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Mesenchymal Stem Cells: Potential Role against Bacterial Infection

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Abstract

The worldwide spread of bacterial resistance makes finding new therapeutics to overcome this ongoing problem an urgent need. Mesenchymal stem cells (MSCs) exert potential inhibiting activity against bacterial infections. The antimicrobial activity of MSCs relies on direct and indirect effects by secreting paracrine factors with potential inhibiting activity against bacterial growth or stimulating the phagocytic activity of the immune cells. These effects appeared when MSCs or its secreted factors are administrated therapeutically. Therefore, MSCs based cell therapy could be considered as a novel promising strategy to enhance the antibiotic activity in multidrug resistant (MDR) infections.

Keywords

Mesenchymal Stem Cells, Bacterial Infection, Antibiotic Resistance

1. Introduction

Mesenchymal stem cells (MSCs) are multipotent stromal cells initially found in bone marrow but can be also present in many other tissues. MSCs characterized by their differentiation ability producing different cell types, ease of isolation and intrinsic tropism toward injured area. They can also activate other stem cells and stimulate neoangiogenesis [1] [2]. They have been largely used for multiple clinical applications including autoimmune disease, bone diseases, skin burns, myocardial infarction and severe chronic wounds [3].

MSCs have a potential tendency to migrate to the site of infection and exert immunosuppressive and anti-inflammatory properties. MSCs can be introduced systemically or by local injection. The systemic delivery of MSCs can be performed by intravenous (IV) or intraarterial (IA) administration. The optimum

method of administration depends on the therapeutic purpose of using MSCs and their mechanism of action [4]. When MSCs were administrated by intraperitoneal injection, the cells were migrated to the inflamed colon [5] and when MSCs injected near the ischemia site in the brain, the cells migrated to the ischemic lesions [6]. On the other hand, intravascular and intraarterial injections are less invasive methods and allow for a wide distribution of the cells through the body. Although, when the MSCs were administrated by intraarterial injection the cells were more distributed throughout the animal body in comparison with intravenous injection [7]. The non-target organs MSCs engraftment may have some adverse effects in the lungs, but in the liver and the spleen, CD3 lymphocytes were upregulated when the MSCs were administrated intravenously. For this reason, the intravenous systemic administration of the MSCs demonstrated clinical efficacy in different clinical studies [8]. Many methods are being developed to increase MSCs efficacy to target organs and tissue by genetic modifications or coating cell surface with specific antibodies or peptides to specifically deliver the cell based therapy [9]. These exceptional characteristics make MSCs an appropriate approach and useful therapeutic strategy in different disorders. Therefore, MSCs are widely studied for their therapeutic application and considered as an immunomodulatory agent in the regenerative medicine [10] [11]. The rapid global spread and increasing incidence of drug resistant and multi-drug resistant bacterial infection with few therapeutic options make finding new alternative therapeutics an essential need to confront this emerging problem. The overuse and inappropriate use of antibiotics contribute to the continuous spread of bacterial resistance which become a global threat [12]. Different studies proposed MSCs to be used as an alternative to the ineffective antibiotics or in combination with antibiotics recently being used to increase their sensitivity against infections [13]. Chronic bacterial infections are major cause of mortality and are difficult to be cured without extended course of antibiotic treatment [14]. Also, these chronic resistant infections are often characterized by biofilm formation and generate a structure like a niche that provide bacterial persistence, and evasion of bacteria from the immune defence mechanisms. For example, Methicillin resistant *staphylococcus aureus* uses these biofilms as a shield against antibiotics being used [15]. Furthermore, it was found that *Mycobacterium tuberculosis*, the causing agent of tuberculosis which is the oldest known infectious disease in human, use MSCs for their long term survival in a dormant resistant state [16]. Recently, new studies have demonstrated the antibacterial activity of the MSCs and considered MSCs as an important player in immune regulation and confirmed the potency of MSCs to ameliorate outcomes of patients with severe infection [17]. The inhibiting activity of MSCs against bacterial infection can be direct and indirect effect, although the different mechanisms behind this effect have not been fully understood and there is a need for more studies to elucidate MSCs therapeutic properties. This review highlights the MSCs therapeutic applications in various bacterial infections and exhibits different mechanisms of this action.

