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MINI REVIEW

Exploring therapeutic avenues: mesenchymal stem/stromal cells and exosomes in confronting enigmatic biofilm-producing fungi

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Abstract

Fungal infections concomitant with biofilms can demonstrate an elevated capacity to withstand substantially higher concentrations of antifungal agents, contrasted with infectious diseases caused by planktonic cells. This inherent resilience intrinsic to biofilm-associated infections engenders a formidable impediment to effective therapeutic interventions. The different mechanisms that are associated with the intrinsic resistance of *Candida* species encompass drug sequestration by the matrix, drug efflux pumps, stress response cell density, and the presence of persister cells. These persisters, a subset of fungi capable of surviving hostile conditions, pose a remarkable challenge in clinical settings in virtue of their resistance to conventional antifungal therapies. Hence, an exigent imperative has arisen for the development of novel antifungal therapeutics with specific targeting capabilities focused on these pathogenic persisters. On a global scale, fungal persistence and their resistance within biofilms generate an urgent clinical need for investigating recently introduced therapeutic strategies. This review delves into the unique characteristics of Mesenchymal stem/stromal cells (MSCs) and their secreted exosomes, which notably exhibit immunomodulatory and regenerative properties. By comprehensively assessing the current literature and ongoing research in this field, this review sheds light on the plausible mechanisms by which MSCs and their exosomes can be harnessed to selectively target fungal persisters. Additionally, prospective approaches in the use of cell-based therapeutic modalities are examined, emphasizing the importance of further research to overcome the enigmatic fungal persistence.

Keywords Fungal persisters · Mesenchymal stem · Stromal cells · Exosomes · Immune-stimulatory agents · Antifungal peptides

Introduction

The prevalence of fungal infections induced by pathogenic fungi has experienced a significant increase globally, resulting in a considerable number of annual deaths (Bongomin et al. 2017; Rokas 2022). Overcoming these infections has become progressively more challenging due to the high occurrence of immunogenic diseases, malnutrition, and aging (Garcia-Cuesta et al. 2014). In recent times, the increasing number of immunocompromised individuals, coupled with the extensive utilization of medical devices and immunosuppressive drugs, has contributed to a surge in cases of invasive fungal infections (Rokas 2022). The economic impact of fungal diseases is a matter of concern, with the United States expending approximately $11.5 billion in 2019 to address serious fungal diseases, encompassing direct medical costs and productivity losses attributed to premature deaths (Benedict et al. 2022). Among the various fungal pathogens, *Candida albicans* stands out as the most prevalent agent responsible for causing persistent infections (Hawser et al. 1998). Nevertheless, there has been a concerning uptrend in the occurrence of infections instigated by alternative *Candida* species, including *Candida auris, Candida parapsilosis*, *Candida glabrata, Candida tropicalis,* and notably *Candida krusei* in case of invasive persister infections (Hawser and Douglas 1994; Chandra and Mukherjee 2015). In an effort to address the urgency of combating fungal contagion, the World Health Organization (WHO) introduced a catalogue of prioritized fungal pathogens on 25 October, 2022 (Parums 2022). This catalogue, termed "the critical priority group" by the WHO, includes *Candida*

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albicans, Candida glabrata, Aspergillus fumigatus, Candida auris and *Cryptococcus neoformans*. Notably, scholarly outputs concerning *Candida* species, particularly *Candida auris*, have shown a progressive increase, as evident from PubMed searches conducted between 2018 and 2023.

Treatment options available for managing invasive fungal infections are restricted in scope. Despite developments in antifungal pharmaceutical agents, mortality percentages pertaining to disseminated candidiasis remain elevated, particularly among immunocompromised patients (Rex et al. 1994; Scriven et al. 2017). Natural herbal compounds and bioactive agents exhibit intrinsic antimicrobial attributes. Garlic extract, as an example of a natural product, can be specifically employed for the administration of infections arising from multidrug-resistant biofilm-forming strains. These natural antimicrobial treatments, like garlic extract, have been developed with the intent of countering drug-resistant polymicrobial biofilm infections associated with *C. albicans* (Ashrit et al. 2022). Even though fungicidal compounds have demonstrated the ability to eliminate fungal cultures in vitro, their effectiveness in clinical settings is not always satisfactory (Muzny and Schwebke 2015). Treatment failure can be attributed to various factors, encompassing the presence of resistant isolates that can survive high drug concentrations and continue to grow, as well as the adaptability of fungal cells producing biofilms to develop tolerance to antifungal drugs (Delarze and Sanglard 2015; Brauner et al. 2016). Fungal biofilm refers a dynamic microbial community capable of thriving and reproducing as a colony, which primarily comprise of polysaccharides, consisting of 50%–90% of the organic component (Sharma et al. 2023). These biofilms attach to surfaces and medical devices, significantly contribute to heightened resistance against antifungal agents and host immune responses, ultimately culminating in treatment ineffectiveness (Mathé and Van Dijck 2013). Extensive research has been dedicated to the study of bacterial persister cells, yet the investigation into fungal persister cells and the potential therapeutic avenues remains limited (Balaban et al. 2004; Fisher et al. 2017; Rosenberg et al. 2018). Recently, there has been an escalating inclination toward exploring the remedial prospect of MSCs for fungal infections, particularly in cases where conventional antifungal drugs have proven ineffective. MSCs have been investigated for their outstanding anti-inflammatory and immunomodulatory properties which present promising prospects in addressing the challenges posed by fungal infections (Schmidt et al. 2017). However, the precise underlying mechanisms responsible for these properties remain incompletely elucidated. Further investigations are imperative to devise targeted strategies and therapies for handling these fungal infections, most particularly in individuals with compromised immune systems. This review aims to provide insights into the probable therapeutic attributes of MSCs and their exosomes for combating fungal persistence infections by targeting various mechanisms of antifungal resistance.

