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REVIEW

Can mesenchymal stem/stromal cells and their secretomes combat bacterial persisters?

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Abstract

The increasing number of life-threatening infections caused by persister bacteria is associated with various issues, including antimicrobial resistance and biofilm formation. Infections due to persister cells are often difficult to suppress without the use of last-resort antibiotics. Throughout the world, bacterial persistence and resistance create an unmet clinical demand for the exploration of newly introduced therapeutic approaches. Mesenchymal stem / stromal cells (MSCs) have an antimicrobial activity to protect against bacterial infections, including those caused by bacterial persisters. MSCs have substantial potential to secrete antimicrobial peptides (AMPs), including cathelicidin, beta-defensins, lipocalin-2, hepcidin, indoleamine 2,3-dioxygenase (IDO), cysteine proteases, and inducible nitric oxide synthases (iNOS). MSCs possess the potential to contribute to innate immunity by regulating the immune response. Recently, MSCs and their secreted components have been reported to improve antimicrobial activity. Bactericidal activity by MSCs and their secretomes has been shown to be mediated in part by the secretion of AMPs. Even though they were discovered more than 80 years ago, therapeutic options for persisters are restricted, and there is an urgent need for alternative treatment regimens. Hence, this review intends to critically assess the current literature on the effects of MSCs and their secretomes on persister bacteria. MSCs and their secretome-based therapies could be preferred as an up-and-coming approach to reinforce the antimicrobial efficiency in persister infections.

Keywords Mesenchymal stem / stromal cells · Secretomes · Bacterial persisters · Antimicrobial peptides

Introduction

In recent years, the global spread of antibiotic resistance, coupled with few therapeutic options, has made it challenging to explore suitable alternative therapies to combat this emerging issue (Russell et al. 2020). The inappropriate and excessive usage of antibiotics gives rise to the rapid global spread of antibacterial resistance, which has to lead a worldwide threat to public health (Battah 2021). Chronic bacterial infections are particularly difficult to treat and can result in long-term morbidity and mortality, partly driven by biofilm formation that contributes to bacterial persistence and damage to the host tissue (Johnson et al. 2017). Due to the strong unmet need for the management of chronic infections, MSCs have shown promise in targeting persister cells and enhancing the immune response against persister infections (Park et al. 2019; Ren et al. 2020). Recently, the potential of MSCs has also gained attention in the treatment of a variety of immune-mediated disorders and conditions, due to their antibacterial activity. MSCs have been investigated in non-human animals, and preliminary clinical experiments have been conducted in patients exposed to infectious diseases (Ren et al. 2020). In particular, MSCs can up- or down-regulate the immune response, and this has been attributed to their ability to polarize into pro-inflammatory MSC1 or immunosuppressive MSC2 phenotypes (Waterman et al. 2010). To combat bacterial persisters, MSCs can contribute via direct and indirect mechanisms, but these have still not been fully understood. This review highlights the therapeutic properties of MSCs and their secretomes against bacterial persistence infections through different mechanisms.

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Bacterial persisters

Bacterial persisters were first observed in 1942 when penicillin killed 99% of streptococcal culture and left 1% of the culture that did not respond to antibiotic treatment (Hobby et al. 1942). In 1944, this phenomenon was described as persisters. Persisters are a subpopulation of stationary and quiescent bacteria which are not killed by antibiotics, despite being genetically identical to the susceptible cells. In fact, this phenomenon can allow the cells to regrow and remain susceptible to penicillin (Bigger 1944). With the progress of understanding bacterial persisters over time, the definition has become as follows: bacterial persister cells have a unique physiological state that makes them unremarkably non-genetically tolerant to antibiotics, which supports their ability to remain alive even when exposed to bactericidal drugs and have the capability to regrow under highly specific conditions (Zhang 2014).