2. Immunomodulation by Mesenchymal Stem Cells

MSCs have been shown to influence the immune system by secreting soluble factors including indoleamine 2,3-deoxygenase (DOI), nitric oxide (NO), transforming growth factor beta (TGFß) and prostaglandin E2 (PGE2) [9]. The response of MSCs to the microenvironment during inflammation and injury can be differentially regulated through Toll-like receptors (TLRs) [18]. Activation of TLRs by signals released from injured tissues triggers systemic cellular adaptive and innate immune response. MSCs can be migrated to the site of injury in the same way through activation of TLRs 3 and TLRs 4 which are predominantly expressed in MSCs. Activation of MSCs promotes its polarization to a pro-inflammatory MSCs 1 or an immunosupressive MSCs 2 phenotype [19]. MSCs use TLRs as a sensor damage which sense to the pro-inflammatory cytokines through INFα, INFδ and IL 1ß. In response, MSCs secret different cytokines for activation or suppression in order to maintain the immune system in balance [19]. Activation of TLR4 trigger MSCs 1 phenotype which recruit and activate the immune cells by producing higher amount of IL 6, CXCL8, CXCL10, while stimulating TLR3 triggers MSCs 2 immunosuppressive state by producing immunosuppressive molecules like prostaglandin E2 (PGE2) which have suppressor activity for granulocytes and natural killer (NK) T-cells. Also, MSCs 2 produced indoleamine 2,3-deoxygenase (IDO) which is an enzyme involved in tryptophan catabolism and inhibits T-cell proliferation [20]. MSCs use these different immunomodulations to regulate both innate and adaptive immunity. It was shown that MSCs by secreting IL-6, INFß and macrophage—colony stimulating factor (GM-CSF), enhance neutrophil phagocytic activity where IL6 promotes neutrophil survival through activation of (STAT-3) pathway [21] [22]. In addition, the cleavage products of complement system which is another component of the innate immunity (C3a and C5a) promote MSCs migration to the site of infection and increase MSCs resistance against oxidative stress and apoptosis [23]. Furthermore, MSCs can inhibit allergic response and chronic inflammation through suppressing mast cells activation. It was demonstrated that MSCs conditioned media indirectly reduce IgE production and histamine release via upregulation of cyclooxygenase 2 (COX2) and PGE2 production [24]. When MSCs contact directly the mast cells, suppress its degranulation and proinflammatory cytokines production and these effect results from PGE2 binding on the prostaglandin E2 receptor (EP4) which is present on the surface of the mast cells. Thus, as a result MSCs lead to mast cell suppression [25]. Undifferentiated MSCs don't express class II major histocompatibility complex (MHC) and low levels of class I MHC and both types of MSCs differentiated and undifferentiated don't trigger T-cells response to the MHC complexes which make MSCs tolerated between HLA incompatibles [26]. NK have an important role in viral infection clearance and stressed cells elimination. MSCs interfere with natural killer (NK) T-cells proliferation and cytotoxicity by suppressing IL2, IL15 and INFδ production [27]. In contrast, MSCs can enhance NK cells proliferation when available in a low ratio to NK [28].

Another type of the lymphocyte which can be activated by MSCs is regulatory B-cells through IL10 which promote regulatorty B-Cells production. MSCs express inducible nitric oxide synthase (iNOS) which generate nitric oxide (NO) by metabolizing L-arginine. NO have inhibitory effects on IL2 pathway and also inhibits T-cell proliferation and major histocompatibility complex II (MHCII) expression [28]. MSCs can modulate helper T cells and promote the immunosuppressive effect by inhibiting Th1 pro-inflammatory cytokines (INFδ, TNFα and IL1ß) and secreting IL10 [28]. Dendritic cells (DCs) play an important role to link between innate and adaptive immunity and presenting antigen to T-cells and interacting with B-cells and NK [29] [30]. MSCs inhibit DCs antigen presenting ability. Therefore, indirectly suppress T-cell activation and stimulate T-cell proliferation [31]. Although the interaction between MSCs with different immune cells (T-lymphocyte, B-lymphocyte, NK and DCs) considered as an important modulatory pathway for MSCs to alter the microenvironment, but macrophages remain the major type of immune cells which MSCs depend on to exert their therapeutic activity [32].