The prominence of fungal persisters and their resistance mechanisms across various disease scenarios

Persister cells represent a minor subset within microbial populations, characterized by their capacity to endure lethal concentrations of antimicrobial agents, a phenomenon often leading to a biphasic pattern of cell killing (Lewis 2010). Compared to planktonic form, biofilm formation proceeds through a series of morphological changes in fungal persister cells, an increase in cell numbers, and the synthesis of extracellular polymeric substances (EPS), all of which collectively influence the ultimate architecture of the mature biofilm (Cavalheiro and Teixeira 2018). Fungal persisters constitute a distinct subgroup within biofilms that display resistance to high concentrations of antifungal agents (Lamfon et al. 2004; Vandenbosch et al. 2010). Contrary to bacterial pathogens, which can be targeted with a diverse array of antibiotic drug classes, the therapeutic interventions for invasive fungal infections revolve around four categories of antifungal medications: azoles comprising voriconazole, posaconazole and fluconazole; polyenes including nystatin and amphotericin B (AMB); echinocandins such as micafungin, anidulafungin and caspofungin; and pyrimidine analoques (Jabra-Rizk et al. 2004; Arendrup 2010; Chen et al. 2011; Gutiérrez-Correa et al. 2012; Houšť et al. 2020). Each of these classes exerts its therapeutic action by targeting distinct components within the fungal cell. The polyene class acts through interaction with ergosterol, a predominant component found in the fungal cellular membrane. Remarkably, AMB demonstrates high fungicidal activity against *Candida* species (Kumar et al. 2018). Echinocandins operate by impeding the synthesis of β-D-glucans situated in the fungal cell wall. Notably, echinocandins are fungicidal for *Candida* spp. and fungistatic for *Aspergillus* spp. (Patil and Majumdar 2017). Subsequently, azoles disrupt the ergosterol biosynthesis and manifest a fungistatic effect against yeasts (Geißel et al. 2018). Lastly, the pyrimidine analogue flucytosine (5-FC) interferes at the nuclear level of the fungal cell, impacting both protein and DNA biosynthesis (Houšť et al. 2020). *Candida* species pose a particular challenge in treatment due to their proficiency in constructing biofilm structures, thereby demanding notably elevated dosages of antifungal agents compared to their planktonic counterparts (Barantsevich and Barantsevich 2022). Nevertheless, the prevailing effectiveness of extant antifungal pharmaceutical agents is hindered by several distinct challenges and underlying mechanisms. These impediments encompass, inter alia, a scarcity of comprehensive research studies, the development

of resistance to antifungal drugs, constraints related to fungal diagnostic methods, the inadequacies in molecular diagnostic methodologies, and a prevailing dearth of awareness in the field of mycology (AlMaghrabi et al. 2023).

The resistance phenomenon of *Candida* biofilm was first stated in 1995 for *C. albicans* by Hawser and Douglas (Hawser and Douglas 1994), and since then, numerous researchers have investigated the capability of *Candida* biofilms to withstand high antifungal concentrations (Silva et al. 2012; Fernandes et al. 2016; Rodrigues et al. 2016). The biofilms formed by *C. albicans* display a natural propensity for intrinsic resistance against a majority of established antifungal agents (Lewis 2008). This inherent resistance can be attributed to a triad of pivotal factors, which encompass drug sequestration by the extracellular matrix (ECM), persister cells characterized by multidrug tolerance, and the up-regulation of drug efflux pumps (Fig. 1) (Mathé and Van Dijck 2013; Fisher et al. 2022).