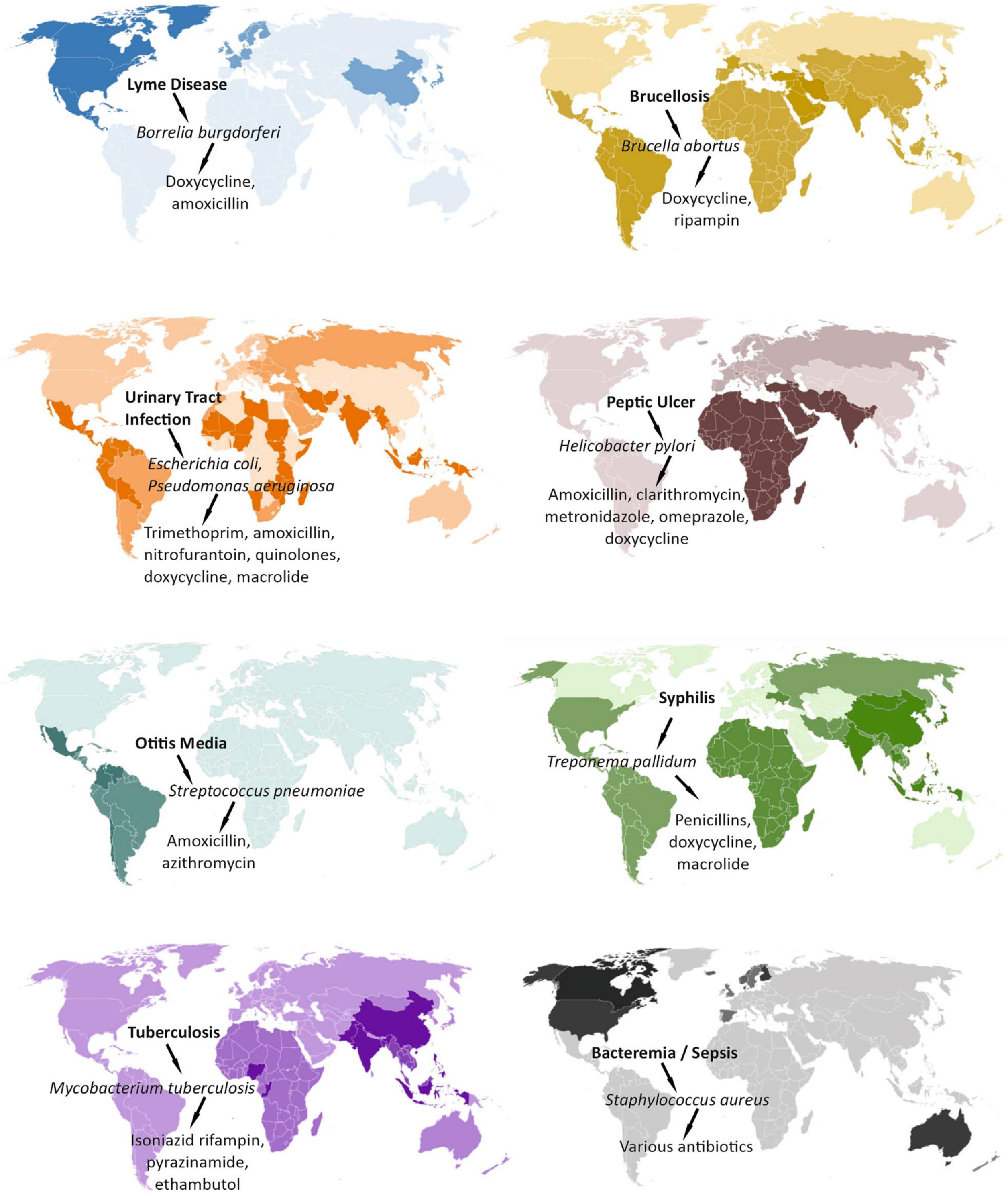
The propensity for persister formation has not been well understood yet due to certain features of persister cells, such as being elusive, heterogeneous, and transient, with alterations linked to environmental conditions. Bacterial persister formation can be promoted by bistable gene expression and regulated by the random variability of gene expression related to persister formation. This can result in changes in signaling protein modifications or DNA modifications that affect the incidence of persister cells (Veening et al. 2008; Rotem et al. 2010). Such diverse factors might generate a huge diversity and heterogeneity of persister cells. A wide variety of persister-related genes have been discovered, yet how bacteria sense the need to form persisters remain unclear (Zhang 2014). There are detailed review articles on these persister genes (Lewis 2012; Zhang 2014; Eisenreich et al. 2022).

Persister bacteria have been implicated in various chronic bacterial infections, including tuberculosis (Zhang et al. 2012), and Lyme disease (Stricker and Johnson 2011), which are challenging to treat due to the presence of persisters. A large spectrum of persister bacteria and their diseases have been treated with current therapeutic approaches, including antibiotic groups ranging from penicillins to doxycycline (Stricker and Johnson 2011; Zhang et al. 2012). As a result, even after an initial course of antibiotics, persisters seem to remain in the body, and may result in a recurrence of bacterial infections. This can lead to chronic or long-lasting infections that can be challenging to treat. As shown in Fig. 1, different bacterial species seem to cause various features for bacterial persistence infections. For instance, *Streptococcus pneumoniae* shows weakness in forming persisters since it can be treated within a week or two with the help of a single antibiotic. On the contrary, *Mycobacterium tuberculosis* and *Pseudomonas aeruginosa* bring about chronic persistent infections that require treatment for at least 6 months (Mulcahy et al. 2010; Zhang et al. 2012). Furthermore, *Borrelia burgdorferi* has been found in biofilms related to Lyme disease, not only in vitro but also in vivo, which can assist their bacterial persistence in tissues. Persister cells have been studied and detected in animal models, and the persistence of bacterial infections showed long-term survival in infected animals, even with antibiotic treatment (Barthold et al. 2010; Embers et al. 2013). Although there has been significant progress in understanding the mechanisms and treatment of bacterial persisters in recent years, novel treatment strategies only provide temporary relief, and there is still a need for the development of novel and efficient alternative treatment options for persistent infections. Recently, evidence has emerged suggesting that MSCs and their secretomes could be an effective therapy for bacterial persistent infections.

