation or depletion over time, especially under dynamic fluid conditions and mechanical stress. The lubricant can be displaced by cloaking, where lubricating liquid spreads over a droplet of contaminating liquid, potentially removing the lubricant from the surface as the contaminant is repelled (Tripathi et al. 2023). To address these challenges in SLIPS, there is a need to develop multifunctional coatings that incorporate bactericidal agents, capable of activating when lubricant levels deplete, to enhance the effectiveness and longevity of the coatings against BAIs.

Hydrophilic antifouling polymer coatings are designed to minimize protein adsorption and cell adhesion by reducing the interfacial energy between the surface and water, thereby decreasing the thermodynamic drive for these processes. Given the diverse materials used in medical applications, including ceramics, metals, and polymers, various strategies have been developed to apply these coatings. Common techniques include self-assembled monolayers (Choi, Tran, and Lee 2022), physisorption of block- and graft-copolymers (Guo et al. 2013; N.-P. Huang et al. 2001; Kenausis et al. 2000), as well as end-tethered polymers (Advincula et al. 2004; Edmondson, Osborne, and Huck 2004; Rodriguez-Emmenegger et al. 2011; X. Xu, Chang, et al. 2023). Depending on the grafting density of the end-tethered polymers, they can adopt either a mushroom or brush conformation. Brushes are characterized by very high grafting density, where the strong overlapping of the polymer chains force them into a preferentially stretched conformation. They can be synthesized using the "grafting-to", "grafting-through", or "grafting-from" approaches. In the grafting-to process, the end-group of a semitelechelic polymer is used to ligate to the surface. The immobilization of the first polymer chains results in strong steric repulsion for further grafting which usually leads to low densities. This can be partially improved by performing the immobilization in theta conditions or in a melt where the polymer coils are less expanded. In the grafting-through method monomers are immobilized at the surface and the polymerization (chain-growth type) is carried out in solution. The growing chains incorporate the immobilized monomers and continue to grow. This method is the least frequently utilized. The grafting-from approach is the most widely utilized method. In this process, the initiator is immobilized on the surface, whereupon polymerization is initiated. In comparison to grafting-to, where a small entropic contribution of a single bond that is formed cannot overcome the loss of entropy, in the grafting-from process every monomer contributes enthalpically when added to the growing chains, enabling the formation of the brush. In this regard, the most favorable polymerization is that of radical types of acrylic monomers. Examples include atom transfer radical polymerization (Kostina et al. 2016; Rodriguez-Emmenegger, Houska, et al. 2012), NMP (Brinks and Studer 2009), and SET-LRP (Laun et al. 2015) with fewer examples of RAFT (Kuzmyn et al. 2020; Zamfir et al. 2013). This approach enables the synthesis of well-defined polymer chains with tunable chain lengths and high grafting densities (Obstals et al. 2018; Rodriguez-Emmenegger, Hasan, et al. 2012).

At high grafting densities: When biomolecules such as proteins or cells adhere to the polymer brushes, they cause the unfavorable compression of the polymer chains and the displacement of associated water molecules into the bulk, which leads to entropic and enthalpic penalties that repel biomolecules from the surface. Our group has focused on synthesizing polymer brushes composed of zwitterionic monomers such as sulfobetaines, phosphorylcholines, and carboxybetaines as well as *N*-(2-hydroxypropyl) methacrylamide monomer (HPMA). Zwitterionic monomers, in particular, offer significant advantages due to their potential for further functionalization with active molecules, as they possess functional groups amenable to conjugation. Notably, we demonstrated that these brushes were capable of completely suppressing fouling from single protein solutions, including human serum albumin, fibrinogen (Rodriguez-Emmenegger et al. 2011), cerebrospinal fluid, saliva, and urine (Rodriguez-Emmenegger, Houska, et al. 2012). Poly(carboxybetaine) and poly(HPMA) brushes have even provided surfaces where fouling from undiluted human blood plasma has not been detectable, even when using surface plasmon resonance (SPR) analysis with a detection limit of 0.03 ng cm^{-2} (Rodriguez-Emmenegger et al. 2011). Furthermore, these brushes have exhibited the ability to inhibit the adhesion of fibroblasts, platelets, leukocytes, and red blood cells (Obstals et al. 2018, 2021), as well as bacteria (Quandt et al. 2022). However, a significant limitation is their stringent polymerization conditions, which require an inert gas atmosphere and careful deoxygenation of solvents and polymerization vessels. These demanding conditions are challenging to achieve in large-scale setups and restrict the size and shape of substrates, thus hindering their practical application. Moreover, grafting these polymer brushes onto the surfaces of medical devices requires the attachment of an initiator moiety to the material surface. Oxidizing the surface with oxygen plasma and then functionalizing it with silane-containing initiators is a frequently employed tactic. However, plasma treatment can damage the substrate, and the generated functional groups may diminish over time due to reorganization effects. Additionally, the formed siloxane bonds exhibit only limited stability under aqueous conditions, which can lead to a delamination of the polymer brushes, thereby limiting their applicability in biological systems (Ataman and Klok 2016; Ozdemir, Yurteri, and Sadikoglu 1999; Tugulu and Klok 2008; J. Wang and Klok 2019). In light of these challenges, several research groups have introduced alternative concepts to simplify the formation of a brush-like coating on medical devices. The most effective include surface-attached hydrogels (Bentley et al. 2022; Englert et al. 2023; Prucker, Brandstetter, and Rühe 2018; Witzdam et al. 2022) and the use of protein–polymer hybrid macromolecules (Dedisch et al. 2019; Garay-Sarmiento et al. 2022; Söder et al. 2021; Witzdam et al. 2024; Z. Zhao, Pan, et al. 2023). The former strategy relies on a hydrogel precursor solution consisting of a benzophenone crosslinking group and an antifouling moiety. When exposed to UV light, the benzophenone groups form biradical intermediates that crosslink the polymer to the surface and in solution by inserting into carbon–hydrogen bonds via C,H-insertion (Witzdam et al. 2022). Notably, when these coatings integrated HPMA or poly(carboxybetaine) as their antifouling moiety, they were able to suppress fouling from whole blood plasma and provide a barrier to the adhesion of Gram positive and negative bacteria (Witzdam et al. 2022). These results are comparable to the most effective grafting-from polymer brushes discussed above, with the added advantage of a significantly more straightforward and single-step application process. The