Research conducted in the early twenty-first century has revealed that biofilm formation contains a complex interplay between physiological processes and natural forces. The life cycle of fungal biofilms encompasses five main phases: (1) initial attachment, which involves both reversible and irreversible adhesion of individual fungal cells; (2) fungal aggregation; (3) microcolony formation; (4) maturation; and (5) dispersion and detachment. These stages collectively contribute to the intricate architectural configuration of biofilms, thereby influencing their antibiotic resistance (Fig. 2) (Talapko et al. 2021). The fungal biofilm's matrix, consisting of proteins, carbohydrates, lipids and DNA plays a critical role in mediating antifungal drug resistance by facilitating drug penetration and promoting biofilm formation (Baillie and Douglas 2000). In the case of *C. albicans* biofilms, the matrix is notably enriched with glucans and mannans, reinforcing resistance to antifungal drugs compared to the dormant state (Mitchell et al. 2015). This mechanism involving matrix glucans and mannans appears to be conserved among biofilms generated by other *Candida* species, inclusive of *C. auris, C. tropicalis, C. glabrata* and *C. parapsilosis* (Dominguez et al. 2018). Furthermore, the presence of biofilms in *C. albicans* has been correlated with the elevated expression of drug-efflux pump genes, specifically MDR1 and CDR1, substantiating the underlying antifungal drug resistance (Prasad et al. 1995). Another specific mechanism of drug resistance in biofilms involves the presence of persister cells, which represent a subset of tolerant cells capable of surviving exposure to high doses of antifungal drugs, primarily comprising wild-type variants (Bonhomme and d'Enfert 2013). The establishment of surface attachments within the biofilm structure has been linked to the occurrence of persister cells in fungal biofilms (Lee et al. 2021). Fungal persisters possess the ability to withstand high concentrations of antifungal agents that stimulate the accumulation of reactive oxygen species (ROS) (Li et al. 2015a, b). The resilience of persister cells to antifungals is attributed to several factors. First, persister cells exhibit heightened expression of superoxide dismutases (SODs), which confer protection against ROS production induced by agents like miconazole (Bink et al. 2011). Second, a minor heat-shock protein, Hsp21, is upregulated in persister cells and plays a pivotal role in ROS generation (Li et al. 2015a, b). Third, the interaction between the expression of alkyl hydroperoxide reductase 1 (AHP1) and persister cells is notably positive, especially when imposed upon increased AMB levels (Truong et al. 2016). Fungal persisters are regulated by various factors, including nutrient sensing, glucose starvation,

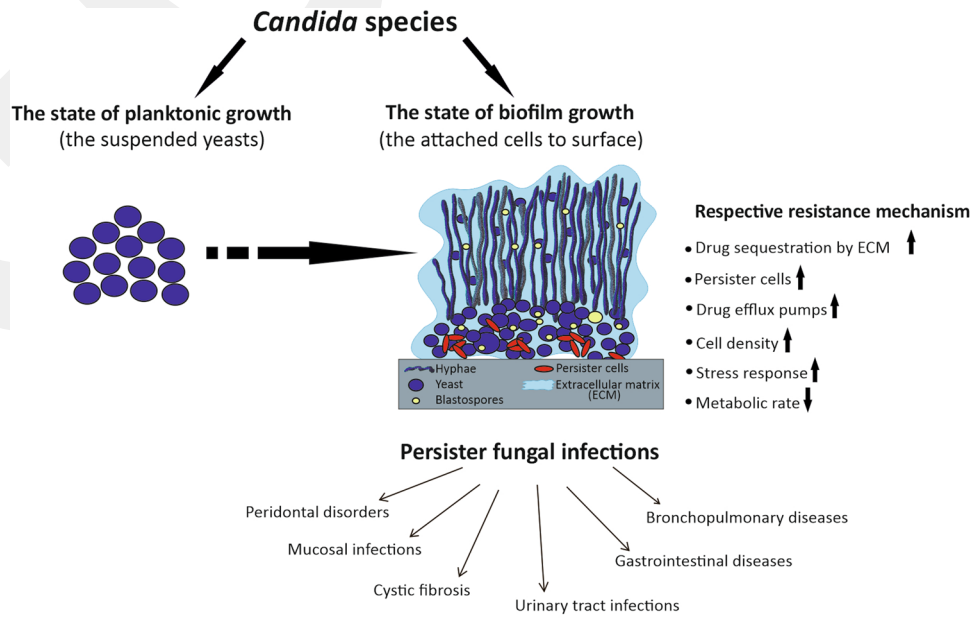

Fig. 1 The figure illustrates the *Candida* species commonly encountered in biofilms, along with their respective resistance mechanisms, associated diseases and conditions. The figure emphasizes the formidable challenge posed by the significant resistance of biofilm-related fungal persisters to conventional antifungal drugs, thereby hindering the development of highly efficacious therapies