Fig. 1 The figure represents some infectious diseases, due to bacterial persisters, their causative pathogens, and current treatment options. The data has been gathered from the World Health Organization (WHO) and indicates a concerning global trend in the dissemination of bacterial outbreaks. The geographical regions most affected by these diseases are as follows; Lyme disease: The United States and Canada experience a significant burden of reported cases. Tuberculosis: The South-East Asia bears a substantial number of cases; Syphilis: Africa, South and South-Eastern Asia are particularly affected by the disease. Brucellosis: West Asia, India, the Middle East, Southern Europe and Latin America report a notable incidence of the disease. Otitis media: Latin America shows a significant prevalence of cases. Peptic ulcer: Africa, Pakistan, Turkey and India exhibit a considerable number of cases. Bacteremia/sepsis: The United States, Canada, Scandinavia countries and Australia are highly impacted. Urinary tract infection: Afghanistan, India, Indonesia, Iran, Malaysia, Mexico, Papua New Guinea, various African nations, and Central and South America are vulnerable to the infections ▶

Interaction of bacterial persisters and MSCs

The pathogenesis of bacterial infections involves different mechanisms, such as the capability of bacteria to attach to host cells and secrete toxins to evade the host's immune response (Powers 2004). Chronic bacterial infections are characterized by biofilm formation that generates bacterial persistence, making them difficult to treat without broad-spectrum antibiotics and/or the last resort of antibiotics (Johnson et al. 2017). Despite all the methods used today, there is still no definitive solution to combat bacterial infections due to bacterial persister cells. Hence, it is very significant to develop new therapeutic strategies to struggle against the emergence of resistant bacteria, rather than relying solely on combining more than one antibiotic to tackle bacterial resistance (Battah 2021). In order to combat bacterial infections, different alternative strategies have been proposed, including the use of beneficial microorganisms, the



modified genetic material of bacteria, and various stem cells (Kumar et al. 2021). Recently, MSCs have been extensively studied to orchestrate the immune response to ameliorate patients with severe infection by interacting with the potential to reduce inflammation and regulate the immune system (Ren et al. 2020). Notably, in addition to their well-known negative influence on immune system activity, MSCs can positively modulate the immune system if polarized into the MSC1 phenotype (Waterman et al. 2010). Since there are not many studies based on bacterial persisters and clinical studies have not yet been published, bacterial infections supported by biofilm formation and antibiotic resistance were defined as persistent infections and the potential treatment of these structures with MSCs might be considered as a potential method.

The diversity of AMPs allows them to modulate the immune response, with the function of being the primary defense against pathogens and thus displaying a broad spectrum of antimicrobial activities (Brogden 2005). Their selective biological activities, which can target a wide range of organisms, render them potentially promising therapeutic agents (Zhang and Gallo 2016). To date, there are 3569 AMPs listed in the antimicrobial peptide database from various sources, including plants, animals, bacteria, and fungi. 153 of them are human host defense peptides, some of which have already been confirmed to be present in MSCs (Wang et al. 2016). Certain AMPs such as human α-Defensins and human β-Defensin 1 are vital components of the innate defense system and are produced constitutively. Conversely, others, such as human β-Defensin 2, 3 and 4 are induced in response to infection and injury (Tobin and Zhang 2023). The induction of these peptides can be triggered by pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides, bacterial DNA, flagellin and certain metabolites. For instance, *Streptococci* utilize cell surface-associated histidine kinases CsrS to directly sense peptide molecules (Tran-Winkler et al., 2011). An example of an AMP's effect on bacterial virulence is LL-37, which alters *Streptococcus pyogenes*'s surface architecture, leading to the formation of extracellular vesicles containing numerous virulence factors (Uhlmann et al., 2016). Another instance involves rhamnolipids, a virulence factor in *Pseudomonas aeruginosa*, which activates transcription factors, such as nuclear factor kappa B (NF-kB) and activator protein-1, inducing hBD2 in keratinocytes (Wehkamp et al. 2006; Gerstel et al. 2009). Furthermore, various small metabolites like acetate, propionate, and butyrate have been shown to induce expression of antimicrobial peptides produced by host defense system (Chen et al. 2020; Tobin and Zhang 2023). For example, butyrate was found to induce MAPK-p38 and ERK pathways in Caco-2 cells, leading to LL-37 synthesis (Schwab et al. 2007). It can also stimulate the mTOR and STAT3 pathways in intestinal epithelial cells, resulting in β-Defensin synthesis (Zhao et al. 2018). AMPs possess diverse biological activities that allow them to be essential mediators of the immune response against various pathogens including bacterial proteins. Their potential and their modulation through different cellular pathways make them intriguing targets for further research in antimicrobial therapies.