3. Modulation of Macrophages by Mesenchymal Stem Cells

Monocyte modulation is a critical step in the MSCs immunomodulation. Monocytes represent 10% of the total circulating leukocyte characterized by CD14 and CD16 expression [33]. It was determined that after microbial infection bone marrow MSCs trigger movement of monocyte and macrophages from the bone marrow to the site of infection through production of different chemokines (CCL2, CCL3 and CCL12) [34]. Monocyte expressing CD14 respond to the hepatocyte growth factor (HGF) secreted by MSCs and rapidly spread to the circulation before differentiation to macrophages [35]. Macrophages are characterized by two different phenotypes, the M1 pro-inflammatory macrophages and M2 anti inflammatory macrophages. It was found that MSCs under inflammatory modulators (TNFα, INFδ and LPS) stimulate switching of macrophages from M1 pro-inflammatory phenotype to M2 anti inflammatory phenotype through secretion of IDO and PGE2 [36] [37]. This correlates with high level expression of (IL10 and IL6) and with low level of (IL12 and TNFα) and functionally higher phagocytic activity [23]. Secretion of IL10 from anti inflammatory phenotype macrophages inhibits neutrophils migration into inflamed tissue but recruit more neutrophils in the blood which play an important role in bacterial clearance [38]. It has been demonstrated that MSCs when present in contact with gram negative and gram positive bacteria promote the pro-inflammatory phenotype which increase neutrophils migration and activation to the site of infection with increase phagocytic ability by secreting different immunomodulators (IL6, IL8, INFß and GM-CSF), where MSCs promote M1 macrophages phenotype by secreting GM-CSF and enhance bacterial clearance [23]. A study conducted *in vivo* in a mouse model, showed that the bacterial clearance of *Pseudomonas aeroginosa* from infected mice was related to the enhancement of

pohagocytic activity of the peripheral blood mononuclear cells after intravenous administration of MSCs. The study showed increase in the percentage of phagocytosis in the mononuclear cells isolated from the mice treated with MSCs in comparison with the control group [39]. It was reported that coculturing of macrophages with MSCs *in vitro* promoting macrophages M2 phenotype with greater anti-inflammatory ability and with more potent phagocytic activity. It was also observed and increased expression of surface biomarkers CD163 and CD 206 which indicate alternative macrophages activation and defined the MSCs-educated macrophages with different cytokines expression (IL-10 high, IL-12 low, IL-6 high and TNF-α low) [32]. MSCs can activate monocyte phagocytosis by another different mechanism. Interestingly, it was also found that the complement proteins could be modulated by MSCs effects. The plasma levels of C5a which is a complement fragment were higher in MSCs treated mice than control group. The MSCs administration was associated with 15% upregulation of the C5a plasma levels. C5a plays an important role in increasing the expression of the phagocytosis receptors Cb11 in peripheral blood monocytes. The results of this study showed an increase in the expression level of the Cb11 receptor on the surface of monocyte in the MSCs treated group with respect to control group [40]. Hence, phagocytosis activation considered as the main indirect functional mechanism that MSCs recruit when responding to various bacterial infection.

4. Mesenchymal Stem Cells as an Alternative Strategy to Combat Bacterial Infection

The common mechanism of pathogenesis of bacterial infection includes adherence to the host cells, entry, toxins secretion and inhibition of the host immune response mechanisms [41]. The inappropriate use of antimicrobial agents and lack of specific microorganism identification considered as the main reasons behind emerging of bacterial resistance. Despite all efforts, the bacterial resistance is still a main threat in public health and there is an urgent need to control this diffusing problem by finding new alternative therapeutic strategies rather than combining more than one antibiotics in serious resistant infection [12]. Hence, it is essential to find alternative non-antibiotic strategies to fight infectious pathogens [42]. Recently, different alternative strategies to eridictae bacterial infection were proposed to be used like probiotic therapy, bacteriophage viral therapy, genetic therapy and stem cells like a cell based therapy [42]. It was established that MSCs produce antimicrobial factors that eliminate bacteria from the site of infection through different mechanism including bacterial cell wall synthesis [43]. Several studies have demonstrated the potential role of the MSCs stem cells to control bacterial infection *in vivo* and in *ex vivo* models [44]. The anti bacterial activity of the MSCs stem cells derived from its immunomodulatory effects by secreting immunomodulations like transforming growth factor (TGF-ß), tumour necrosis factor-α (TNF-α), prostaglandin E2 and antimicrobial peptides like LL-37 by direct cell contact dependant or independent mechanisms [45]