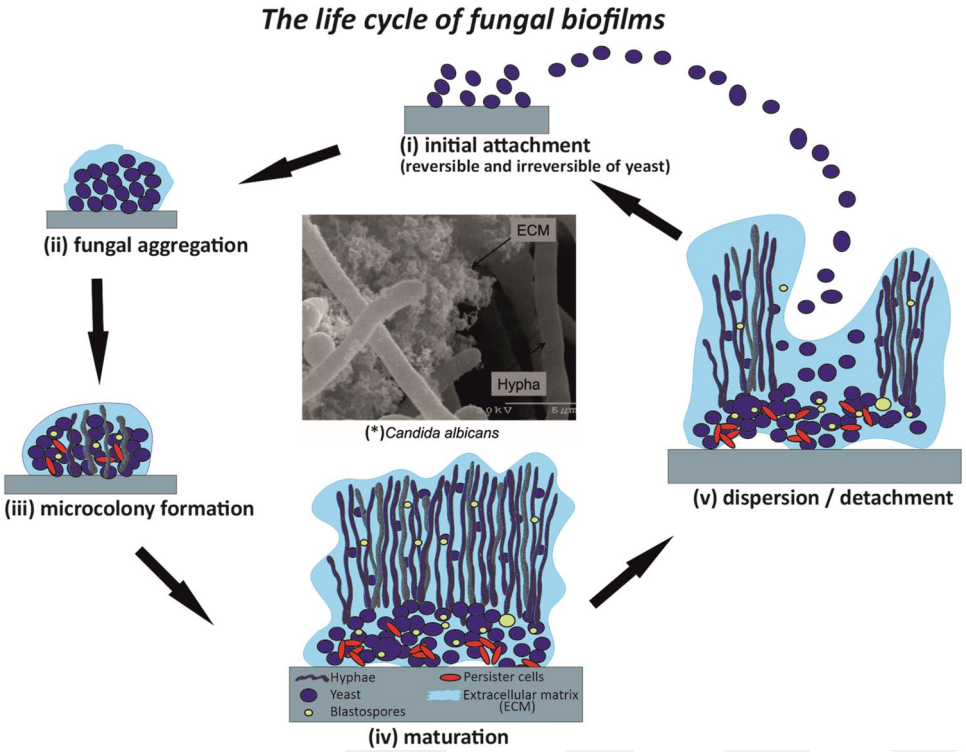

Fig. 2 The figure depicts the sequential phases inherent to the formation of *C. albicans* biofilms. Commencing this developmental process is the initial attachment of fungus to a substrate surface, a phenomenon significantly influenced by the chemical composition and properties of the encountering material. This adherence event entails a molecularly coordinated binding mechanism that is closely associated with the aggregation of fungal cells. In the early stages of biofilm development, microcolonies emerge as a distinctive feature of this process. Subsequently, the biofilm advances with the production of an ECM, which plays a fundamental role in the structural integrity of the biofilm. As the biofilm matures, a critical phase unfolds involving the excretion of signaling factors by the fungal cells that have firmly adhered to the substrate. This secretion culminates in the activation and expression of genes specific to biofilm development. The structural configuration of the biofilm itself serves as a triggering factor for the accumulation of the ECM. In the concluding stage, fungal cells disperse from the mature biofilm to colonize new sites, initiating the formation of fresh biofilm communities. This multi-phased process underscores the intricate and dynamic nature of *C. albicans* biofilm development, with molecular interactions and material properties governing the various stages. * The micrographs above show a Scanning Electron Microscope view of *C. albicans* in vitro biofilm cells. This figure is reproduced from PLoS Pathog. 2012; 8(4): e1002585. This article is open access and distributed under the terms of the Creative Commons Attribution License, allowing unrestricted utilization, distribution, and reproduction in any format, with attribution to the original author and source (Fanning and Mitchell 2012)

and increased oxidative stress responses, all of which collectively empower their survival even when confronted with elevated concentrations of antifungal agents, resulting in the accrual of ROS production (Lopes and Lionakis 2022; Brown 2023).

Effectively addressing the challenge of biofilm-associated fungal infections holds significant importance in combating severe diseases, such as periodontal disorders, mucosal infections, cystic fibrosis, bronchopulmonary diseases, pneumonia, gastrointestinal diseases and urinary tract infections (Fig. 1) (Silva et al. 2017). Additionally, the considerable antifungal resistance exhibited by fungal persisters poses a formidable obstacle to the development of successful therapeutic methods. Despite progress in comprehending the mechanisms and management of fungal infections, exploring alternative treatment approaches specifically targeting fungal persisters remains an urgent priority (McCarthy and Walsh 2017). Recently, emerging evidence have suggested that MSCs and their secreted exosomes could serve as promising therapeutic options for tackling fungal persister infections.

Harnessing MSCs for immune responses against fungal persisters

Pathogenic biofilm formation is accountable for a majority of microbial infectious diseases, including superficial mucosal infections and severe systemic infections with high mortality rates. For instance, vaginal yeast infections affect around 75% of women at least once during their lifetimes while certain cases of infections exhibit mortality rates as high as 47% (Nobile and Johnson 2015; Gulati and Nobile 2016).

The formation of drug-resistant biofilms by *Candida* species significantly contributes to their involvement in human diseases, as highlighted by Taff et al. (Taff et al. 2013). Despite the presence of novel antifungal medications, effectively addressing invasive fungal infections continues to pose a considerable challenge, largely attributed to the existence of fungal persister cells. MSC-based therapy has so far shown an attractive avenue for the remedy of diverse tissue and immune diseases. While numerous successful applications of MSCs have been reported in managing infectious diseases and their associated complications, there is a scarcity of literature concerning their specific host response against fungal infections (Keshtkar et al. 2022). Therefore, detailing the MSCs and their immune response to biofilm-associated fungal diseases and elucidating the associated mechanisms could pave the way for combating fungal persisters.