It was reported that MSCs have antimicrobial potential, which can be directly mediated by secreting AMPs including hepcidin, cathelicidin (also known as LL-37), lipocalin 2, and β-Defensin 2 (hBD2) (Marrazzo et al. 2019; Yagi et al. 2020). AMPs play a direct role in bacterial killing, listed in Table 1. Yagi et al. (2020) reported that MSCs inhibited methicillin-resistant *S. aureus* via AMPs secreted by MSCs. In this in vitro study regarding joint infections, the bacteria were integrated into the synovial fluid to stimulate bacterial transmission, and then bone marrow derived MSCs were injected into the environment. The authors found a significant inhibition of MSCs against the bacterial growth of *S. aureus* (Yagi et al. 2020). Furthermore, it was found that biofilm formation could be an effective mechanism for mediating antibiotic resistance in bacteria, including methicillin-resistant *S. aureus* and *E. coli* (Scherr et al. 2015). Another study suggested that MSCs secrete antimicrobial factors to attenuate biofilm formation of methicillin-resistant *S. aureus*, thus enhancing defense mechanisms to prevent bacterial infections in a rat model (Yuan et al. 2014). In addition, MSCs demonstrate potential as an alternative antibacterial agent against multidrug-resistant (MDR) bacterial pathogens such as *Vibrio cholerae*. Due to their anti-biofilm activity, MSCs combined with chitosan nanoparticles were used as a promising therapy against MDR strains (Saberpour et al. 2020). Moreover, a significant effect of the AMPs produced by MSCs and an increase in antibiotic susceptibility were also reported in cystic fibrosis infections (Sutton et al. 2016). This study showed an MSC-mediated decrease in the amount of colony-forming units (CFUs) of antibiotic-resistant bacterial strains such as *Pseudomonas aeruginosa*, *Streptococcus pneumonia*, and *Staphylococcus aureus* in a mice model (Sutton et al. 2016).

MSCs may have two distinctive aspects in cell therapy. First, MSCs possess a unique capacity to regulate the immune system, predominantly by suppressing specific immune responses. This immunosuppressive attribute of MSCs is critical in dampening deleterious immune reactions, thus facilitating tissue repair in various cell therapy applications. Moreover, MSCs exhibit an antigenic role by enhancing the defense mechanism within the immune system through the activation of neutrophils and macrophages (Hosseiniyan Khatibi et al. 2020). Conversely, the function of MSCs can also engender on opposing effect; wherein they augment the antibacterial functions of neutrophils to fight bacterial infections (Marrazzo et al. 2019). Thus, the interactions of MSCs with the immune system encompass two major facets, involving both immunosuppressive and immunostimulatory responses (Ghasemian 2021). MSCs suppress certain immune responses for reducing immune rejection, treating autoimmune diseases, controlling inflammation. Also, excessive inflammation can lead to tissue damage. MSCs can modulate the production of inflammatory molecules and promote an anti-inflammatory environment, which aids in tissue repair and regeneration (Han et al. 2022). It suggests that the interaction of MSCs with

Table 1 Direct mechanisms of MSCs and their antibacterial/immunomodulatory effects