[46]. In addition, several studies showed the ability of MSCs to control bacterial infection and life threatening septic shock by increasing production of the anti inflammatory cytokines IL-10 [47] [48] and secretion of anti microbial peptides (human cathelicidin, LL37 and lipocalin-2) [39] [49]. The anti septic activity of MSCs could be also relevant to its ability to increase phagocytosis in peripheral blood mononuclear cells (PBMCs) [50]. Chronic bacterial infection and drug resistant bacterial infection need a long term course of antibiotic therapy. Therefore, a lot of studies focused on the novel role of MSCs and its secreted peptides to control such infections alone or in combination with other antibiotics to increase its effectiveness in bacterial killing. It was reported that MSCs stem cells collected medium indirectly inhibited the methicillin resistant *staphylococcus aureus* and confirmed that these effect related to antimicrobial peptides secreted by these cells (cathelicidin LL-37, beta defensin (hBD2), hepcidin, surfactant protein D (SPD), and lipocalin) [51] [52]. Furthermore, it is well known that biofilm formation could be one of the antibiotic resistance mechanisms created by different bacterial strains like methicillin resistant *Staphylococcus aureus* and *Eschcerichia coli* which can affect macrophages polarization and inhibit bacterial phagocytosis within biofilm [53]. It was reported that MSCs stem cells secret factors reduce methicillin resistant *Staphylococcus aureus* biofilm formation and enhance bacterial clearance *in vivo* [54]. Multidrug resistant (MDR) *Vibrio cholerae* strains are diffused in developing country and using MSCs was suggested as an alternative antibacaterial agent. Moreover, using of chitosan nanoparticle combined with Mesenchymal stem cells conditioned media was proposed to be an alternative nanodrug against MDR *vibrio cholerae* and showed an anti biofilm activity [55]. In another study regarding the role of bone marrow MSCs, the synovial fluid was used to mimic the joint infection environment. This study showed that bone marrow derived MSCs were able to inhibit bacterial growth of *Staphylococcus aureus* when the bacteria were added to the synovial fluid in an *in vitro* assay [52]. Another study has verified the effect of MSCs soluble products from different origins like bone marrow or adipose tissue in cystic fibrosis infection. The study demonstrated that MSCs soluble product was able to decrease *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pneumonia* colony forming units (CFUs) *in vivo* mice model. Furthermore, this activity has increased the antibiotic susceptibility used in treating this infection [56]. Bacterial pneumonia infection is a common cause of death worldwide. A study conducted *in vivo* demonstrated that the administration of intra-tracheal MSCs improved lung injury and increased the bacterial elimination in C57BL/6 mice with *Escherichia coli* pneumonia and bacterial elimination effect was due to increased production of lipocalin 2 from MSCs [49]. In another study the immunomodulatory effect of MSCs was also demonstrated *in vivo* where was used a mouse model of acute bacterial pneumonia. The results obtained showed that MSCs increased survival and decreased lung injury and alveolitis caused by *Klebsiella pneumonia* [57]. *Klebsiella pneumonia* are a magior cause of sepsis and

