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Antibiotic drugs have revolutionized the field of medicine for almost 90 years. However, continued use has led to the rise of antibiotic resistant bacteria, motivating the need for alternative treatments. Several strategies to combat this phenomenon have been investigated, with biomimetic strategies gaining significant appeal due to inherent compatibility with physiologically relevant environments. In this review, we will discuss current antimicrobial strategies and then present an overview on biomimetic antimicrobial material-based strategies for combating antibiotic resistant bacteria.

Introduction

The discovery of the antibiotic penicillin by Alexander Fleming in 1928 has long revolutionized the field of medicine[1] . However, continued use of penicillin, and similar antibiotic drugs, have led to the rise of strains of antibiotic resistant bacteria, which has since motivated the need for alternative treatments. According to the Centers for Disease Control (CDC), antibiotic resistant bacteria affect at least 2 million individuals annually in total[2]. In particular, high threat antibiotic strains exist across several species. Most notably, there exists Methicillin-resistant *Staphylococcus aureus* (also known as MRSA), leading to approximately 80,000 infections annually, and drug-resistant *Streptococcus pneumoniae*, leading to approximately 1.2 million infections annually[2]. These antibiotic resistant bacteria can greatly worsen prognosis for patients for whom bacterial infection is a high-risk factor, such as those with chronic injuries, burns, or compromised immune systems.

In the human body, bacterial infections are fought off by the immune system. In particular, neutrophils, monocytes and macrophages are key in fighting off bacterial pathogens as these three cell types are those most involved in phagocytosis and ultimately clearing the body of said pathogens[3]. Additionally, immune cell responses can be augmented by platelets. During the immune response, platelets will change expression of signaling molecules that direct neutrophil and monocyte behavior to form aggregates consisting of platelets, neutrophils, and monocytes. In turn, this process activates the neutrophils and monocytes towards responding to invasion by bacteria. Furthermore, platelets themselves are able to bind to bacteria and release antimicrobial substances[4]. Because these mechanisms are already functional under *in vivo* conditions, biomimetic methods for recapitulating such behavior has been very attractive as a means of designing new strategies for fighting off antibiotic resistant bacteria. Thus, researchers have explored incorporation of these antimicrobial mechanisms in order to combat antibiotic resistant bacteria for a multitude of applications.

Commonly used strategies to combat antibiotic resistant bacteria include molecular based strategies, biopolymers, micro-organisms and materials derived from naturally antimicrobial substances such as platelet-rich plasma (PRP)[5-8]. These strategies are summarized in Table 1. Molecular based strategies are focused around functionalizing materials with molecular substances that are antimicrobial. Notable materials within this field include antimicrobial peptides (AMP) and nanometal particles (including gold, silver, and zinc oxide)[7]. Biopolymer strategies are based around functionalizing polymeric materials towards antimicrobial activity. Notable antimicrobial strategies include molecular structure modifications, incorporation of leukocyte migration inducing materials, and incorporation of antimicrobial substances[8]. Antimicrobial derived substances are based around incorporating the use of biologically natural antimicrobial substances. Notable within this field are platelet rich plasma (PRP) and essential oil-incorporated materials.[9,10] Bacteriophages are also a notable strategy for combatting bacterial infection due to their high efficiency in killing bacteria[11] .

While these strategies have shown great potential for antimicrobial efficacy, modifications of synthesis methods, molecular structure, or antimicrobial range could potentially improve efficacy, delivery profiles, and associated toxicity. Some molecular strategies are often associated with difficult or time-intensive synthesis means and, in the case of nanometals, harmful components that may still remain in residual amounts. Strategies based around antimicrobial peptides also face issues with ensuring that peptides are not broken down until delivery to intended treatment sites[12]. Polymeric-based strategies can face similar issues depending on the synthesis methods (e.g.: residual presence of harsh organic solvents). For derived substances, there are issues with means of supply of raw materials and consistent processing. For example, PRP relies on a patient source, which can face regulatory barriers and donor shortages. Furthermore, while PRP has shown potential for antimicrobial applications, Fernandez-Moure has reported that clinical trials utilizing PRP have reported varying levels of antimicrobial efficacy and even recurrence of infections in certain applications (e.g: chronic injury treatment)[13-15].

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Additionally, essential oils, while reported to have components that are antimicrobial against bacteria strains like MRSA, also require some fabrication precautions to prevent essential oil droplets from forming masses during incorporation into other materials[8] .

In this review, we discuss current biomimetic antimicrobial strategies including surface mimicry, biomimetic functionalization of existing strategies, and biomimetic assemblies. The strategies discussed in this review are summarized in Table 2. Surface mimicry consists of strategies based around mimicking the structure of known naturally antimicrobial surfaces such as cicada wing and crab carapace. Biomimetic functionalization of existing strategies consists of the use of biomimetic materials to enhance existing antimicrobial strategies. In particular, these strategies seek to modify existing approaches in order to reduce cytotoxicity, improve delivery profile, and to improve antimicrobial efficacy. As an example, nanometal cytotoxicity can be reduced by using reduction reactions mimetic of chemical processes in microorganisms and plants. Biomimetic assemblies consist of antimicrobial materials that have been constructed into assemblies with other components, such as leukocyte mimetic materials that consist of polymeric particles enclosed with leukocyte membranes. Due to this structure, the resulting assembly can result in better targeted delivery towards sites of infection by mimicking leukocyte targeting mechanisms. These biomimetic methods present potential for versatile solutions for combatting infection by antibiotic resistant bacteria across a wide range of applications and treatment delivery means.