Antimicrobial Features	Direct/ Indirect Mechanism	Sources of MSC	Infected Bacteria	Outcomes	Reference
Cathelicidin (LL-37)	Direct	Adipose tissue, Bone marrow	*Staphylococcus aureus* *Escherichia coli*, *Pseudomonas aeruginosa* *Staphylococcus pseudointermedius*	*Bacterial-membrane disruption increases. *Bacterial killing increases. *Cytokine levels decreases. *Endotoxin decreases.	(Johnson et al. 2017) (Krasnodembskaya et al. 2010) (Johnson et al. 2022)
β-Defensin 2	Direct	Umbilical cord	*Escherichia coli*, *Staphylococcus pseudointermedius*	*Pore formation of bacteria increases. *DNA, RNA and protein synthesis decreases.	(Sung et al. 2016) (Johnson et al. 2022)
Lipocalin 2	Direct	Peripheral blood, Bone marrow	*Escherichia coli*, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Staphylococcus pseudointermedius*	*Depriving bacteria of iron increases. *Bacterial growth decreases.	(Harman et al. 2017) (Dahl et al. 2018) (Gupta et al. 2012) (Johnson et al. 2022)
Hepcidin	Direct	Bone marrow	*Staphylococcus aureus*, *Escherichia coli*, *Staphylococcus pseudointermedius*	*Iron accessibility to bacteria decreases. *Bacterial growth decreases.	(Chow et al. 2019) (Johnson et al. 2022)
Surfactant Protein D	Direct	Adipose tissue	*Escherichia coli*, *Staphylococcus pseudointermedius*	*Bacterial-membrane disruption increases *Bacterial killing increases	(Johnson et al. 2022)
Inducible Nitric Oxide Synthases Pathway	Direct	Bone marrow	*Mycobacterium tuberculosis*	*Bacterial growth decreases. *NO Production increases.	(Yang et al. 2016)
Cysteine Proteases	Direct	Peripheral blood	Methicillin-Resistant *Staphylococcus aureus*,	*Degradation of extracellular proteins increases. *Penetration of antimicrobials in biofilms increases.	(Marx et al. 2020)
Indoleamine2,3 dioxygenase	Direct	Bone marrow	*Staphylococcus aureus*, *Staphylococcus epidermidis,* *Toxoplasma gondii*	*Tryptophan levels decreases. *Bacterial growth decreases.	(Meisel et al. 2011)
Phagocytic Activity	Indirect	Umbilical cord, Bone marrow	Septic mice/C57BL/6 Diabetic wound	*T cell proliferation decreases. *B-cell, Natural-Killer, and Dendritic cell proliferation decreases. *The functional phenotype of macrophage for anti-inflammatory roles (such as M2 phenotype and Tregs) increases.	(Song et al. 2017), (Liu et al. 2020)

immune system are multifaceted, and they can exert diverse effects depending on the context. Additionally, MSCs can induce immunomodulatory effects when Tregs interact with monocytes (Weiss and Dahlke 2019). This interaction with immune cells also contributes to the immunomodulatory activity when MSCs are involved (Zhou et al. 2019). Together with the adaptive and innate immunity, MSCs from adipose tissue were reported to convert inflammatory macrophages with an M1-like phenotype to an M2-like phenotype, and also prostaglandin E2 (PGE2) was found to induce this transition of macrophages (Manferdini et al. 2017). Due to the AMPs secreted by MSCs, they have the potential as a therapeutic tool in clearing bacterial infections and maintaining tissue homeostasis (Arabpour et al. 2021). MSCs have been explored for their ability to settle in appropriate tissues and to strengthen the immune cells by releasing pro-inflammatory factors. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin types (IL-2, IL-3, IL-6, IL-8, and IL-1β), contribute to tissue repair (Ding et al. 2011; English 2013). MSCs have the capability to impede lymphocyte proliferation the secretion of specific bioactive molecules. Among these soluble factors are hepatocyte growth factor (HGF), prostanglandin-E2 (PGE2), transforming growth factor (TGF)-1, indoleamine 2,3-dioxygenase (IDO), nitric oxide, and interleukin (IL)-10. These aforementioned factors possess the ability to attenuate or regulate specific immune responses, particularly those pathways associated with lymphocyte proliferation (DelaRosa and Lombardo 2010).

In conjunction with in vitro assays, many studies have revealed the prospective function of MSCs in restraining bacterial infections in vivo models (Park et al. 2019; Ren et al. 2020). They have also been presented to influence the immune system by releasing pro-inflammatory factors (Battah 2021). The behavior of MSCs indicates different immune regulations in inflammation that are either short-term or long-term (Gu et al. 2022). In acute infections, MSCs induce the regulation of the immune system through both pro-inflammatory and immunosuppressive regulatory directions (Kim and Cho 2016). The response of MSCs in acute inflammation can be expressed by Toll-like receptors (TLRs) (Bernardo and Fibbe 2013). MSCs have an active role in settling at the site of bacterial infection through recruiting TLRs, which are receptors that perceive pro-inflammatory cytokines, including interferons (e.g. INFα and INFδ) and IL1β (Waterman et al. 2010). TLR4 has the function of triggering the MSCs-1 phenotype to build up the immune cells by secreting chemokines (C-X-C motif) ligand (e.g., CXCL8 and CXCL10) and pro-inflammatory cytokines (e.g., IL-6). In contrast, activating TLR3 triggers MSCs-2 to induce immunosuppressive molecules such as PGE2, indicating their potential role in regulating the immune system (Terness et al. 2002). In acute infection, MSCs exert the pro-inflammatory effects mediated by TLR4, while TLR-3 regulates immunosuppressive effects. At this point, MSCs are able to transform M1 macrophages into the M2 type (Cho et al. 2014). In fact, TNF-α and the NF-kB signaling pathway are continuously activated in chronic infections. The activation of M1 macrophages continuously produces cytokines and leads to a disproportion of M1/M2 macrophages (Pajarinen et al. 2019). It has been found that MSCs contribute to a raise in the biosynthesis of the anti-inflammatory cytokine IL-10 in cases of life-threatening septic shock (Németh et al. 2009). Additionally to their immunomodulatory activities, MSCs have been shown to acquire anti-septic activity, and their ability to enhance the phagocytic activity of immune cells, including peripheral blood mononuclear cells (PBMCs), is mediated to ameliorate tissue injury (Krasnodembskaya et al. 2012). Chow et al. (2019) stated that the activation of phagocytic activity in a mouse model was due to the secretion of IL-6 by MSCs, which triggered the immune cells, particularly monocytes, and neutrophils. They also found an independent potential of MSCs for treating antimicrobial-resistant bacteria, particularly those that exhibit multi-resistance (Chow et al. 2019).