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analysis of the component of the free energy and nanoindentation demonstrated that the excellent antifouling properties are related to a very strong hydration and the imperfect nature of the hydrogel, resulting in the formation of dangling chains at the periphery of the hydrogel, leading to the formation of a brush-like structure at the interface.

Another feasible approach for the generation of brushes at the surface is the synthesis of bifunctional molecules comprising a fragment with high affinity for the surface and another fragment composed of a hydrophilic polymer that can generate the brush-like interface. However, the generation of the brushes requires that both modules of this macromolecule have substantially different properties. In synthetic polymers, this typically results in the formation of aggregates such as micelles, which negatively impact the process of brush formation. Our group developed a new concept to achieve brushes using bifunctional molecules. These molecules consist of a hydrophilic polymer on one side and a of a protein on the other. Both components are water soluble and do not phase separate in water but in the present of a surface, the protein drives the adsorption process to the surface, resulting in the formation of a brush-like coating at the interface. This strategy leverages the promiscuity and surface affinity of the protein component to achieve a dense coating on the substrate surface through simple physisorption, eliminating the need for additional surface treatment steps or energy input. A significant advantage of these coatings is their versatility, as they are not restricted to polymer substrates but can also be applied to a variety of metals and natural surfaces. This universal character stems from the amphiphilic nature of proteins, which can adapt their conformation to expose those amino acid residues that maximize physical interactions with the surface. Namely, proteins can interact with surfaces through a multitude of molecular interactions, including van der Waals forces, Coulombic forces, hydrophobic interactions and hydrogen bonding. Albumin is one of the most commonly used proteins for coating surfaces and achieving surface passivation. Its adsorption hydrophilizes the surface, thereby reducing the thermodynamic drive for fouling. However, such coatings lack stability due to the susceptibility of albumin to adsorption- and aging-induced unfolding which would compromise the integrity of the coating. Moreover, the conformational change of albumin exposes binding sites for platelet adhesion and proteins of the complement system, which may result in coagulation and the formation of thrombi at the surface (Sivaraman and Latour 2012).

Our group developed a protein–polymer coating based on the AMP liquid chromatography peak I (LCI) (Dedisch et al. 2019; Garay-Sarmiento et al. 2022; Söder et al. 2021; Witzdam et al. 2024). In particular, peptides offer certain advantages over larger proteins. Their smaller size allows them to pack more closely together on a surface, resulting in a higher density of the coating when compared to bulky proteins. Furthermore, peptides have the unique characteristic of forming highly ordered assemblies (Arul et al. 2020; Reches and Gazit 2006). Our synthesized LCI-eGFP-poly(HPMA) and LCI-eGFP-poly(carboxybetaine) hybrid molecules formed one-molecule-thick coatings (5–8 nm) with antifouling properties on par with the best grafting-from polymer brushes and surface-attached hydrogels. These coatings also prevented the adhesion of *E. coli* and *Streptococcus agalactiae* to wound dressings minimizing the risk for BAI development.

In general, over the past few decades, there have been notable developments in the design and synthesis of antifouling coatings. Nevertheless, while numerous research groups have demonstrated the superior efficiency of these coatings in preventing protein adsorption and bacterial adhesion, only a few have been successful in in vivo studies. A significant limitation of these coatings is their inability to provide long-term efficacy. In the presence of coating defects or the ability of bacteria to overcome the antifouling barriers, infection development becomes almost inevitable. Consequently, there is a growing trend toward the design of multifunctional coatings that combine antifouling and bactericidal properties, potentially offering more robust antimicrobial approaches.

3.4 | Multifunctional Coatings

There has been a growing focus on multifunctional antimicrobial coatings that integrate bactericidal and antifouling properties into a single coating. While antifouling surfaces are effective at preventing the initial adhesion of bacteria, they may still allow some bacteria to attach and eventually form biofilms. On the other hand, bactericidal surfaces alone can lead to the accumulation of dead bacteria on the surface, potentially obstructing the bactericidal surface or hindering the release of the bactericidal agents. Therefore, combining both antifouling and bactericidal properties may provide enhanced protection against infections with improved long-term efficacy (Mitra, Kang, and Neoh 2021). Multifunctional coatings can be classified according to their mode of action, which can be broadly categorized as either antifouling-contact-killing or antifouling-release-killing. These approaches gave rise to “Kill&Repel” or “Kill&Release” coatings (Mitra, Kang, and Neoh 2021). The former utilizes reduced adhesion and kills bacteria upon contact with the surface. The latter has an antifouling-release mechanism loaded with antimicrobial agents to kill bacteria. This section will examine the principles, design, and effectiveness of these diverse multifunctional coatings, focusing on fouling-release mechanisms (e.g., superhydrophobic surfaces and SLIPS) and fouling-resistant mechanisms (e.g., hydrophilic polymer coatings).