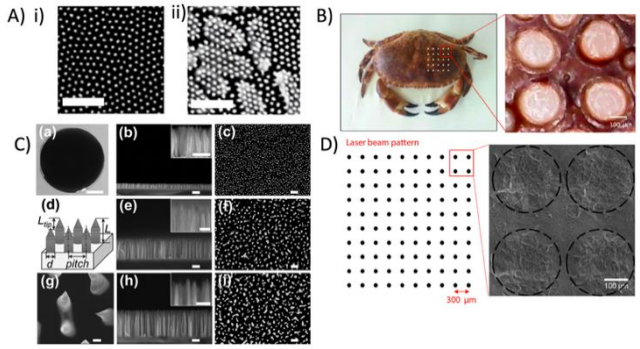

Figure 1: A visual overview of nanopillar and nanowrinkle surface geometry. Section A &C) Comparison of SEM images of natural nanopillar geometry of cicada wing to biomimetic nanopillar surface geometry of varying density and pillar length. All scale bars are for 1 µm. Reproduced from refs 16 and 18 with permission from and Elsevier, copyright (2017) and RSC Publications, copyright (2018) respectively. Sections B & D) Comparison of natural crab carapace nanowrinkle geometry to SEM image of biomimetic patterned nanowrinkles. Reproduced from ref. 22 with permission from Springer Nature, copyright (2016).

Surface Mimicry

Surface mimicry consists of modifying surfaces to mimic naturally antimicrobial surfaces. Most commonly utilized in this field is mimicry of insect wings (particularly of cicadae, damselflies, and dragonflies), shark skin, and the carapace of *Cancer pagurus*[16-19]. The surface geometry of insect wing, *Cancer pagurus,* and their respective biomimetic materials are summarized in Figure 1. These surfaces are known to be self-cleaning due to naturally high hydrophobicity. In addition, these surfaces also kill bacteria by disrupting physical attachment, which prevents the formation of biofilms[17,20]. In insect wings, disruption of physical attachment is achieved by nanopillar structures present on the wings. In the shark skin and *Cancer pagurus* carapace, the surface structure is instead nanogrooves and nanowrinkles, respectively. Biomimetic strategies using nanopillar geometry, nanogrooves, or nanowrinkles are summarized in this section.

Nanopillar Geometry

The nanopillar geometry of insect wings more specifically consists of thick and blunt geometry in high density on the surface. Bacteria will attach to the nanopillars in the space in between nanopillars and remain suspended, which induces mechanical stresses on the cell membrane and wall that will eventually result in membrane rupture[21]. However, Ivanova et al. has reported that cicada wing surface does not prevent attachment of pathological bacteria, though it was able to prevent the formation of biofilms[17]. Thus, current work with nanopillar surfaces focuses on better optimizing the geometry for higher antimicrobial activity. Michalska et al. utilized mimicry of this nanopillar geometry of insect wings by patterning on black silicon, but with a modification of the nanopillar geometry such that the nanopillars themselves will instead penetrate the bacteria directly[18]. Different lengths and density of nanopillars and their effects on resulting antimicrobial activity were investigated. Antimicrobial activity was reported as dependent on nanopillar length and somewhat density dependent, with no significant antimicrobial activity in surfaces with nanopillars shorter than 0.4 µm, an increasing density dependence of antimicrobial activity with 0.7-2.5 µm nanopillars, and density-independent enhanced antimicrobial activity with 3.6-6.7 µm nanopillars[18]. Overall, these results demonstrate that nanopillar geometry and density are important factors for enhancing antimicrobial activity and that the nanopillar geometry can have sufficient antimicrobial activity needed to deal with antibiotic resistant bacteria once the geometry is modified from the normal geometry observed on actual insect wing.

Nanogrooves and Nanowrinkles

While nanopillar surface geometry has been frequently investigated as a means of mimicking the antimicrobial behaviour of insert wings, there remains an issue of optimization towards antimicrobial efficacy, with base nanopillar geometry still allowing for attachment of bacteria and findings showing dependence on nanopillar dimension parameters. Thus, other biomimetic geometries such as the nanogroove geometry of shark skin and nanowrinkle geometry of crab carapace have also been investigated in the literature[16,19,22,23].