Bacterial pneumonia is a familiar infection that can persist over time. An in vivo study demonstrated the immunomodulatory properties of MSCs to combat acute bacterial pneumonia (Hackstein et al. 2015). It was found that MSC treatment not only decreased the intestinal lung injury caused by *K. pneumonia* but also increased survival rates for pneumonia. In another study, adipose-derived MSCs and their anti-inflammatory potential were evaluated to modulate the immune response and promote the body's defense mechanisms in treating *K. pneumonia*-induced pneumosepsis. The results demonstrated that MSCs were able to reduce lung inflammation in pneumosepsis supported by *K. pneumonia* when administrated intravenously to animal models (Perlee et al. 2019). Depending on a report by Li et al. (2020a), it was evaluated the therapeutic potential of adipose-derived MSCs in treating acute lung infections, including those caused by *P. aeruginosa*. MSCs treatment of infected mice resulted in the improved elimination of bacterial pathogens in the context of lung infections. The obtained results revealed that MSCs were responsible for the reduction in the nod-like receptor containing a caspase activating and recruitment domain 4 (NLRC4) inflammasome, which is a key inflammatory mediator, specifically through the mechanism of stimulated phagocytosis. An increase in the amount of stanniocalcin (STC-1) protein was also reported in the study when MSCs were administrated intravenously to the infected animals. The systemic administration of MSCs led to the inhibition of NLRC4 inflammasome activation, thereby reducing tissue damage in mice with lung infections (Li et al. 2020a). In an alternative study to verify the potency of MSCs against different MDR bacteria, such as *E. coli, P. aeruginosa, K. pneumonia* in chronic infections, it was demonstrated that MSCs were associated with an increase in the ability of antibiotics to kill bacteria. Additionally, the intravenous injection of MSCs improved antibiotic efficacy when combined with various groups of antibiotics, including penicillin, aminoglycosides, carbapenems, and fluoroquinolone, (Johnson et al. 2017).