MSCs exhibit a versatile capacity for immunomodulatory attributes that induce both innate and acquired immunity. This immunomodulation is achieved through the secretion of bioactive molecules, including interferons (IFN) and interleukins (IL) (Zhang et al. 2020). A wealth of experimental and clinical studies has provided compelling evidence supporting the immunosuppressive capacities of MSCs, thereby positioning them as magnificent candidates for the therapeutic management of various inflammatory and autoimmune disorders. These capacities include inhibiting immune cell proliferation and function, with specific targeting dendritic cells, T and B lymphocytes, as well as natural killer (NK) cells (Uccelli et al. 2008). Moreover, MSCs release a diverse array of cytokines and chemokines that further contribute to their immunomodulatory functions. Noteworthy examples of these secreted factors comprise prostaglandin E2 (PGE2), interleukin 10 (IL-10), nitric oxide (NO), transforming growth factor β (TGF-β), tumour necrosis factor-inducible gene 6 (TSG-6), indoleamine 2,3-dioxygenase (IDO), and Chemokine (C–C motif) ligand 2 (CCL2) (Nauta and Fibbe 2007; Shi et al. 2010; Choi et al. 2011). MSCs play a pivotal role in the immune response during fungal infections and injuries by interacting with pathogen-associated molecular patterns (PAMPs) at the injury site or during inflammatory processes where endogenous danger signals are released (DelaRosa and Lombardo 2010). Notably, various membrane-bound immune receptors can recognize beta-glucans, the predominant polysaccharide structure in human fungal pathogens (Camilli et al. 2018). C-type lectin receptors (CLRs) are particularly significant in recognizing fungal components, with Dectin-1 being a well-studies CLR. Activation of Dectin-1 can induce phagocytosis in macrophages and dendritic cells upon stimulation with *C. albicans* or zymosan (Herre et al. 2004). Furthermore, research by Gantner et al. has demonstrated how the recognition of zymosan by phagocytes triggers a response mediated by Toll-like receptor (TLR) and Dectin-1 (Gantner et al. 2003). In this context, the overexpression of Dectin-1 in macrophages enhances the production of IL-12, mediated by nuclear factor kappa B (NF-κB) and TLR-2. Therefore, besides its primary role as a phagocytic receptor, Dectin-1 also interacts with other PAMPs, such as TLR-2, to modulate the antimicrobial response of immune cells. Understanding how MSCs engage in the immune response against fungal infections and the relevant signaling pathways are critical for the development of MSC-based therapies in this context.

Some research has provided persuasive insights into the role of TLRs in modulating the immunosuppressive properties of MSCs. Investigations undertaken by Liotta et al. (2008) and Opitz et al. (2009) have reported that the interference of TLRs with MSCs gives rise to divergent effects, either augmenting or diminishing their immunosuppressive functions (Liotta et al. 2008; Opitz et al. 2009). Conversely, other investigations have defined a distinct subset of MSCs exhibiting immune-stimulatory effects, with TLRs being attributed to the range of their various biological functions (Yang et al. 2013). Among of the family of TLR, TLR4 has been extensively studied owing to its synergistic interaction with IL-17, facilitating the synthesis of pro-inflammatory mediators (Waterman et al. 2010). Recent research findings have indicated that MSCs possess the capability to directly influence the immune characteristics of neutrophils and macrophages through the excretion of proinflammatory cytokines such as IL-8 and IL-6 (Chow et al. 2020). Simultaneously, these MSCs exhibit a concomitant dampening effect on the expression of immunomodulatory cytokines and chemokines, including IL-4, IDO and PGE2 (Waterman et al. 2010). Marx's research revealed that the secretome of equine MSCs exhibits the capacity to impede both the initial and mature biofilm formation formed by various bacterial strains, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* (Marx et al. 2020). Given the noteworthy anti-biofilm properties exhibited by MSCs, they were subsequently explored in conjunction with chitosan nanoparticles as a promising therapeutic strategy targeting multidrug-resistant (MDR) pathogens (Saberpour et al. 2020). The formation of biofilms constitutes an effective mechanism employed by microorganisms, such as *S. aureus*, to confer resistance to antibiotics. Furthermore, the author's findings documented an inhibition of *S. aureus* growth by MSCs (Yagi et al. 2020). Additionally, IL-17 exerts a noteworthy influence on the immune system's defensive modalities, effectively combating both extracellular and intracellular pathogenic fungi, such as *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans* (Matsuzaki and Umemura 2007; Zelante et al. 2007; Yang et al. 2013; Schinocca et al. 2021). On the contrary, TLR3 has gained the recognition for its role in triggering immunosuppressive effects, functioning as a constituent of MSCs responsible for immunomodulation (Waterman et al. 2010;

Pierce and Kurata 2021). Some research has also revealed the presence of a specific IL-17$^+$ MSCs subset that can restrain the growth of *C. albicans*. Yang et al. closely examined how IL-17, excreted by these specific MSCs, enables the activation of the NF-κB pathway. This, in turn, results in the downregulation of the TGF-β production within MSCs, thereby counteracting the elimination of MSC-based immunomodulation. Thus, this study highlights the presence of an IL-17$^+$ subset within MSCs, which not only impedes the proliferation of *C. albicans* but also attenuates MSC-related immunosuppression through NF-κB-mediated downregulation of TGF-β (Yang et al. 2013).