The nanogroove geometry of shark skin consists of a ridged surface with 2 µm width and spacing and 3 µm heights[19]. Unlike nanopillars, this surface structure disrupts any attachment of cells and bacteria entirely. However, an accumulation of bacteria in the bottom of grooves has been reported. Sakamoto et al. have observed a decrease in bacteria presence when cultured on top of shark skin mimetic surfaces when the depth of the nanogrooves is shallow (0.4 µm)[19,24]. These findings imply that the nanopillar mimetic geometry may also require further optimization for enhanced antimicrobial activity.

Similarly, crab carapace geometry consists of a surface with protrusions much like ridges. However, these nanowrinkles originate from a hierarchical geometry, in which there are smaller winkles along the fold of larger wrinkles, with wrinkle frequency ranging from 50 nm to 500 µm[25].

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Table 1: Overview of Current Antimicrobial Material Strategies

Category	*Strategy*	*Description*	*Pros*	*Cons*	*References*
Molecular	Nanometal	Creation of nanosized particles of metal and metal oxides.	-Wide range of affected bacteria -Less toxic than bulk antimicrobial metal	-Has varying dose-dependent cytotoxic effects. -Synthesis process can result in toxic byproducts.	7
	Antimicrobial peptides (AMPs)	Creation of AMPs for combat against drug resistant bacteria	-Capable of targeting drug resistant bacteria -Based on peptides naturally produced in animals	-High toxicity -Low in vivo efficacy -Difficult to scale up	6, 7
	Bacteriophages	Viruses capable of selectively killing bacteria	-Low toxicity -Targeting does not overlap with antibiotic drugs	-Can become resisted by bacteria -Narrow range of effect	11, 55-57
Biopolymers	Molecular structure modification	Polymers designed with molecular structure that is mimetic of AMPs	-Allows for tunable polymer with antimicrobial activity -Has potential for efficient scale-up of peptides	-Heterogeneity of chain length and copolymerization -Antimicrobial capability and toxicity dependent on amphiphilic balance	5
	Inclusion of pro-leukocyte migratory materials	Polymers including materials that encourage the migration of leukocytes at implantation sites.	-Directs local immune system cells towards sites of infection	-Requires specific molecular structure or substances	8
	Inclusion of antimicrobial materials	Polymeric materials incorporated with antimicrobial materials such as AMPs and nanometals	-Allows for delivery of antimicrobial materials on both macro- and micro-scales -Allows for tunable construction with nanofiber production methods	-Associated disadvantages of incorporated materials (e.g.: cytotoxicity of nanometals, solvent residues) -May reduce antimicrobial activity (e.g.: AMP nanofiber production)	7,8
Antimicrobial Derived Substances	Platelet rich plasma (PRP)	The use of PRP towards treating infected sites while enhancing tissue regeneration	-Autologous treatment -Has seen use in clinical trials	-Varying efficacy -Potential regulatory barriers	9,13-15
	Essential oils	Incorporation of extracts from plants into materials for antimicrobial function	-Easy to obtain synthesis materials	-Requires specific fabrication set up to prevent oil aggregation during incorporation into materials	10

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Table 2: Overview of Antimicrobial Biomimetic Strategies

Category	*Strategy*	*Description*	*Pros*	*Cons*	*References*
Surface Mimicry	Nanopillars	Patterning of surfaces with nanopillars	-Mechanical mechanism -Translatable across materials	-Requires optimization of surface geometry with regards to pillar length and density. -Cannot be used for applications inside the body	16, 17, 20
	Nanogrooves/wrinkles	Patterning of surfaces with nanogrooves or nanowrinkles	-Mechanical mechanism -Translatable across materials	- Requires optimization of depth for nanogrooves as bacteria can settle at the bottom of grooves. -Cannot be used for applications inside the body	19, 22-25
Biomimetic Functionali -zation	Optimization of nanometal synthesis to reduce toxicity	Enhanced biocompatibility functionalization of nanometal-based strategies by use of organism mimetic molecules to reduce cytotoxicity	-Can circumvent the need for synthetic synthesis of nanometals -Dopamine based catechol structure allows for chemical versatility.	-Effectiveness of reduced cytotoxic effects dependent on incorporation means (e.g.: surface adhesion vs. copolymerization) -Does not remove inherent nanometal cytotoxicity	26-42
	Antimicrobial peptide modification for improved delivery	Modification of AMP function by alternate structures (e.g.: as fibers in materials or the molecular structure)	-Provides alternatives to purely nanometal-based strategies -Improves stability and delivery of antimicrobial molecules such as AMPs	-Time-intensive fabrication methods -Harsh components involved in fabrication (e.g.: solvents, radiation)	43-54
	Bacteriophages	Functionalization of bacteriophage function by genetic engineering to enhance antimicrobial ability or biocompatibility	-Can improve antimicrobial efficacy of bacteriophages -Tunable to desired functions. (e.g.: longer circulation time)	-Time-intensive production methods -Standard production methods have low yields of modified bacteriophages	55-59, 61,62
Biomimetic Assemblies	Biomimetic assembled particles	Creation of materials by methods that mimic natural assembly of lipids into membranes, including polymers and nanometals	-Versatile in material components -Addresses issues with existing strategies such as nanometal and polymer cytotoxicity	-May not be as effective on bacteria species with thicker or less negatively charged cell walls -Antimicrobial activity may be compromised due to decreased contact area	63-70
	Antimicrobial peptide-based particles	Creation of antimicrobial peptide-based particles by assembly with membranes surrounding AMP core.	-Allows for enhanced delivery of AMP by reducing potential contact with proteases -Reduced cytotoxicity	-Antimicrobial activity limited to surface-based interactions -Reduced antimicrobial activity in comparison to free form AMP	71-73
	Cell mimetic materials	Materials designed around mimicking the function of cells capable of combating infections	-Compatible with physiological environment -Can allow for improved delivery of existing antimicrobial material strategies	-Requires significant continued investigation of function as antimicrobial delivery or efficacy of antimicrobial activity -Some methods require extraction of membranes from pre-existing cells.	74-80