Therapeutic potential of secretomes of MSCs against bacterial persisters

Due to the spread of bacterial persisters and the alarming concern regarding antibiotic resistance, research into new therapeutic agents continues rapidly today. MSCs have been investigated in past decades as a possible therapy for the remedy of a wide range of illnesses. MSCs possess the capability to manifest their antimicrobial effects through two principal modalities: direct and indirect mechanisms. The direct mechanisms encompass MSC-mediated bacterial eradication, achieved via phagocytosis, the production of antimicrobial peptides as well as theactivation of IDO and iNOS pathways. Conversely, the indirect mechanisms entail the ability of MSCs to promote the host's immune system, accomplished through direct cell-to-cell interactions and the release of paracrine factors (Russell et al. 2020). In recent times, stem cell-derived extracellular vesicles (SCEVs) have emerged as a favorable approach for the therapy of various diseases and injuries because of their unique properties. These include several beneficial effects, such as antimicrobial, anti-scarring, anti-apoptotic, wound healing, and tissue repair. SCEVs, which can be easily isolated, contain a range of bioactive molecules that can be transported to other cells to adjust immune response and encourage tissue regeneration (Ha et al. 2020; Raghav et al. 2021). Previous studies have reported that the administration of MSCs and their secreted extracellular components reinforce immune cells against bacterial infections (Li et al. 2020b). Indeed, the impact of direct cell-to-cell interaction is indisputable. However, of particular significance for prospective clinical and commercial deliberations is the validation that the bioactive agents secreted by MSCs can be cryopreserved, concentrated, and lyophilized to facilitate cost-effective, extended-term storage while retaining their antimicrobial efficacy (Russell et al. 2020). The fractionation of this secretome of MSCs further holds promise as a critical procedure to enhance potency or selectively target specific bacterial persisters. As demonstrated in an in vivo study with *Haemophilus influenzae* infections in a C57BL/6 model, the mice's immune system showed a significant effect due to the increased activity of alveolar macrophages in destroying bacterial infections (Li et al. 2020b). The impact of adipose-derived MSCs against different bacteria strains, including *Salmonella typhimurium* and *Lactobacillus acidophilus*, on the intestinal system, was investigated. The authors found that MSCs increased the upregulation of ILs (e.g., IL-6 and IL-8) and cyclooxygenase 2(COX-2), potentially by modulating these immunomodulatory genes to promote tissue repair. Additionally, it was shown that when MSCs were introduced to *S. typhimurium*, they enhanced their ability to re-enforce the modulation of T-cell activity through the production of PGE2 (Kol et al. 2014). An alternative study on the pro-inflammatory role of MSCs revealed that a high dose of MSC derived from adipose tissue led to an inhibition of bacterial load and downregulation of PGE2 in chronic lung injury induced by *P. aeruginosa* (Mao et al. 2015). It was found that the downregulation of PGE2 resulted in an improved immune response and a higher bactericidal effect during mucosal bacterial infection (Agard et al. 2013). Evidence suggests that MSCs can induce polymorphonuclear (PMN) cells and also be involved in activating certain immune cells, such as neutrophils, through the secretion of cytokines including IL-6 and IL-8, which may contribute to their recruitment (Brandau et al. 2014). Aggarwal and Pittenger (2005) observed that MSCs can reinforce the function of immune cells involved in the adaptive immune response, including T lymphocytes and dendritic cells (DCs). In this context, MSCs have been informed to reinforce the function of Tregs, allowing them to more effectively suppress immune responses and maintain immune tolerance (Aggarwal and Pittenger 2005; Jiang et al. 2005). Some studies indicate that MSCs and their secretomes can enhance the immune response against bacterial infections by modulating the capability of immune cells, including neutrophils, through increasing phagocytic activity and preventing apoptotic activity (Harrell et al. 2019; Qian et al. 2021). An in vivo study assessing the administration of exosomes containing miR-146a from MSCs demonstrated that they polarized macrophages toward the M2 phenotype, which eventually led to an increase in the viability of the mouse model. This study showed evidence for the potential therapeutic use of exosomes containing miRNAs in response to sepsis (Song et al. 2017).

Overall, multiple studies have reported on the antimicrobial efficacy of MSCs and their secretomes. However, the potential of MSCs and their secretomes against persister bacterial strains remains underexplored. There is some evidence to present MSCs and their antimicrobial effect on chronic infections related to biofilm formation. Biofilms cannot be treated with antibiotics, and thus the presence of persister bacteria, including biofilms, is associated with antibiotic resistance. It has been stated that MSCs' secretomes have fighting potential against gastrointestinal bacterial pathogens such as *Vibrio cholerae*. It was found that MSC-derived secretomes inhibited bacterial growth and biofilm formation, especially those that are effective against multi-resistant strains (Bahroudi et al. 2020). An in vivo study in rabbit models with chronic inflammation demonstrated a significant reduction in TNF-α expression when treated with MSCs from Wharton's Jelly (WJ-MSCs), and this is attributed to the improved secretion of oviduct glycoprotein in animals suffering from chronic salpingitis (Li et al. 2017). In another study by Liao et al. (2019), MSCs obtained from the umbilical cord (hUC-MSCs) were depicted to have a positive effect on reproductive health by protecting cells from apoptosis, which reduces the expression level of caspase-3. The authors also reported that hUC-MSCs have the potential to alleviate the level of inflammatory cytokines, such as IL-10, in the oviduct, which is likely based on the anti-inflammatory properties observed in animals treated with hUC-MSCs (Liao et al. 2019). Ebrahim et al. (2018) suggested a notable decrease in intrauterine adhesions in female rats when treated with hUC-MSC and their secreted exosomes, combined with/without estrogen. The treatment with hUC-MSC and their secretomes led to a decline in the expression of inflammatory cytokines as well as fibrotic markers (Ebrahim et al. 2018). Marx et al. (2020) also administered a study to investigate the effect of MSC secretomes on treating bacterial skin infections. They found that MSC-secreted factors resulted in a significant reduction of bacterial survival, particularly in antimicrobial-resistant bacteria, including MRSA. This effect was especially prominent in disrupting biofilm formation (Marx et al. 2020). These studies indicate interesting insights into the potential