pneumonia, another study were developed to evalute the effect of adipose-derived MSCs on the host respons to improve host defense against *Klebsiella pneumonia* in pneumosepsis. Depending on this study, it was found that when MSCs when adminstrated intravenoulsy to the infected Mice, MSCs were able to decrease *Klebsiella pneumonia* growth in the lung and its dissemination in the late phase of infection with a reduction of lung inflammation. It was also observed that the MSCs reduced the pro-inflammatory cytokines in the lung and improved the lung pathology [58]. Another study was performed to verify the effect of adipose-derived MSCs on the lung infection induced by *Pseudomonas aerugenosa*, treating infected mice with MSCs reduced bacterial load and tissue lung inflammation, the observed results showed that MSCs stimulated the phagocytosis by reducing expression of nod like receptor containing a caspase activating and recruitment domain 4 (NLRC4) inflammasome which is activated after infection, the obtained results suggested that the increasing production of stanniocalcin (STC-1) from MSCs is responsible for inhibitory effect of the MSCs on NLRC4 inflammasome activation [59]. Furthermore, the results obtained from a study conducted *in vivo* to verify the effects of MSCs in chronic infection, showed that systemic administration of activated MSCs exhibited elimination of different MDR bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*). Also, the combination of MSCs with different classes of antibiotics like penicillin, aminoglycosides, carbapenems and fluoroquinolone increased the susceptibility of the bacteria to antibiotic killing [14]. The other mechanisms behind this effect could be explained by the ability of MSCs to trigger the phagocytic activity of the immune cells like monocytes and neutrophills [51]. In addition, the function of the MSCs could be carried out by generating extracellular vesicles (EVs) filled with biological modulators (transcription factors, cytokines, growth factors and miRNA) regulate migration and activation of the immune cells [60]. Opportunistic infection are very common in patients who receive immunosuppressant and considered as a major cause of death in patients who receive immunosuppressive therapy as a treatment of autoimmune disease like systemic lupus erythematosus (SLE), systemic sclerosis, rheumatoid arthritis and autoimmune vasculitis [61]. It is well known that the immune cells wich are rapidly proliferating cells are more susceptible to immunosupressive therapy [62]. As a result, the probability of patients to develop infectious disease may increase [63]. In a study conducted in C57BL/6 mice was demonstrated that MSCs increase number and phagocytic activity of alveolar macrophages in the lung after infection with *Haemophilus influenzae* which are frequently isolated from patients who received immunosuppressive therapy. The results showed a significant protection against bacterial infection after MSCs infusion [64].

5. Mesenchymal Stem Cells and *Mycobacterium tuberculosis*

Tuberculosis remains a major infectious disease worldwide with more than an-

nually million deaths in the world. *Mycobacterium tuberculosis* (*Mtb*) is still an important human pthogen despite effective drugs available against this pathogen. Emerging of *Mtb* drug resistance increases the global threat of tuberculosis. *Mtb* resistant strains against isoniazid and rifampicin are the main cause of MDR tuberculosis. While, *Mtb* resistant strains against more drugs like any fluoroquinolone and the second line anti TB drugs like kanamycin and amikacin considered as extensively drug resistant tuberculosis (XDR) [65] [66]. The tuberculosis patient should be treated for long time 6 - 9 months with more than one antibiotics. In addition, emerging of MDR tuberculosis makes the treatment complicated and cost. Therefore, finding a new therapeutics against resistant tuberculosis with lower toxicity and shorter duration of treatment is fundamental and costly effective [66]. Tuberculosis stimulates a strong inflammatory response which is responsible for consequent formation of an organized cellular aggregation surrounding the mycobacterial cells called granuloma [67]. Several studies have found that in addition to the variety of the immune cells that generate granuloma, like macrophages forming foaming cells and migrated lymphocytes which subsequently arrive at the site of infection, bone marrow derived MSCs stem cells surround the external part of the granulomas provide a favourable niche contains persistent mycobacteria and hold the infection in balance [68] [69]. *Mtb* uses these cells for its survival and to be hidden from the response of the immune system, while the mechanism by which the MSCs manipulate the infection is still completely undiscovered [70]. It is not clear if MSCs modulate the *Mtb* infection or if the mycobacteria use this cell as a favourable place to evade immunity. Also, it was found that MSCs exhibit direct and indirect anti bacterial activity either by modulating the anti-inflammatory and pro-inflammatory response or directly by secreting anti microbial peptides and cytokines like IL-17 [43]. The capacity of the MSCs to exhibits immune-suppressive activity by producing nitric oxide (NO) requires a physical contact with T cells [68]. In contrast, it was found that MSCs play an essential role in monocyte differentiation to macrophages and increase the bactericidal activity of the macrophages by increasing the respiratory burst of the infected macrophages [71]. The presence of MSCs inside *Mtb* containing granuloma makes these cells able to play an important role in *Mtb* phagocytosis. It was reported that there is no *Mtb* replication within MSCs after phagocytosis and it was also found that MSCs express a few scavenger receptors (SRs) and endocytose lipids [70]. It is well known that SRs bind mycobacterial lipids and glycoproteins. After phagocytosis of the mycobacteria by macrophages, the phagolysosomal fusion kill *Mtb*. In addition, reactive oxygen species (ROS) and nitric oxide which secreted by macrophages in response to the infection also kill *Mtb*, while inside MSCs *Mtb* remain in a non replicative state which suggest other mechanism probably regulate the *Mtb* presence inside these cells [72]. It seems that MSCs facilitate mycobacterial entry during phagocytosis through SRs on the surface of MSCs which play an important role in lipid and mycobacterial uptake [73]. The foaming macrophages inside granulomas are rich in lipid bodies which help the *Mtb* to persist inside the granulomatous niche [74]. In contrast, it was found