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Work by Efimenko et al. has demonstrated that surfaces with this geometry are capable of an antibiofouling capability that prevents attachment of microorganisms, which includes bacteria[25]. Papi et al. created a graphene-oxide based hydrogel material that was patterned with this geometry by laser printing and demonstrated enhanced antimicrobial capability against several species of relevant bacteria (e.g.: *S. aureus* and *E. Coli*) when the hydrogel is printed with the crab carapace surface geometry[22]. Overall, antimicrobial results for surfaces using nanogrooves and nanowrinkles show potential as antimicrobial materials.

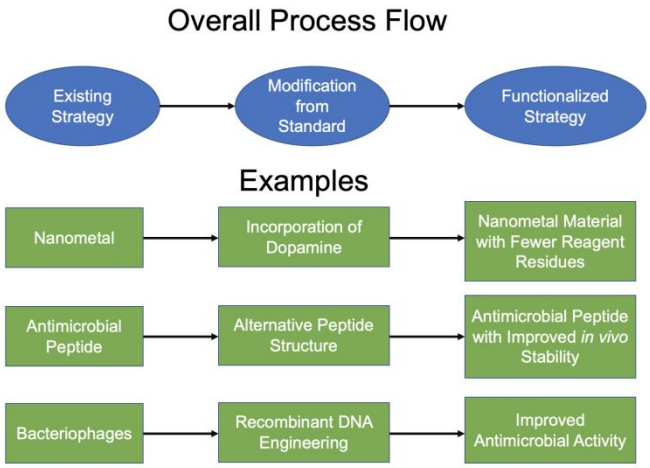

Figure 2: Overview of biomimetic functionalization of existing antimicrobial strategies.

Biomimetic Functionalization of Existing Antimicrobial Strategies

Beyond surface mimicry, another major strategy for creating novel antimicrobial materials is to utilize biomimetic functionalization approaches to address limitations of existing antimicrobial strategies. In particular, this section will discuss improvement of nanometals, antimicrobial peptides, and bacteriophages. These strategies, while promising as means for combatting antimicrobial resistant strains of bacteria, have issues with cytotoxicity or effective delivery. Thus, the strategies in this section will discuss means to overcome these shortcomings.

For this section, we will discuss the functionalization of naturally antimicrobial substances including nanometal, antimicrobial peptides, and bacteriophages. For nanometals, we focus on methods of synthesis that reduce the cytotoxicity associated with the reactions. These strategies include the use of dopamine and green methods of synthesis and all focus on reducing the toxicity of nanometals by reducing the amount of residue reactants. For antimicrobial peptides, modifications in peptide structure have been investigated to enhance delivery. These alternate structures can entail either the form of delivery (e.g: molecules vs. as a material) or modification of the molecular structure itself. For bacteriophages, genetic engineering has been the primary means of enhancing function. These modifications can range from expanding targeting capacity to enhancing selectivity of the bacteriophages.[7,26-33] Figure 2 summarizes the types of strategies that are described in this section.

Optimization of Nanometal Synthesis to Reduce Toxicity:

Metals such as silver and gold have been known to exhibit broad antimicrobial activity for some time by targeting multiple cellular processes in bacteria cells. However, bulk metals can cause cytotoxicity, therefore, nanometals have been widely investigated as an alternative to bulk metals due to decreased cytotoxicity. This effect is achieved by the nanoscale particle size, which vastly decreases the overall metal content as well as increases the total surface area that can come into contact with bacteria[7]. However, syntheses of nanometals typically entail the chemical reduction of metal ions, which can be left in residue after production and are harmful to the physiological environment if they remain during delivery to the body[7]. Therefore, there is a need to optimize nanometal synthesis to decrease toxic byproduct production. Mussel mimetic materials, which are naturally nontoxic and have the ability to serve as a reduction agent, have been used frequently to reduce the cytotoxicity of nanometals by providing an alternative synthesis method. The reductive property of mussel inspired materials is due to the content of dopamine in their adhesive proteins and dopamine's catechol structure, which consists of a benzene ring with two hydroxyl side groups[26-31]. Because of this reductive capacity, dopamine and dopamine-inspired materials are a popular choice for less harmful production of nanosilver nanoparticles (NPs). Additionally, dopamine-based synthesis strategies have seen use for improving other existing antimicrobial strategies, such as serving as a selective delivery vessel for peroxides[31]. Other methods of nanometal synthesis with reduced cytotoxicity include green methods of nanometal synthesis. Dopamine and other green synthesis based methods for reducing cytotoxicity are discussed in subsequent sections.