The combination of antifouling properties with antimicrobial-eluting activity represents an attractive approach, as it allows for the killing of bacteria on and around biomaterial surfaces while preventing the accumulation of residue on the surface, which otherwise could obstruct the effective release of antimicrobials. Accordingly, this strategy enables a more sustained and prolonged release of antimicrobials, reducing the quantity of antimicrobials required. This reduction is in alignment with global efforts to minimize the use of antibiotics and antimicrobials, thereby contributing to the mitigation of antibiotic resistance (Liu et al. 2020; Zhan et al. 2021). Most of these multifunctional coatings utilize antibiotics, cationic molecules, metal nanoparticles and their oxides, incorporating them directly into the matrix or texture of the antifouling coatings (Liu et al. 2020). Kill&Release coatings are usually fabricated by adding metals into superhydrophobic or SLIPS coatings as antibacterial additives which are continuously

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released. Examples of the bactericidal metals include Ag (Agbe et al. 2020; Z. Li, Liu, et al. 2022; S. Zhang, Teng, et al. 2023), Cu (J. Zhang, Pei, et al. 2023), and Zn (Ozkan et al. 2020). Additionally, some Kill&Release coatings have been developed to release antibacterial agents, compounds or macromolecules such as triclosan (Manna et al. 2016), nitric oxide (NO) (Chug and Brisbois 2022; Homeyer et al. 2019; Ozkan et al. 2024) and lysozyme enzymes (S. Li et al. 2021) to inhibit biofilm formation. Manna et al. (2016) developed multifunctional SLIPS by incorporating triclosan into porous coatings on glass and catheter surfaces, achieving both antifouling and antibacterial properties. However, the use of triclosan posed risks of resistance in clinically relevant pathogens (Q. E. Yang, Ma, et al. 2024). Consequently, they replaced triclosan with quorum sensing inhibitors (QSIs), which are nontoxic to bacteria but disrupt their virulence or halt their activity, effectively preventing biofilm formation by *P. aeruginosa* and mitigating the resistance issues commonly associated with traditional antibiotics (Broderick et al. 2013; Kratochvil et al. 2016). Homeyer et al. (2019) created a liquid-infused nitric-oxide-releasing (LINORel) urinary catheter by combining the NO donor *S*-nitroso-*N*-acetylpenicillamine (SNAP) with silicone oil, significantly reducing bacterial adhesion and biofilm formation for up to 60 days. S. Zhang, Teng, et al. (2023) developed silver-releasing silicone catheters with infused silicone oil, demonstrating long-term antibacterial effects against *E. coli* and *Proteus mirabilis (P. mirabilis)*. These studies show that SLIPS with a lubricant layer improve the loading and controlled release of biocides, making them promising for antifouling-release-killing coatings. However, their limited capacity to accommodate antibacterial agents can lead to reduced efficacy over time, highlighting the need for precise design of the carrier matrix or material to maintain long-term antimicrobial action, potentially using stimuli-responsive mechanisms.

Antifouling-contact-killing coatings can be generated through either mechanobactericidal effects or the immobilization of contact-active antimicrobial molecules, in combination with antifouling properties (H. Zhou et al. 2023). Superhydrophobic-mechanobactericidal coatings represent an advanced antibacterial strategy by combining physical and chemical mechanisms to combat bacterial adhesion and proliferation. These Kill&Release coatings achieve dual functionality: their superhydrophobic nature repels bacteria, while engineered nanostructures physically disrupt bacterial cells (S. Wang, Liu, et al. 2022). Surface roughness is crucial in creating superhydrophobic surfaces, which are often constructed with sharp nanostructures that offer both super-repellence and mechanobactericidal activity (Catley, Corrigan, and Parnell 2023). By mechanically rupturing bacterial cell membranes without the use of antimicrobial agents, these coatings effectively prevent biofilm formation, minimize the risk of bacterial resistance, and avoid damaging host tissues and cells. R. Jiang et al. (2020) developed a superhydrophobic surface with micro-cylinder arrays and ZnO nanoneedles that exhibited high antibacterial efficacy, repelling over 99% of *E. coli* and destroying bacteria upon contact. This approach offers high-performance antibacterial action through physical mechanisms rather than chemical agents. However, the durability of such micro- and nanostructures can be problematic, as they may degrade with extended use, leading to decreased effectiveness. Additionally, they may be less effective against Gram-positive bacteria, which have thicker peptide layers in their cell membranes, and involve high costs and complex manufacturing, limiting their broader biomedical application (Hasan et al. 2013; R. Jiang et al. 2020; X. Zhao, Xu, et al. 2023).