Antimicrobial peptides (AMPs) constitute a crucial component of the first immunity and allow them diminish the virulence factors of pathogens by encouraging the immune response (de Oca 2013). The Antimicrobial peptide database has classified 153 human peptides as host defence peptides, with some of them identified in MSCs (Wang et al. 2016). Human AMPs expressed by MSCs display antimicrobial activity against various microorganisms such as bacteria, viruses and fungi. Among human AMPs, five have been identified as antifungal peptides effective against *Candida* species, namely CGA-N46 Peptide, Psoriasin Peptide, Human β-Defensins, Histatins, LL-37 Peptide (Perez-Rodriguez et al. 2022). For instance, CGA-N46, predominantly expressed in neurons, demonstrates antifungal activity against pathogenic *Candida* species, including *C. albicans, C. parapsilosis*, *C. krusei, C. glabrata* and *C. tropicalis* by impairing yeast cell mitochondria and by disrupting DNA synthesis (Li et al. 2015a, b). In a murine model with compromised immune responses and subjected to *C. krusei* infection, the administration of CGA-N46 demonstrated immunomodulatory effects, ameliorating organ damage attributable to the *C. krusei* infection (Li et al. 2017). Psoriasin, initially identified in a patient with psoriasis, plays a significant role in reducing susceptibility to skin infections and decreases the adhesive capacity of *C. albicans* by binding to the β-glucan component on the cell wall of pathogenic fungi (Harder and Schröder 2005; Brauner et al. 2018). Furthermore, psoriasin has potential for targeting biofilms by causing cell disaggregation and rendering them more susceptible to antifungal agents (Brauner et al. 2018). Human *β-Defensins*, essential for safeguarding the intestinal mucosa, contribute significantly to the defence mechanism within the lower genital tract of women during *C. albicans* infections (Kotani et al. 2020; Fusco et al. 2021). Histatins are integral episodes of the congenital immune response and are also responsible for antimicrobial defence within the oral cavity (Khurshid et al. 2017). Numerous in vitro experiments extensively document the antifungal activity of histatins against *Candida* species. In particular, histatins have exhibited promising antifungal properties and proteolytic stability, making them potential candidates for treatment options (Konopka et al. 2010; Ikonomova et al. 2020; Moghaddam-Taaheri et al. 2021). Human cathelicidin LL-37, extensively studied among human AMPs, plays a pivotal role in various defence responses, including inhibiting microbial adhesion, promoting leukocyte chemotaxis, and counterbalancing endotoxins (Nijnik and Hancock 2009; Chen et al. 2021). While most investigations have predominantly focused on LL-37's ability to combat bacterial infections, it also exhibits antifungal activity against the establishment of biofilms by *Candida* strains obtained from vaginal infections (Scarsini et al. 2015; Rather et al. 2022). Additionally, human LL-37, along with its constituent fragments, namely LL13-37 and LL17-37, has demonstrated comparable efficacy in inhibiting the proliferation of C. *albicans*. However, the mechanism of cell death within *C. albicans* cells might not be exclusively attributed to the heightened membrane permeability induced by LL13-37; it may involve specific intracellular targets as well (Wong et al. 2011).

Collectively, these AMPs offer promising avenues for therapeutic interventions against *Candida* infections, highlighting the potential of AMP-based strategies for combating fungal infections. Moreover, subsets of MSCs expressing immune-stimulatory agents, such as TLR4 and IL-17$^+$, which might be associated with AMPs, could serve as promising candidates for the host's antifungal response against persistent fungal infections. If substantiated by further investigations, these findings could pave the way for a novel therapeutic approach to combat fungal persisters.

Therapeutic approaches of MSCs and their exosomes against fungal persisters

The emergence of fungal persisters and the alarming mortality rates associated with fungal infections have encouraged extensive research endeavors to identify novel therapeutic strategies. MSCs have found extensive application in managing inflammatory and autoimmune disorders (Zhou and Xu 2020). There is increasing interest in utilizing exosomes and secretomes derived from MSCs as an alternating approach to stem cell therapy for combating a diverse array of illnesses. Exosomes present an enticing avenue for cell-free therapy, given their inherent lack of tumor formation risk and their replication. Furthermore, exosomes can undergo sterilization through filtration procedures and exhibit a prolonged shelf-life when compared to intact cells. Their smaller size enables efficient systemic circulation, thereby enhancing targeted delivery to injury sites. Additionally, the extended and repetitive administration of exosomes does not induce deleterious toxic effects (Mendt et al. 2018). Due to advantages of exosomes, exosome-based therapies might be considered as superior to stem cell therapy.

Numerous preclinical and clinical studies, including those focused on Graft-versus-host disorder, have demonstrated that exosomes derived from MSCs possess regenerative capabilities comparable to MSCs themselves (Kordelas et al. 2014; Li et al. 2021; Norooznezhad et al. 2022). Subsequently, the field has witnessed rapid advancements, with extracellular vesicles (EVs), including exosomes and secretomes, being investigated in a multitude of clinical trials for diverse medical indications. Based on information sourced from the United States National Institutes of Health (NIH) through clinicaltrials.gov, a noteworthy upswing has been observed in the quantity of clinical investigations oriented toward EVs within the preceding year. As of August 2023, a total of 1362 trials focused on MSC therapy have been formally recorded in the ClinicalTrials.gov database (http://clinicaltrials.gov). These trials are distributed as follows: secretome trials amount to 18, exosomes trials to 35, and EVs trials to 23 (with the data retrieved on 13/08/2023). In Fig. 3A, a comprehensive global overview of trials involving MSC therapy is presented, incorporating trials focused on secretome (18 trials), exosomes (35 trials) and EVs (23 trials). Within the spectrum of clinical trials registered for the MSC-secretome, one was categorized as early Phase I, ten as Phase I, ten as Phase II, and one study as Phase III. In the context of MSC-exosomes, three trials were listed as early Phase I, 18 as Phase I, 21 as Phase II and 4 as Phase III trials. Regarding MSC-EVs, two trials were recorded as early Phase I, fourteen as Phase I, ten studies as Phase II, and one study as Phase III clinical trials (Fig. 3B).