Dopamine-based Methods for Reducing Cytotoxicity:

Dopamine has frequently been used as a means of less harmful production of antimicrobial nanometals, particularly nanosilver. Under artificial synthetic means, the production of nanosilver entails the use of silver ions and harsh solvents. Residual ions or solvents can have damaging effects on nonpathogenic cells[26-29]. However, because silver is known to be antibiotic against many pathogenic species, the material still has great appeal and has thus led to great interest in seeking means to synthesize nanosilver by less toxic means[7]. Many investigators have utilized the reductive property of dopamine to create composite materials with antimicrobial nanosilver with reduced cytotoxicity.

Methods of incorporation of dopamine into materials vary from direct surface functionalization by dopamine[26-28] to hydrogels that have been conjugated with dopamine proteins[30] or copolymerized with dopamine-incorporated monomers, particularly dopamine methacrylamide (DMA).[29,31,32] For fabrication of antimicrobial functionalized surfaces, base materials are treated with a solution of dopamine for many hours and then immersed in silver nitrate solution[26-28]. Kung et al., Liu et al., and Wu et al., show that the manufacturing process can be applied across different materials and report significant antimicrobial activity[26-28]. When incorporated into hydrogels, DMA is typically produced and then included as a

copolymer component. Once the dopamine composite hydrogel is complete, nanosilver is then incorporated by contact with silver nitrate solution[29]. GhavamiNejad et al. created such a composite hydrogel for wound healing applications using a zwitterionic hydrogel incorporated with silver nanoparticles. The composite material was reported to have significant antimicrobial activity for bacterial culture over the course of 24 hours[29].

Though silver is the main focus of functionalization, dopamine has been used to reduce cytotoxicty of other antimicrobial materials as well. Cheng et al. used dopamine to deposit zinc-oxide nanoparticles onto Poly(ethylene terepthlate) (PET) films and has reported significant antimicrobial activity[32]. Additionally, dopamine's biochemical properties can also be used as a means of delivery of other antimicrobial substances. Wang et al., fabricated peptide composite hydrogels by conjugating ε-poly-L-lysine (EPL) to polyethylene glycol (PEG) using dopamine[30]. Additionally, dopamine has been used to engineer a delivery system of hydrogen peroxide to address the issue of hydrogen peroxide transportation and stabilization. While known to be antimicrobial, hydrogen peroxide is relatively volatile, which can make transportation of viable solutions over long distances difficult. Additionally, hydrogen peroxide is very strong as an antimicrobial agent and is typically diluted to 3%, which can further contribute to problems with storing large volumes of ready to use solutions.[33] To address these issues, Meng et al. fabricated dopamine inspired hydrogels that can be repeatedly activated to produce hydrogen peroxide depending on environment pH. These dopamine-mimetic hydrogels utilize the catechol groups of dopamine to generate hydrogen peroxide by autoxidation and were reported to completely reduce bacteria colony formation after 24 hours at concentrations significantly lower than the market 3% hydrogen peroxide solutions[31]. Overall, dopamine-based materials allow for chemically versatile means of including antimicrobial function using known antimicrobial materials, particularly nanometals.

Additional Green Synthesis Methods:

Due to residue of harmful reagents and involvement of ions that come from synthetic synthesis of metal nanoparticles, there has been much interest in the investigation of alternate methods of nanometal synthesis, including dopamine based strategies as discussed above. Beyond dopamine based strategies, other green synthesis schemes have also been explored, including the use of naturally derived reduction agents or the direct use of microorganisms. In nature, there exist several components and microorganisms capable of reducing ions into nanoparticles. Examples include compounds derived from plant matter essence, such as citrus fruit peels, coffee, tea, lemon verbena, and sorghum bran, which contain organic molecular structures capable of contributing to reduction reactions[34-39]. Production of nanoparticles by these methods produce no known toxic material[35].

Microorganisms capable of contributing to reduction reactions include bacteria, fungi, and algae[40-42]. However, the synthesis of nanometal particles by use of microorganisms is difficult to scale up, with algae seeing some greater appeal as the culture conditions are not as demanding as bacteria or fungi[35,42]. Ebrahiminezhad et al. achieved a synthesis of silver nanoparticles by use of supernatant fluid from *Chloerlla vulgaris* algae culture. Increasing concentrations of these silver particles was directly correlated to increasing antimicrobial activity and increasing cytotoxicity[42]. Overall, green syntheses show potential towards improving production of antimicrobial material strategies by providing an alternate means to producing nanometals via more ecologically favourable and less cytotoxic methods.