Kill&Release coatings can also exert contact-killing properties by integrating contact-active antimicrobial agents into superhydrophobic or SLIPS coatings (Figure 6a,c). Superhydrophobic coatings with contact-active antimicrobial agents are created by adding antibacterial nanoparticles to the surface, forming micro- and nano-roughness with low surface energy to prevent bacterial adhesion and kill any adhering bacteria (Mu et al. 2023; Zhan et al. 2021). A spray coating was created with wrinkled polydimethylsiloxane microparticles and biocidal gold nanoparticles, achieving 99.9% reduction in bacterial adhesion for *S. aureus* and *P. aeruginosa* (Abu Jarad et al. 2023). However, the use of gold nanoparticles raises concerns about production costs, and detailed studies on the durability of these coatings are necessary for their application in biomedical materials. Mu et al. (2023) and Ye et al. (2021) suggested additional treatments, like fluorinated compounds, to maintain superhydrophobicity alongside bactericidal properties. Liu et al. (2020) developed a bactericidal-superhydrophobic surface using organofluorosilane modification (Figure 6b), showing high water contact angles and effective bacterial prevention. QACs were incorporated into nanoparticles, demonstrating effective antibacterial properties (Ye et al. 2021). Rauner et al. (2018) functionalized SiO_2 nanoparticles with quaternary ammonium salt (QAS), achieving superhydrophobicity and significant bacterial reduction, though mechanical durability was not tested. SLIPS with AgNPs were developed, demonstrating antibacterial effects against *E. coli* (Lee et al. 2019). B. Zhang et al. (2022) developed a porous SLIPS with antimicrobial properties, effective against both Gram-positive and Gram-negative bacteria (Figure 6d). There are also studies exploring the use of lubricants with bactericidal properties to synergistically inhibit biofilm formation, rather than relying on antibacterial agents. Cinnamaldehyde-infused SLIPS, showing high antibacterial efficacy (Cox et al. 2021), though cinnamaldehyde's volatility limits stability (C. C. Huang et al. 2023). Crystal violet (Patir et al. 2021), QAS ionic liquid (H. Li, Yan, and Zhao 2022), and soybean oil (Jing et al. 2023) infused SLIPS showed strong antibacterial properties. Since research on these biocidal-lubricant-infused SLIPS is still in its early stages, it is essential to thoroughly examine their mechanical durability and assess whether they maintain their properties after liquid loss to evaluate their potential for long-term application against BAIs.

Furthermore, a common approach to fabricate contact-active multifunctional antimicrobial coatings involves combining antifouling hydrophilic polymers with cationic bactericidal polymers, AMPs, or enzymes (Table 3). These Kill&Repel coatings can be generated by synthesizing stimulus-responsive polymers that switch between zwitterionic and cationic states, or vice versa (S. Jiang and Cao 2010; Pang et al. 2022; Paschke et al. 2021; Sun et al. 2024), through the grafting of antifouling and bactericidal molecules simultaneously from the surface (Fu et al. 2019; Thongthai et al. 2020; G. Xu et al. 2017) or by generating multiple-layer coatings (W. Peng et al. 2022). However, the switching process is often irreversible, causing the coating to lose

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one of its functions over time (Paschke et al. 2021). Additionally, such coatings may not be optimal for in vivo settings, as the triggering effect cannot be controlled once the device is implanted. Furthermore, a significant limitation of the coatings comprising cationic monomers is their toxicity, which can harm not only bacteria but also host cells. AMPs and enzymes are gaining significant attention as alternatives due to their higher selectivity toward bacterial cells. In this context, hierarchical "Kill&Repel" coatings have been developed that consist of a bottom block of antifouling polymer brushes or brush-like structures and a

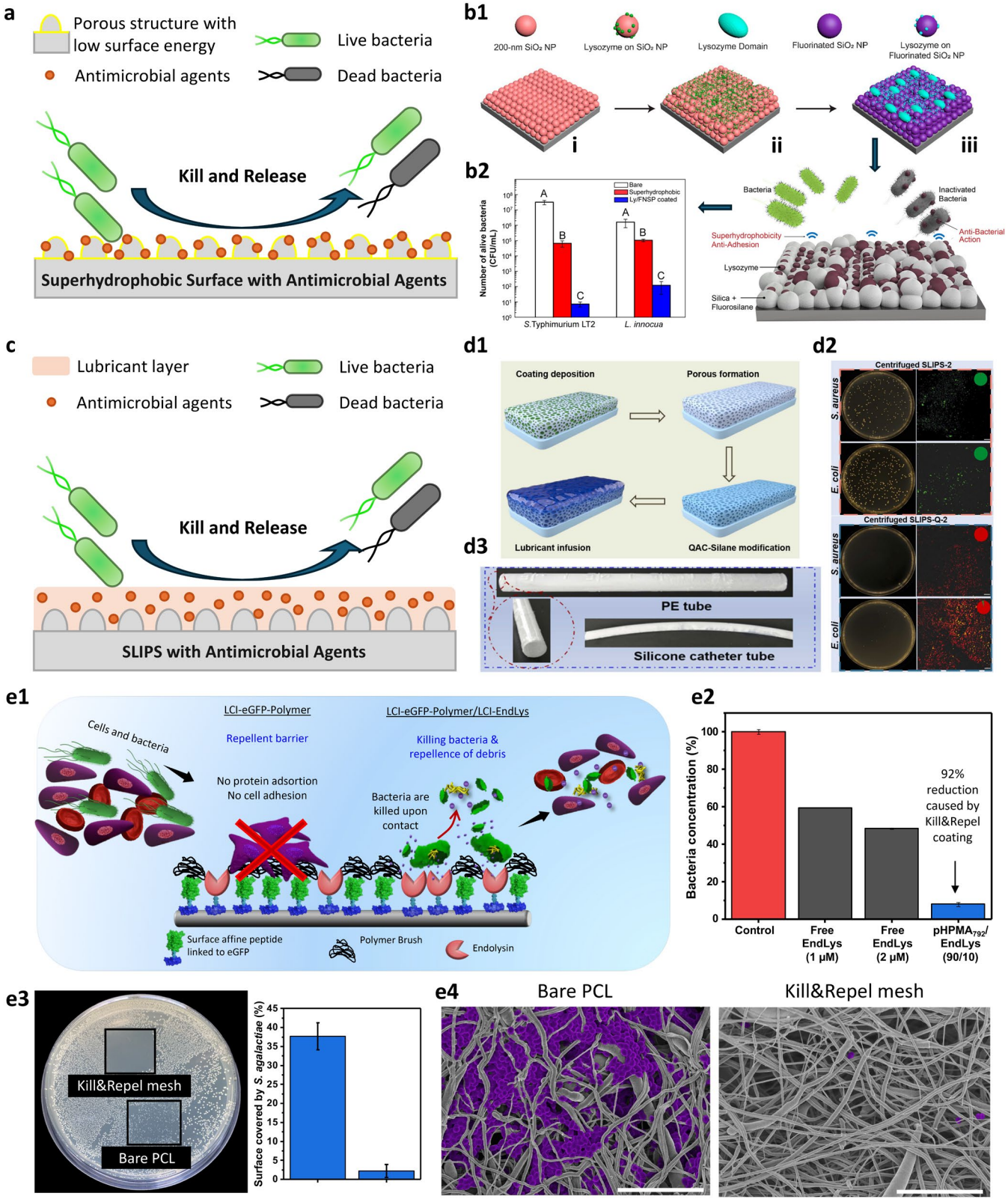

FIGURE 6 | Legend on next page.