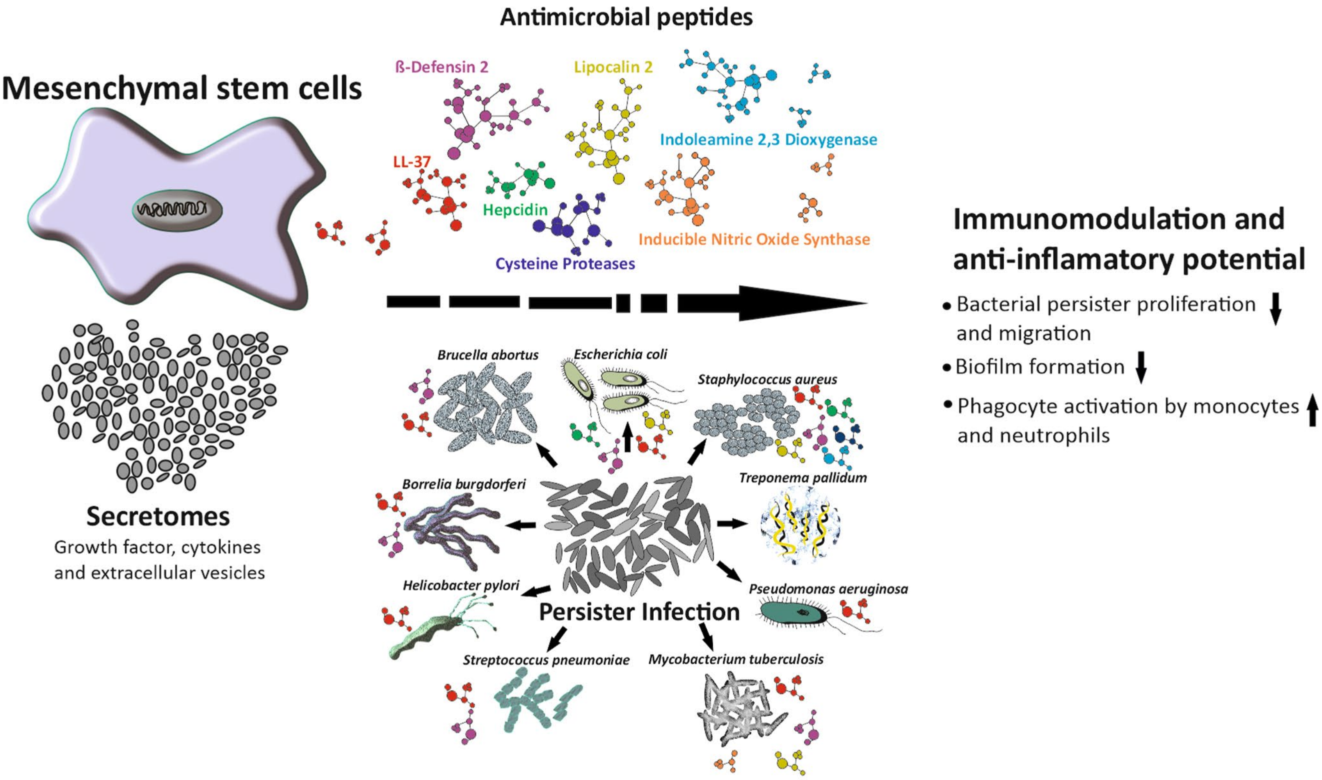


Fig. 2 The figure depicts the ability of MSCs and their secretomes through secreting different AMPs against bacterial persister infections. The regulation of the expression of AMPs is based on different mechanisms: (i) inhibition of bacterial persister proliferation and migration, (ii) prevention of biofilm formation, and (iii) activation of phagocytosis by stimulating monocytes and neutrophils

therapeutic approaches of MSCs and their secreted extracellular components, making them a novel and promising therapy to reinforce the immune cells against bacterial persisters.

Concluding remarks

MSCs and their secreted extracellular components have been considered and studied for their immunomodulation and anti-inflammatory potential on different immune cells to combat various bacterial infections. MSCs and their secretomes can be promising agents that modulate the immune response by utilizing different mechanisms. One of these mechanisms is to encourage biofilm disruption; the second is to secrete a variety of AMPs, and the last is to enhance the phagocyte activation by macrophages and neutrophils (Fig. 2). The curative potential of MSCs and their secretomes lies in their capability to treat inflammatory and microbial diseases. Therefore, MSCs and their secretomes could be attractive candidates for therapy against chronic and untreatable resistant infections. Compared to stem cell-based therapy, priority has been given to MSC-secretomes due to their better safety profile. They can also activate phagocytes, which are immune cells that inhibit bacterial growth, improving their survival and protecting them against bacterial infections. Moreover, MSC and their secretomes could be crucial in regulating the immune response, polarizing macrophages toward the M2 phenotype. Finally, MSC-secreted extracellular components make them promising agents for the development of cutting-edge therapies for bacterial persisters.

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Declarations

Ethics approval We confirm that this work is original, has not been published elsewhere, and is not currently under consideration for publication elsewhere.

Consent to participate Not applicable.

Consent to publish Not applicable.

Conflict of interest We have no competing interests with regard of this work.

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