Antimicrobial Peptide Modifications for Improved Delivery:

Antimicrobial peptides have been seen as a promising potential platform for combatting antimicrobial resistant strains of bacteria due to killing bacteria by disrupting necessary lipid components instead of metabolic mechanisms[43-46] . However, they can be difficult to deliver due to their sensitivity to amphiphilic balance and difficult to administer due to in vivo toxicity at high doses.[47-49] Xi et al. investigated the use of antimicrobial peptides with enhanced functionalization for better biocompatibility. This functionalization was achieved by focusing on making the material biomimetic of the application environment, in this case, skin in wound healing applications, by creating a peptide composite polymer and then electrospinning the composite material into a matrix mimetic of skin extracellular matrix. The peptide composite material created was reported to significantly inhibit bacterial growth with incorporation of as little as 10% antimicrobial peptides. Notably, lower cytotoxic effects were also observed in the presence of 10% antimicrobial peptide incorporated material, which indicates potential antimicrobial efficacy with reduced cytotoxicity due to lower antimicrobial peptide content[50]. Also notable is the conjugation of antimicrobial peptides to carrier materials for stabilization and modulation of potential cytotoxic effects[6,7]. To diminish the harsh effects of antimicrobial peptides, Chen et al. investigated inducing self-assembly of the antimicrobial peptide SFT onto the surface of nanogold particles, using the nanogold as a stabilizing agent. These gold-peptide composites were reported to effectively inhibit growth of multi drug resistant strains and disrupt bacterial membrane structure[51]

In addition, direct modification of antimicrobial peptide structure has been investigated. As an example, Xiong et al. created antimicrobial peptide mimics that relied on radial amphiphilicity as opposed to facial amphiphilicity. This structural difference allows for a reduction in self aggregation and was reported to have better stability in physiologically relevant buffers (e.g.: human serum, fetal bovine serum). The peptide mimetics were also found to have significant antimicrobial activity against drug resistant strains of *E. Coli*, *S. aureus*, and *Bacillus cereus*[52]. Helix-coil structure has also been investigated as a means of allowing antimicrobial peptides to gain pH activated antimicrobial ability. This structural modification reduces the toxicity of antimicrobial peptides by increasing selectivity towards bacteria of interest (e.g.: only in active form when in pH 2 for treating *Helicobacter pylori* in the stomach).[53,54]

Bacteriophages:

Bacteriophages are viruses that target bacteria and kill them. They have previously seen use as a strategy towards combatting bacterial infection due to their ability to dose automatically, low inherent toxicity, and high efficacy[11]. However, without modification bacteriophage are limited by a narrow range of effect and can be resisted by bacteria via evolution of resistance[55-57]. To better enhance the antimicrobial capability of bacteriophages, a range of genetic modifications and engineering have been utilized, including expansion of effect range and targeting of bacteria by mechanisms different from antimicrobial drugs[55,57]. Lu et al have developed recombinant genetic engineering techniques to achieve these modifications in bacteriophages[58]. These genetic modifications can allow bacteriophages to directly infiltrate bacteria and disrupt bacterial function, such as DNA repair in *E. coli*[55,57,59]. Other modifications have been investigated including gene

functionalization towards longer circulation time, reduced toxin release of lysed bacteria, and suppression of bacterial resistance to antimicrobial drugs[60-62].

Overall, functionalization of existing strategies present alternative methods of enhancing the performance of nanometals, antimicrobial molecules, and bacteriophages in a wide range of aspects including biocompatibility, delivery efficiency, and efficacy.

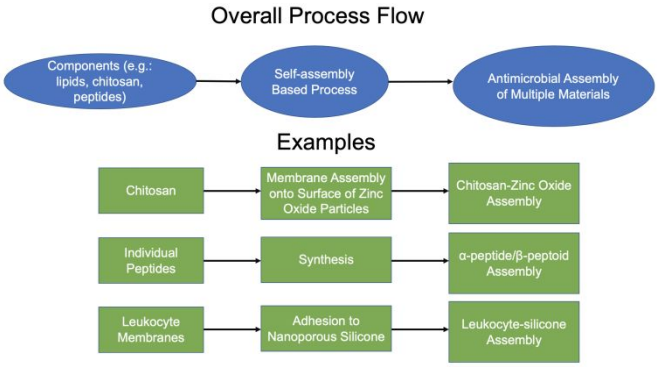

Figure 3: Schematic of biomimetic assemblies

Biomimetic Assemblies

In this section, we will discuss antimicrobial biomimetic assemblies, which we define as antimicrobial materials that consist of an assembly of components, frequently including use of a cell-membrane like structure or cell-mimetic morphologies and function. In particular, biomimetic assembled particles, such as bioactive supramolecular assemblies, antimicrobial peptide-based particles, and cell mimetic particles will be discussed. A schematic summarizing the types of strategies discussed in this section is shown in Figure 3.