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TABLE 3 | Summary of recent studies on multifunctional coatings with antifouling and bactericidal properties.

Bactericidal component	Antifouling component	Tested pathogens	References
Superhydrophobic			
Ag	Fluorosilane-modified fluorosilicone resin–polysulfone coating	*S. aureus* *E. coli*	(Y. Jiang et al. 2024)
Ag and NO	Silicone-based coatings with fluorinated silicon dioxide and Ag nanoparticles	*S. aureus* *E. coli*	(Ozkan et al. 2024)
Cu	Laser-processed stainless steel, magnesium, and aluminum alloy substrates coated with hexadecyltrimethoxysilane, epoxy resin, and silanized Cu_2O	*S. aureus* *E. coli*	(W. Zhang et al. 2024)
ZnO	Polypropylene fabric with ZnO nanoparticles–modified perfluorodecyltriethoxysilane, glycidyloxypropyltrimethoxysilane, and SiO_2 nanoparticles	*E. coli*	(Tian et al. 2024)
SLIPS			
Ag	Silicone oil infused Ag nanoparticle–coated catheters	*E. coli* *P. mirabilis*	(S. Zhang, Teng, et al. 2023)
QAS	QAS-silicone oil infusion onto anodized and silanized aluminum substrates	*Bacillus* sp. *V. natriegens*	(Z. Yang, He, et al. 2024)
Hydrophilic			
AMP melittin and the lipolytic enzyme phospholipase A2	Surface-attached carboxybetaine-based hydrogels	*E. coli* *B. subtilis*	(Witzdam et al. 2022)
Endolysin (PlyGBS94)	Protein–polymer hybrids	*S. agalactiae*	(Garay-Sarmiento et al. 2022)
Ag nanoparticles	Tannic acid–based zwitterionic polymer coatings	*S. aureus* *E. coli*	(Imbia et al. 2024)
Cationic polymers	pH-responsive zwitterionic polymer brushes	*S. aureus* *E. coli*	(Sun et al. 2024)
QAS cationic coating	Sulfobetaine methacrylate (SBMA)–based zwitterionic coatings.	*S. aureus* *E. coli* *P. aeruginosa*	(H. Wei et al. 2024)

FIGURE 6 | Multifunctional strategies to combat BAIs. (a) Schematic illustration of superhydrophobic coatings combined with bactericidal properties. (b) (1) Schematic of lysozyme-added superhydrophobic coating production: silica particles are deposited on an aluminum substrate, lysozyme is adsorbed via dip-coating and freeze-drying, and the surface is functionalized with organofluorosilane molecules. (2) Survival of *Salmonella typhimurium (S. typhimurium)* LT2 and *Listeria innocua (L. innocua)* on bare, superhydrophobic, and lysozyme-added superhydrophobic aluminum samples, assessed by plate count method. Letters A, B, and C denote statistically significant differences ($p < 0.05$). Reprinted with permission from Liu et al. (2020). Copyright 2020, American Chemical Society. (c) Schematic illustration of SLIPS incorporated with antimicrobial agents. (d) (1) Schematic illustration showing the preparation of QAC-silane–modified SLIPS using a microphase separation technique. (2) Photo images of *S. aureus* and *E. coli* colonies after incubation with centrifuged SLIPS and QAC-silane–modified SLIPS samples. Fluorescence micrographs show live (green) and dead (red) bacteria after exposure to live/dead stains. (3) Photo images of the prepared coatings on various substrate materials. Reprinted with permission from B. Zhang et al. (2022). Copyright 2022, Elsevier B.V. All rights reserved. (e1) Illustration showing the concept of the Kill&Repel coating generated through the physisorption of protein–polymer and protein–endolysin hybrids to the substrate. (e2) Kill&Repel coating demonstrates higher efficiency at killing planktonic bacteria when compared with free endolysin, highlighting the synergistic effect of the antifouling and bactericidal properties. (e3) Kill&Repel coatings clears contamination of *Streptococcus agalactiae* on agar plates after treatment for 24 h (e4) Throughout the treatment, the coating successfully prevented the adhesion of bacteria and bacterial debris to the surface. Scale bars are 10 μm. Reprinted and adapted with permission from Garay-Sarmiento et al. (2022). Copyright 2021, The Authors. Advanced Functional Materials published by Wiley-VCH GmbH.