that MSCs secret NO after *Mtb* infection more than THP1 human macrophages. Thus, it was hypothesized that MSCs use SRs to capture lipid and mycobacteria, but inhibit *Mtb* growth through NO-mediated mechanisms [70]. Recently, a phase 1 clinical trials have shown a clinical improvement in MDR tuberculosis and XDR tuberculosis patients after infusions of MSCs when administrated with standard drug regimes. These trials considered MSCs as a safe adjunct therapy in MDR/XDR tuberculosis [75]. Furthermore, MSCs can restore lung epithelium and increase proliferation of broncho-alveolar stem cells [65]. For this reason, the administration of MSCs or its secreted extracellular components could be functional to reinforce the immune cell against the *Mtb* and open new avenue for advanced tuberculosis treatment and other bacterial infections in antibacterial resistant patients.

6. Application of MSCs Treatment against Other Types of Microbial Infections

Different studies were demonstrated that in addition to the antibacterial properties of the MSCs, these stem cells are typically more resistant to viral infection than differentiated cells and may also have a potential antiviral activity. MSCs exert anti viral properties via different mechanisms including blocking of viral entery, viral mRNA reverse transcription, viral genom integration and amplification into the host DNA, viral protein translation and viral assembly [76]. These effect related to INF-stimulated genes (ISG) which are expressend by MSCs and target many steps during viral cycle [76]. IDO is one of the anti viral ISGs that are overexpressed by MSCs as a fundamental antiviral molecule by limiting viral protein biosynthesis. It was found that IDO can inhibit HIV-1 replication [77]. Moreover, EVs derived from MSCs Carry some miRNA that have antiviral activity like miRNA-145 and miRNA-221 which have been demonstrated to have anti HCV properties [78]. The anti viral activity of MSCs derived EVs was also demonstrated against influenza virus in a pig model where intratracheal administration of MSCs derived EVs reduced viral replication in the lung and reduced the pro-inflammatory cytokines production in the lung of infected pigs [79]. Lung is the first line barrier against respiratory pathogens [80]. It is well known that MSCs promote Microvascular remodeling and tissue repair in the lung by modulating the inflammatory mediators [81]. Therefore, using of immunomodulators is of critical importance for treatment and prevention of cytokines storm triggered by respiratory tract viral infection like coronavirus disease 2019 (COVID-19), the leading cause of morbidity and mortality during the recently diffused pandemic worldwide [82]. The anti inflammatory and immunomodulatory ability of the MSCs could play an important role in preventing or attenuating of cytokines storms caused by COVID-19 and could be the main mechanism of MSCs in treating COVID-19 [83]. In a study conducted on patients with COVID-19 pneumonia aimed to evaluate the efficacy of MSCs transplantation, MSCs were administrated to COVID-19 hospitalized patients and after 14 days from MSCs infusion, the magority of patients showed improvement in the clinical response and immunological profile with negative PCR test results, this study