Biomimetic Assembled Particles

Like surface mimicry discussed in earlier sections, biomimetic assembled materials can disrupt bacteria structure by mechanical means. This method of antimicrobial activity results from a charge on the material causing attachment to bacterial cell walls, which results in lysis of the bacteria[63]. Examples of such materials include the use of charged lipid layers and polymeric coatings on nanoparticles. Xavier et al. investigated the use of a cationic bilayer with polystyrene core, which has been reported to mimic histones with DNA compaction[64], with incorporation of the antimicrobial peptide gramicidin. The particles were reported to have higher positive charge when including gramicidin and had enhanced antimicrobial effects against *S. aureus* but no significant effects against *E. coli*. The authors hypothesized that this difference in efficacy may be the result of steric hindrance by the inclusion of the peptide[65]. Similar principles has been applied to assembled particles based around polymer cores by utilizing cationic polymers to provide antimicrobial function, such as Polydiallyldimethylammonium chloride (PDDA) and Poly(methyl methacrylate) (PMMA). These materials were found to be a capable of reducing bacterial cell viability to 0%, but did require higher dosage when combatting hardier species of bacteria, such as *S. aureus*. [60,66]

This type of membrane-enclosed particle can also be used with antimicrobial nanometals, antimicrobial peptides, and polymers by changing the core to which the coating materials adsorb[63,64,67]. For nanometals, incorporation is achieved by loading a porous core and then enclosing it with a biomolecular layer. This construction achieves a means to control the amount of exposure to nanometal contact and, in combination with chitosan, has been reported to achieve antimicrobial activity while improving cytotoxicity for zinc oxide and silver with a membrane structure mimetic of organisms like yeast[68-70].

Antimicrobial Peptide-based Particles

Antimicrobial peptide-based particles represent another class of biomimetic assemblies utilized for antimicrobial purposes. Antimicrobial peptide based particles include approaches which create particles that mimic the structure of antimicrobial peptides themselves or deliver antimicrobial peptides via particles as a means for improving delivery[49,52]. Particles based on directly mimicking the antimicrobial peptide structure are focused on altering structures in ways that can still retain antimicrobial activity while allowing the molecules to undergo less degradation and off-target interactions in the physiological environment before reaching target sites[53]. Commonly investigated designs seeking to reduce premature degradation and off-target interactions include peptide-peptoid composites and α-peptide/β-peptoids[49,71-73].

Particles can also be used to entrap antimicrobial peptides to improve their delivery and decrease systemic toxicity. By enclosing antimicrobial peptides with a membrane, peptides are allowed a means of delivery for difficult to reach targets, such as sites beyond the blood-brain barrier, and can be protected from premature degradation. Enclosed peptides have also been reported to still retain the antimicrobial efficacy of the peptide alone. Such approaches have been discussed in detail in previous sections. Overall, biomimetic assembled materials show great potential for attaining improved delivery means for a variety of antimicrobial materials.

Cell Mimetic Materials

An additional class of biomimetic assemblies includes cell mimetic materials, including particles which mimic various immune cell function. Native immune cells have intricate mechanisms for fighting bacterial infection. For this reason, there has been appeal in investigation towards the creation of mimetics of cells involved in infection combat, including the investigation of leukocyte-mimetic materials[74]. Molinaro et al. produced lipid nanoparticles incorporated with leukocyte membrane proteins, which have been termed leukosomes. The leukosomes are capable of drug delivery and targeting inflamed vasculature[75]. Hammer et al. produced a hybrid particle termed as “leuko-polymersome” that consists of polymeric vesicles coated with binding motifs mimicking leukocyte interactions in the physiological environment[76]. Parodi et al. investigated the construction of porous silicone coated with leukocyte membranes, which are termed as leuko-like vectors (LLV)[77]. Both leukopolymersomes and LLVs were reported as capable of targeting inflamed endothelium, which presents potential for targeted drug delivery to infected tissue[76,77]. In general, these materials show high potential towards targeted delivery of antimicrobial agents towards sites of infection to drug resistant bacteria.

In a similar vein, cell mimetics have also been used to combat infection by reducing bacterial toxin presence. Zhang et al have developed nanosponges consisting of polymeric nanoparticles enclosed by membranes of red blood cells. This construction allows the nanosponges to mimic nonspecific binding of cell membrane components to toxins produced by the likes of MRSA and neutralize toxins. Membranes of other cells, such as white blood cells, were also

found to ward against sepsis as well, presenting potential for tunability to a variety of applications[78,79].

Platelets are also known to contribute to the infection combat process, which gives promise to the investigation of platelet-mimetic materials as an antimicrobial platform. Sproul et al. produced a platelet-mimetic particle capable of antimicrobial activity by creating nanogold composite deformable hydrogels[80]. These composites were found to have significant inhibition of bacterial growth after 24 hours but were not as effective at controlling bacterial growth as ampicillin, a clinically used antimicrobial drug[80]. While cell mimetic antimicrobial strategies show promise in mimicry of leukocyte, red blood cell, and platelet function, further investigation is needed to more thoroughly investigate function and optimize antimicrobial capacity. For leukocyte mimetic materials, behaviour of the materials in combination with delivery of antimicrobial substances needs to be further investigated. For platelet-mimetics, further investigation is needed to optimize the antimicrobial activity.