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functional top block of immobilized AMP or enzymes (Vorobii et al. 2022; Witzdam et al. 2022; X.-Y. Zhang et al. 2019). This architecture facilitates the incorporation of active molecules into the structure without compromising the antifouling properties of the brush coating. Nevertheless, to ensure an optimal balance, the antifouling block must be sufficiently thick to form an effective barrier against adhesion, while the functional block should be optimized to hold a high concentration of active molecules without significantly decreasing the antifouling properties (de los Santos Pereira et al. 2014). Zwitterionic carboxybetaine polymer brushes are particularly well suited for this application, as they not only have demonstrated superior antifouling performance (vide supra) but also feature functional groups that facilitate the immobilization of biomolecules. Nevertheless, these hierarchical Kill&Repel coatings based on grafting-from polymer brushes have shown effective in laboratory settings, they are less optimal for clinical translation due to the stringent synthetic conditions and multistep surface modification required. To overcome this challenge, our group has pioneered the development of Kill&Repel coatings that are easily applicable onto a broad range of biomedical devices without the necessity for surface pretreatment steps. Using surface-attached carboxybetaine-based hydrogels functionalized with the AMP melittin and the lipolytic enzyme phospholipase A2, adhesion of *E. coli* and *Bacillus subtilis* to polyethylene substrates was effectively prevented. Moreover, the concentration of planktonic bacteria in the vicinity of the substrates was reduced by 79% (Witzdam et al. 2022). This coating can be universally applied to polymeric substrates, significantly reducing the risk of BAIs and holding promising potential for clinical applications. The next generation of innovative Kill&Repel coatings was developed through the combination of protein–polymer hybrids with protein–endolysin hybrids within one layer (Garay-Sarmiento et al. 2022). This coating strategy leverages the surface affinity of the protein construct and merges antifouling properties with a biorthogonal bactericidal strategy that causes no harm to eukaryotic cells. Notably, it is applicable not only to polymeric substrates but also to metals, ceramics, and natural surfaces like teeth, making it suitable for modifying a wide range of medical devices without pretreatment steps or additional energy input for coating application. We discovered that the co-immobilization of endolysin with the hydrophilic polymer significantly enhanced the endolysin's enzymatic activity, resulting in a more effective killing of bacteria. Additionally, embedding the endolysin within the hydrophilic brushes in a single layer offers protection from proteases, potentially providing higher stability and reduced degradation. These synergistic effects offer the significant advantage of requiring only minimal amounts of endolysin to achieve an effective antimicrobial coating, thereby lowering production costs. Coated substrates demonstrated efficient at killing planktonic bacteria as well as clearing simulated wound infections from sessile bacterial colonization. Importantly, the surface of the coated substrates remained free from the adhesion of bacteria and bacterial debris throughout the treatment period, highlighting the synergistic action of the Kill&Repel properties.

Overall, multifunctional coatings have demonstrated robust antimicrobial properties and show great promise in combating BAIs. Various scientific groups have developed strategies that provide alternatives to antibiotic use and are specific to bacterial microbes. These coatings not only minimize the risk of bacterial resistance, but also ensure patient safety. These strategies provide valuable insights for future research and development. However, it is important to note that only a few studies on multifunctional coatings have included in vivo validation. This underscores the need for further research to confirm their efficacy and optimize their clinical applications.

3.5 | Bottom-Up Synthetic Biology: A Novel Avenue for Combating BAIs and AMR

Bottom-up synthetic biology aims to construct cell mimics from scratch, utilizing a minimal set of well-characterized building blocks, thereby circumventing the inherent complexity and redundancy present in natural cells (Buddingh and van Hest 2017; Laohakunakorn et al. 2020; Mann 2012; Schwille 2011; Tu et al. 2016). These cell mimics not only imitate the functions and properties of living cells, but they can also exceed their capabilities, offering significant potential for therapeutic applications and paving the way for the next generation of smart biomaterials with life-like behavior (van Stevendaal, van Hest, and Mason 2021; Q. Xu, Zhang, et al. 2023). In this regard, cell mimics have demonstrated potential for a range of biomedical applications, including immunotherapy (Amidi et al. 2011; Lu et al. 2021), bone tissue engineering (Itel, Skovhus Thomsen, and Städler 2018), responsive therapeutics (Lentini et al. 2017, 2014; Toparlak et al. 2020), and antimicrobial purposes (Ding et al. 2018; Kostina et al. 2019; Z. Xu et al. 2021; C. Zhao et al. 2021). Ding et al. (2018) developed cell mimics that are capable of sensing, interacting with, and killing bacteria. This was accomplished by incorporating transcription–translation machinery and a quorum-sensing circuit into lipid-based cell mimics. Upon the production of the molecule *N*-acyl homoserine lactone by bacteria, the cell mimics initiates the expression of the AMP Bac2A, which effectively eliminates bacteria in the surrounding. Moreover, Mann et al. introduced the concept of nonliving predators. Nonliving predators are cell mimics with live-like features capable of hunting down and eliminating targets in aqueous environments (Jaskiewicz et al. 2012; Qiao et al. 2017, 2019; Rodriguez-Arco, Li, and Mann 2017; Smith, Jasnow, and Balazs 2007). These systems give rise to predator–prey dynamics, which can be extended beyond targeting inanimate objects to capturing and eradicating bacterial pathogens. In particular, harnessing this concept in the field of antimicrobial therapeutics could revolutionize our approach to combating infections and open up entirely new avenues for addressing the crisis of bacterial resistance. R. Luo et al. (2020) developed porous microcapsules containing SiO_2 microbeads in their interior and with surfaces decorated with quaternary ammonium groups. The shape of the pores facilitated bacterial entry into the lumen, where then the SiO_2 microbeads killed the pathogens following entry. However, effective bacterial entrapment required either cell motility or flow in the medium to draw bacteria into the lumen, which limits the applicability of this system. More recently, Z. Xu et al. (2021) developed a mean to circumvent this challenge by engineering inorganic colloidal cell mimics with precisely designed micropores and incorporating an internal photoswitchable catalyst. When exposed to blue light and hydrogen peroxide, acting as fuel, the catalyst generates a chemical gradient, which propagates outward through the micropore, functioning as a phoretic tractor beam that effectively draws bacteria inside the cell mimics. However, while this