suggested MSCs as a safe and effective strategy to treat severe COVID-19 condition [84]. Another study was developed on 54 years old patient, positive for COVID-19 suffered from pneumonia. A few days after MSCs infusion the patient showed improvement in some clinical symptoms like fever and shortness of breath, increasing in $CD4^+$ and $CD8^+$ T-cells and decreasing in the C-reactive protein serum levels. Six days later the patients became negative for COVID-19 [85]. Furthermore, MSCs have improved other infection complications like fungal Kiratitis and exhibited improvement in corneal opacity with anti inflammatory effects [86]. It was found that humman cathlecidin LL-37 which is well known immunomodulators produced by MSCs with antibacterial activity have also anti fungal activity against *Candida albicans* [87]. Moreover, it was also demonstrated that IL17 MSCs possessed anti *Candida albicnan* effect and when co-cultured with *candida albicans* inhibited its growth with respect to the control medium [88]. It was also obserevd that MSCs can phagocyte *Aspergillus fumigatus* without altering the level of pro-inflammatory cytokines [89]. Therefore, MSCs based cell therapy considered as a safe and effective intervention in the treatment of different kinds of infections.

7. Concluding Remarks

MSCs have been studied and trialed for their immunomodulatory effect on different immune cells, and appeared to have a different therapeutic role with increasing evidence to control various microbial infections. MSCs exert their antibacterial activity through different mechanisms including phagocyte activation, inhibition of biofilm formation, antimicrobial peptides secretion and further

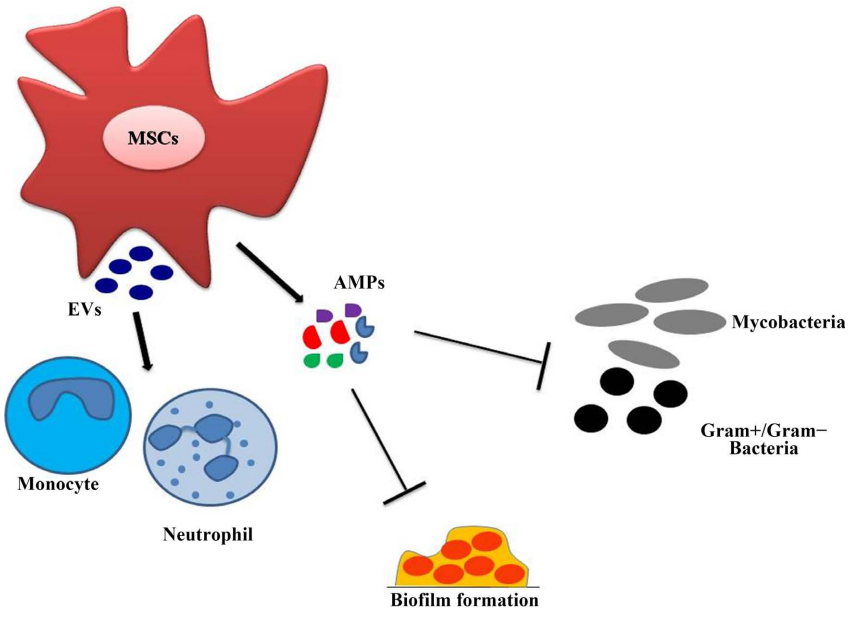

Figure 1. The figure summarizes the potential roles of the antimicrobial peptides (AMPs) and extracellular vesicles (EVs) produced by mesenchymal stem cells (MSCs) against bacterial infection. The antimicrobial effect of MSCs is postulated to be via different mechanisms: 1) inhibiting bacterial proliferation (mycobacteria and Gram −/+ bacteria); 2) inhibiting biofilm formation; 3) activating of monocytes and neutrophils phagocytosis.

changing the microenvironment at the site of infection (Figure 1). Hence, MSCs are considered to be used as novel therapeutic strategies to control chronic and untreatable resistant infectious disease. This potential ability is due to production of several paracrine factors and extracellular vesicles budding from these cells. Finally, this approach could be considered as an alternative or supportive strategy to better control multidrug resistant (MDR) bacterial infections.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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