A mounting body of scholarly investigations has highlighted the therapeutic prospects associated with exosomes derived from MSCs for regenerative and immune therapies. These exosomes, originating from maternal cells, offer a cell-free therapeutic approach by delivering bioactive molecules, such as proteins and microRNAs (Ma et al. 2020). In the scientific domain, MSC-derived exosomes, denoted as MSC-Exo, are garnering attention by virtue of their pronounced anti-inflammatory and immunomodulatory properties. Numerous studies have amassed data supporting the anti-inflammatory properties of MS-Exo in diverse pathological conditions, such as chronic kidney diseases (Nassar et al. 2016), atopic dermatitis (Cho et al. 2018; McBride et al. 2018), neurodegenerative disorders (Katsuda et al. 2013; de Godoy et al. 2018), liver fibrosis (Mardpour et al.

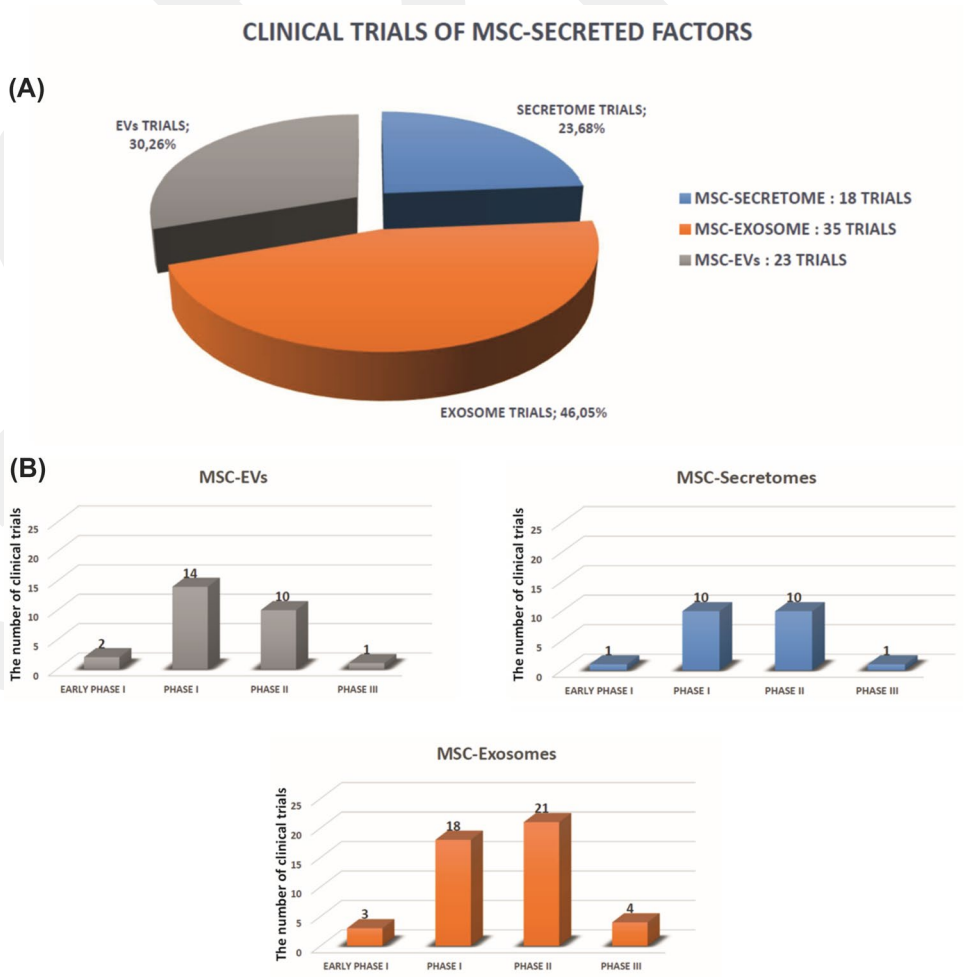

Fig. 3 A comprehensive depiction of the registered clinical trials focused on MSC therapy, categorized according to their respective investigation phases and study statuses. A) A Pie chart delineating the distribution of these trials across different phases of investigation. B) Column charts detailing the status of the clinical trials under scrutiny. All data for this visual representation were acquired on August 13, 2023