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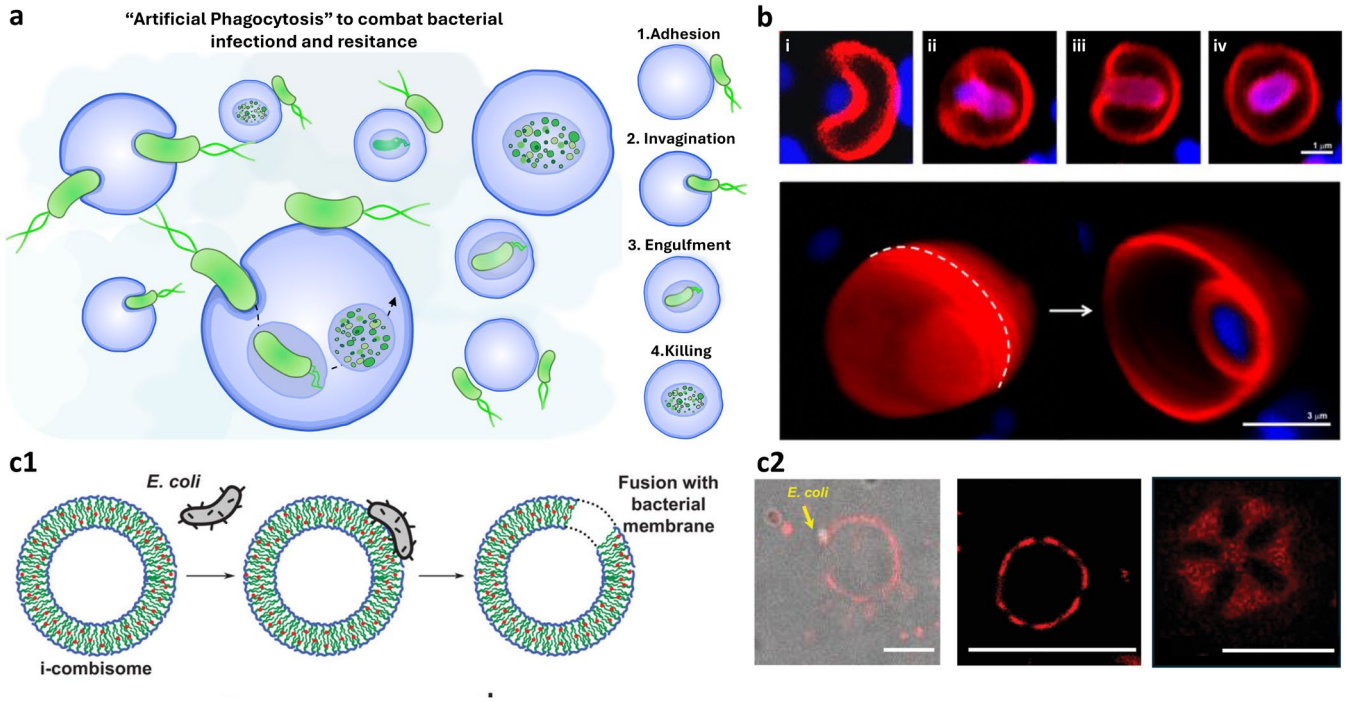

FIGURE 7 | (a) Artificial phagocytosis to combat BAIS and bacterial resistance. Steps involve (1) adhesion of the bacterium to the vesicle membrane, (2) invagination of bacterium into the interior of vesicle, (3) complete engulfment with membrane fission and release of endosome, and (4) killing of bacteria. (b) Confocal laser scanning microscopy images of the process of engulfment of *E. coli* (blue) by dendrimersomes (red) and 3D reconstruction of the finalized engulfment process depicting bacterium inside dendrimersome. Reproduced with permission from N. Y. Kostina et al. (2019). Copyright 2019, American Chemical Society. (c) Schematic illustration of the adhesion and fusion process between i-combs and *E. coli* (1). After 2 min of incubation, bacteria adhere to the membrane on the i-combs resulting in the formation of nonfluorescent elliptical patches (2). Scale bars are 5 μm. Reproduced with permission from Wagner et al. (2022). Copyright 2022, The Authors. Advanced Science published by Wiley-VCH GmbH.

system is effective at capturing bacteria, it still lacks a mechanism to kill them. C. Zhao et al. (2020, 2021) are among the few groups that have developed synthetic cell predators capable of both effectively trapping bacteria and incorporating a killing mechanism. In their first work, they formulated proteinosomes exerting a strongly cationic surface charge (C. Zhao et al. 2020). Their charge enabled the electrostatic attraction of negatively charged *E. coli* and the concomitant disruption of the bacterial membrane upon contact. Nonetheless, this killing mechanism is not specific for bacterial cells and can induce toxicity upon contact with eukaryotic cells. In their second approach, they partly mitigate this limitation by formulating membranized coacervate-based cell mimics that can selectively capture *E. coli* bacteria and subsequently eradicate them in a concerted manner. The membrane was reconstituted from yeast cellular wall fragments which naturally contain mannans, a protein known to induce adhesion between yeast cells and FimH expressing bacteria. Additionally, the coacervates were composed of sodium hyaluronate and quaternized amylose, so that after adhesion and internalization of the bacteria through their interaction with the mannans present on the membrane, killing continues due to exposure to the cationic amylose derivatives. These systems effectively isolate bacteria and their killing action from the environment; however, they also have limitations, such as the depletion of membrane components with each bacterium captured and the inherent instability of coacervates. For example, small pH changes can destabilize coacervates, potentially releasing killed bacteria and endotoxins into the environment.