Conclusions

Biomimetic antimicrobial strategies show great potential and versatility in addressing the rise of antibiotic resistant bacteria. These strategies can produce biocompatible means of dealing with antibiotic resistant bacteria by physical disruption, as observed with surface mimicry, biomimetic functionalization of existing antimicrobial strategies, and biomimetic assemblies. However, there remains much room for optimization.

Surface mimicry allows for disruption of bacteria by mechanical means without the need for inclusion of additional antimicrobial substances, which can allow for safer methods of combating bacterial contamination. However, there remains an issue of geometry optimization as completely mimicking natural surface geometry may not result in the desired antimicrobial capability. Additionally, there may also be dependence on the type of material used as the works involving surface mimicry all use different materials, with some utilizing materials with already reported antimicrobial properties, such as black silicone and graphene-oxide based gels[18,22,81].

Functionalization of existing strategies seeks to improve on previously investigated antimicrobial strategies. Nanosilver, though a popular choice for its antimicrobial efficacy range, is known to be cytotoxic at certain concentrations[6,7]. Similar concerns have also been reported for substances like antimicrobial peptides and peroxides[6,33]. Despite efforts to reduce these negative effects, the concerns associated with the base antimicrobial material still linger. For silver composite surfaces produced by dopamine, it is hypothesized that this may be the result of harmful silver ions leaching off from the nanoparticles despite the less harsh synthesis provided by dopamine's reductive properties[26-29].

In a similar vein, although biomimetic syntheses can reduce the harmful aspects of the nanometal production process, the cytotoxicity problems of the ultimate nanometal product still remains. Furthermore, green syntheses have dependence on the substance used to facilitate nanoparticle production. Synthesis focused around microorganisms may demand very specific culture conditions or even present potential pathogenic effects, particularly in production by bacteria or fungi[42,82]. In addition, it has been reported that plant essence based syntheses can be significantly faster than microorganism strategies due to microorganisms requiring separate culture with varying degrees of specificity (i.e.: culture conditions for algae are less specific than those for fungi and bacteria)[35,37,40,42,82].

Biomimetic assembled particles also present potential in controlling some of the harmful effects associated with antimicrobial strategies. However, they too require further optimization. For strategies including nanometal particles, the cytotoxicity concerns are also still a major point of consideration. Additionally, the creation of these types of particles can be rigorous in the specific chemistry required to produce complex peptide structures or to produce membranes. Cell mimetic materials demonstrate the feasibility of the creation of materials mimicking cells involved in combat of infection. However, much of the investigation conducted in this field requires further study for both the determination of potential inherent antimicrobial activity, its optimization, and potential changes in particle behaviour when loaded. For platelet mimetic materials in particular, there remains a need to investigate the incorporation of other antimicrobial materials for higher antimicrobial activity, such as stronger nanometals like nanosilver.

While versatile in potential for application, these biomimetic antimicrobial strategies may also call for further optimization for cytotoxicity depending on application. For applications focused at applying these antimicrobial materials towards use in the clinical field, the consideration of cytotoxicity is substantially more important than in other applications. Nanosilver-based strategies in particular had reported cytotoxicity concerns in this regard[7,26-30,34,35,37-42,50,83,84]. In contrast, when the application is focused around keeping substances such as medical tools and biosensors from bacterial contamination, the cytotoxicity concern may not be as relevant[83].

Conflicts of interest

There are no conflicts to declare.

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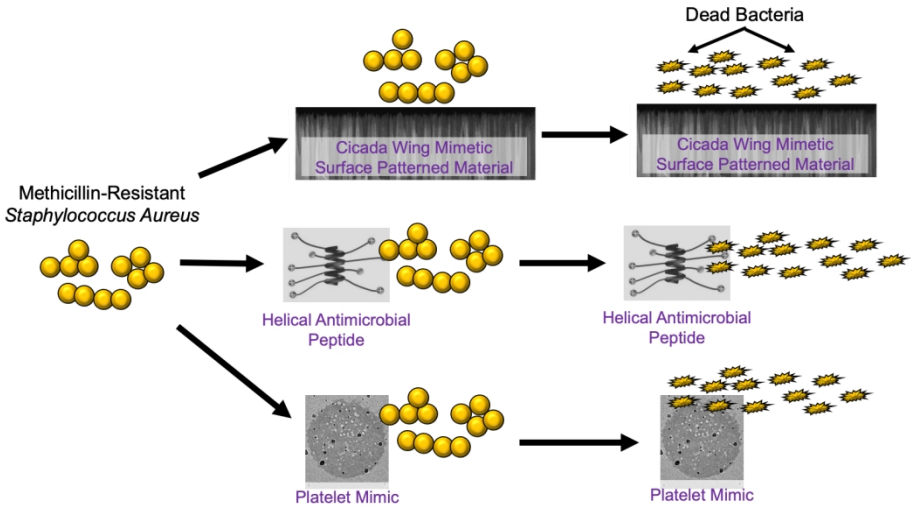

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