2019), among others (Li et al. 2019; Zhao et al. 2020). A substantial corpus of empirical data suggests that MSC-Exo possess the ability to mimic the advantageous impacts attributed to their progenitor MSCs, as demonstrated in animal models simulating a spectrum of human disorders. These encompass instances of multiple sclerosis (Laso-García et al. 2018), rheumatoid arthritis (Cosenza et al. 2018), insulin-dependent diabetes mellitus (Jiang et al. 2016; Sun et al. 2018), and uveitis (Bai et al. 2017). Although numerous preclinical investigations have explored exosomes, the quantity of clinical studies investigating MSC-derived exosomes remains limited (Baharlooi et al. 2020; Gowen et al. 2020), with ongoing studies yet to be published. Within the realm of diverse infectious conditions, the pathogenic mechanisms underlying fungal disorders are notably complex, and reports on the antifungal activity of MSCs and their exosomes are scarce. Notably, MSC-based secretomes have been tested in only one clinical trial for fungal infection treatment (clinical trials number: NCT05777213), while three clinical trials based on MSC-based therapy have been conducted for fungal infections (clinical trials numbers: NCT05934825, NCT04493918 and NCT05777213) (Table 1) (https://clinicaltrials.gov/, data retrieved on 13/08/2023). Furthermore, emerging evidence from preclinical models of fungal diseases has demonstrated the potential benefits of MSC-based cell therapies. One noteworthy study examined the systemic delivery of exosomes acquired from human bone marrow-derived MSCs (BM-MSCs) within an immunocompetent murine model replicating the context of severe intractable neutrophilic asthma prompted by the presence of *Aspergillus* hyphal extract. The study revealed that these exosomes mitigated allergic airway inflammation and improved the diseases through Th17 inhibition (Cruz et al. 2015). The principal objective of the ongoing inquiry exhibited the xenogeneic delivery of conditioned medium or EVs derived from human BM-MSCs and asserted a conceptual framework depicting Th2/Th17-mediated allergic airway inflammation for refractory asthma. The manifestation of this ailment was provoked by recurrent mucosal contingence to *Aspergillus* hyphal extract (AHE) using a murine model of the C57Bl/6 strain, characterized by normal immune competence. A recent investigation showed the antifungal potential of human cervical stem cells extracted from the uterine region, demonstrating efficacy in combatting diverse *Candida* pathogens including *C. albicans, C. krusei, C. parapsilosis* and *C. glabrata* (Schneider et al. 2018). The application of MSCs and their exosomes to treat fungal persisters is confronted with some anticipated limitations for clinical implementation. Fungal diseases, compared to other microbial infections, exhibit greater complexity in their pathogenesis. Fungal pathogens initially subvert the host immune system by employing vesicles generated by monocytes to transport TGF-β (Halder et al. 2020). Furthermore, the challenges lies in the insufficient production of exosomes on a large scale, along with the absence of rapid and highly accurate methods for quantifying exosomes and determining their precise content (Gowen et al. 2020). Further investigations are required to determine the appropriate dosage of MSC-exosomes for clinical trials in order to avert potential adverse effects. Consequently, the exploration of MSC-based therapy for fungal persisters might be considered as a potential approach for research, even though the mentioned obstacles need to be addressed for its successful clinical application.

Overall, a substantial body of literature has explored the rehabilitative action of MSCs and their exosomes in combating fungal persisters. However, the specific impact of MSCs and MSC-derived exosomes on fungal diseases remains in its early stages, warranting further comprehensive investigations. Given the limited body of research on fungal persister cells and the paucity of the published clinical studies in this area, fungal infections characterized by both biofilm formation and antibiotic resistance have been designated as persistent fungal infections. Consequently, the potential application of MSCs for the therapy of such infections is likely to represent a promising therapeutic avenue. Further comprehensive explorations could provide valuable insights into the potential therapeutic applications of MSCs and exosomes, positioning them as innovative and promising therapeutic modalities for enhancing the immune response against fungal persistence.

Conclusions and outlook

MSCs and EVs, particularly MSC-Exo, exhibit remarkable anti-inflammatory, immunomodulatory, regenerative, and antimicrobial characteristics, rendering them efficient in

Table 1 Clinical trials utilizing MSCs-based therapy for fungal infections

ClinicalTrials.gov Identifier	Targeted disease	Treatment	Study status	Study type	Phase
NCT05934825	Hidradenitis Suppurative	MSCs	Recruiting	Interventional	Phase I-II
NCT04493918	*Mycobacterium Tuberculosis* Infection	MSCs	Unknown	Interventional	Phase II
NCT05777213	Trophic Ulcers	MSC-Secretome	Completed	Interventional	Phase I

combating various microbial infections. The specific focus on MSCs-derived exosomes arises from their advantageous characteristics, such as high stability, small size, absence of tumorigenicity, ease of storage, and low immunogenicity. Incorporating MSC-derived exosomes into clinical applications offers a promising solution to address the limited availability of stem cells for treating microbial infectious diseases, thereby transitioning medical practice from conventional cellular therapy to a novel acellular therapeutic approach. In the context of antimicrobial activity, MSCs-derived exosomes are postulated to predominantly contribute through immune cell reprogramming and the initiation of congenital and adaptive immune responses. Additionally, MSCs and their exosomes exhibit antimicrobial effects via the secretion of antifungal peptides. MSCs and their exosomes hold potential for countering fungal infections, presenting them as a promising defense mechanism against fungal invasion. Moreover, a comprehensive understanding of the functional roles of MSCs and their secreted exosomes could maximize their therapeutic potential in fungal infections, especially in cases involving drug-resistant strains. Considering the therapeutic potential of MSCs and MSC-Exo, and the need for further research, they are likely to have the capability to activate the host immune system and combat the immunosuppressive mechanisms of fungal persisters, potentially positioning them as promising agents in the battle against fungal infections.

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