Our research group has put forth the concept of "artificial phagocytosis" as a promising strategy against bacterial infections (Figure 7a). This concept involves the use of synthetic vesicle membranes that mimic the biological process of phagocytosis—one of nature's most effective defense mechanisms, in which living cells engulf and destroy particulate matter. By replicating this natural mechanism, synthetic cells can be precisely engineered to actively target, ingest, and destroy harmful pathogens without the need for any antimicrobial drugs, which gives rise to a new antimicrobial therapeutic platform that can bypass the emergence of resistance. Similar to natural phagocytosis, engulfment and killing occur in a concerted manner, allowing the killing mechanism to be unleashed only during engulfment and otherwise remains dormant. This mechanism allows killed bacteria and endotoxins to remain contained within the vesicle membrane, thereby reducing toxicity to surrounding eukaryotic cells. In this context, in 2019, we demonstrated the exceptional ability of cell mimics based on dendrimersomes to endocytose living *E. coli* bacteria (Kostina et al. 2019) (Figure 7b). Strikingly, engulfment was successfully achieved without the need for cellular machinery and relying only on low binding energies. Furthermore, we have devised a novel family of cell mimics, termed ionic combisomes (i-combs), which demonstrated the capacity to engulf and readily fuse with bacterial membranes (Wagner et al. 2022). Immediately following the mixing process, a significant number of bacterial cells were observed to adhere to the membrane of the i-combs (Figure 7c). Within minutes, the

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adhered bacterial membrane merged with the i-combs, resulting in the formation of dark elliptical patches across the surface of the membrane. This family of cell mimics may represent a novel means of disrupting bacterial cell membranes, thereby inducing cell death following engulfment.

In particular, the concept of artificial phagocytosis introduces a radically new class of "quasi-living" antimicrobial therapeutics, revolutionizing the current paradigm for combating bacterial infections. In contrast to most of the current antimicrobial strategies, where targeting and killing is performed with one molecule, phagocytic synthetic cells (PSCs) decouple these two processes. By separating these activities, it becomes possible to employ one mechanism specific for hunting down pathogens while utilizing another for killing them, thereby reducing the likelihood of evasion and enhancing efficacy. Moreover, it enables the design of specific targeting of certain microbes. For example, the membrane of PSCs may be decorated with specific epitopes that enable them to hunt down bacteria displaying distinct surface patterns while sparing others. Allowing certain bacterial populations to thrive, such as beneficial competitor commensals can create synergistic effects, as these commensals can act as natural predators, further regulating pathogen populations. Furthermore, this specificity can pave the way for designing advanced personalized and precision therapies. The dynamics of quasi-living therapeutics enable the creation of drugless antimicrobial systems that can circumvent the emergence of resistance. It offers a novel perspective on treatment strategies. Moreover, beyond bactericidal applications, the design principles of quasi-living therapeutics could facilitate the development of synthetic defenders that provide innovative solutions and therapeutic interventions for various complex clinical challenges, including viral diseases, by emulating life-like functions.

4 | Conclusion

The use of antibiotics and antibiotic-based coatings is currently facing significant challenges, particularly due to the ever-increasing prevalence of antibiotic-resistant bacterial strains. Consequently, bacterial infections have become a leading cause of implant failure and postoperative complications. This review provides an overview of the current strategies employed to combat BAIs. We discuss the two main classes of antimicrobial coatings: bactericidal and antifouling. Within these classes, we explore a variety of surface modification strategies, emphasizing their respective advantages and limitations. Noteworthy, one of the foremost concerns limiting their clinical applicability is their long-term effectiveness in physiological conditions. Bactericidal coatings, for instance, may suffer from the accumulation of killed bacterial debris on the surface, obstructing the release or accessibility of the bactericidal molecules and reducing their effectiveness. Furthermore, this debris can also create anchoring points for living bacteria to adhere. Conversely, purely antifouling coatings may offer only short-term protection. As soon as some proteins manage to adsorb to the surface, they can facilitate bacterial attachment as the coating does not eliminate bacteria that come into contact with the surface. Therefore, we emphasize that multifunctional coatings, which combine both antifouling and bactericidal properties, may offer enhanced protection against bacterial colonization. This integrated approach may offer a robust solution for preventing BAIs and ensuring the long-term success of medical implants. We provide insights into recent advancement and strategies in the design of such multifunctional antimicrobial coatings. However, a critical aspect that requires further attention is the mechanical and in vivo durability of these coatings. Addressing these concerns will be pivotal in optimizing these coatings for clinical applications and realizing their full potential.

Moreover, in view of the recent progress in bottom-up synthetic biology, we offer a future perspective on the development of antimicrobial synthetic cells. Specifically, we elucidate how recent breakthroughs have established the foundation for realizing synthetic cells capable of performing artificial phagocytosis. It is our contention that harnessing the dynamics of this novel class of quasi-living therapeutics to combat bacterial infections can pave the way for a next generation of antimicrobial materials, transforming the landscape of current antimicrobial technology and offering a more effective and broadly applicable solution against BAIs, ultimately improving patient outcomes and advancing medical device technology.

Author Contributions

Esra Kasapgil: conceptualization (equal), methodology (equal), writing – original draft (equal), writing – review and editing (equal). **Manuela Garay-Sarmiento:** conceptualization (equal), methodology (equal), writing – original draft (equal), writing – review and editing (equal). **César Rodriguez-Emmenegger:** conceptualization (lead), funding acquisition (lead), project administration (equal), supervision (lead), writing – review and editing (lead).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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