Chapter 1

Exploring the Potential Therapeutic Approaches of Mesenchymal Stem/Stromal Cells (MSCs) in the Treatment of Vaginal Candidiasis

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Abstract

Over the past few decades, there has been significant progress in understanding MSC therapy and its antimicrobial effects, leading to a substantial body of literature in this field. MSC-based therapy has emerged as a charming option for treatment modalities, serving as a cellular rehabilitative therapy for various diseases, particularly inflammatory conditions. Despite several clinical trials examining MSC-based therapies to struggle bacterial infections, there are currently insufficient studies specifically focused on vaginal candidiasis. The feasibility of autologous MSC and their targeted delivery to specific cells has resulted in their extensive utilization across various treatment fields. Although there are existing limitations, the transplantation of MSCs represents a remarkable and inspiring approach in the scope of medical science, necessitating further data collection to explore their potential in addressing vaginal candidiasis. Further efforts are warranted to improve efficient therapy using MSCs in therapeutic approaches. Depending upon the findings in pre-clinical experiments, it is crucial to further investigate the antifungal activities of MSCs and conduct translational studies to appreciate their clinical applications. This concise chapter aims to promote such endeavours in the remedial approaches of MSC for the treatment of vaginal candidiasis.

1.Introduction

Candida spp. are widely recognized as the predominant etiological agents responsible for fungal infections, ranging from severe invasive forms to less critical mucocutaneous manifestations. Within *Candida* spp., *Candida*

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albicans holds a prominent position as the most prevalent causative organism (Richards et al. 2000). Notably, *Candida albicans* exhibits a dual nature, acting as a commensal microorganism in individuals with normal health status while posing a substantial risk for morbidity and mortality in human populations (Quindós 2014). This dimorphic yeast species demonstrates a commensal nature by inhabiting the skin, gastrointestinal tract and reproductive tracts of humans. Non-*C. albicans* species also have recognition receptors that are capable of colonizing various mucocutaneous surfaces in the human body (Sobel 2006). Furthermore, mucosal candidiasis, including vaginal candidiasis, is very common diseases. It has been estimated that a remarkable proportion of women, more than 75%, experience vulvovaginal candidiasis at least once in their lifetime (Aguin and Sobel 2015). In addition, approximately 5–10% of women suffer from recurrent episodes of vaginal candidiasis (Weissenbacher et al. 2009). While *Candida albicans* is the most primarily identified agent in invasive candidiasis, it has been a rise in the incidence of candidiasis caused by non-*Candida* species, including *Candida krusei* and *Candida glabrata*, *Candida parapsilosis* (Puig-Asensio et al. 2014). Additionally, *Candida auris* has become universally common among nosocomial pathogens (Chowdhary et al. 2018). The pathogenesis and diagnostic approaches for *candida* colonization are influenced by the host's immune status and display numerous variations depending on the clinical indications of the disease. In terms of therapeutic interventions, the range of antifungal agents accessible for the therapy of patients with invasive fungal illnesses is restricted. Despite the advancement of current antifungal drugs, the treatment options for systemic fungal diseases are constrained, leading to unfavourable outcomes in many cases (Scriven et al. 2017). These emerging *Candida* species often exhibit diminished susceptibility to commonly employed antifungal agents utilized for the treatment of such infections. Examples of these drugs include fluconazole, micafungin, echinocandins, anidulafungin, and caspofungin (Arendrup and Patterson 2017; Chowdhary et al. 2018). Vaginal candidiasis is still an unresolved problem in society. Various factors contributing to the inefficacy of these drugs have been identified, including several molecular resistance mechanisms (Arendrup 2014; Dominique Sanglard 2016). Notably, these resistance mechanisms are closely linked to elevated resistance against antifungal drugs and the host's immune-related factors, consequently leading to treatment failure (Muzny and Schwebke 2015). Novel antifungal agents are urgently needed to address the considerable clinical challenges caused by therapy-resistant fungal candidiasis (McCarthy and Walsh 2017). In recent times, increasing attention has been given to the study of Mesenchymal Stem/Stromal Cells

(MSCs) and their possibilities to treat fungal candidiasis, particularly in cases where conventional antifungal drugs have proven unsuccessful. MSCs possess notable anti-inflammatory and immunomodulatory mechanisms that can contribute to the resolution of fungal infectious episode (Schmidt et al. 2017), although their precise role in the context of vaginal infections remains incompletely understood. Thus, this chapter focuses on elucidating the therapeutic properties of MSCs and their antifungal activity against vaginal candidiasis.

2. Pathogenesis, Epidemiology and Antifungal Resistance of *Candida* species from Vaginal Candidiasis

2.1. The Pathogenesis

When *Candida* is present in the vaginal region without concurrent immunosuppression or mucosal damage, it typically does not manifest any disease-related symptoms and is hereby referred to as fungal alignment. On the contrary, vulvovaginal candidiasis can be characterized by the presence of *Candida* spp. accompanied by signs and symptoms of inflammation, indicating causative contagious agents. More than ten years ago, vulvovaginal candidiasis was divided into two groups: uncomplicated and complicated cases, which have gained international acceptance and verification (Pappas et al. 2009). Uncomplicated vulvovaginal candidiasis refers to sporadic occurrences, primarily caused by *C. albicans,* in immunocompetent women. On the other part, complicated vulvovaginal candidiasis encompasses severe cases of the infection associated with factors such as pregnancy, immunosuppression and uncontrolled diabetes (Sobel et al. 1998). Women who suffer from recurrent episodes of vulvovaginal candidiasis constitute a distinct subgroup within the healthy individuals, setting them apart from those who have sporadic cases of vulvovaginal candidiasis. In comparison to women with chronic vaginal symptoms unrelated to recurrent candidiasis, it has been observed that the symptoms experienced by women with recurrent vulvovaginal candidiasis have the most significant adverse effects on their occupational and social functioning (Nyirjesy et al. 2006).

During the initial phases of fungal pathogenesis, particularly in the case of *Candida albicans*, it has been demonstrated that these pathogens exploit host immune cells, impairing the early induction of proinflammatory cytokines, thereby diminishing their expression. Regardless of how, the immune response becomes intensified in the later phases of *Candida* diseases. A recent investigation focusing on *C. albicans* elucidated that pathogenic fungi downregulate the host immune response during the infections (Halder et

al. 2020). This study indicated that *C. albicans* complies with monocytes through the interaction between its β-glucan and the C3 receptor. By utilizing this involvement to the monocytes, the fungal pathogens induce to secrete proinflammatory cytokines containing transforming growth factor (TGF)-β. These TGF-β-carrying proteins enable the pathogens to dampen the immune response and exert anti-inflammatory effects. Furthermore, the fungal pathogens can suppress the activation of these proteins by means of secreting TGF- β (Netea et al. 2002; Halder et al. 2020). This mechanism allows the fungal pathogens to suppress the immune response in the host, favouring their own survival and persistence.

2.2. Epidemiology

Estimating the global incidence of invasive candidiasis poses challenges due to variations in diagnostic criteria and categorization methods employed. Many factors influence the incidence of this condition, including patients' age, overall health status, the prevalence of immunodeficiency disorders, frequency of organ transplantations, extent of major surgeries and utilization of cancer chemotherapy. It is significant to give due consideration to factors such as genetics, immunity, behavior, nutrition and others. In fact, the scarcity of population- based surveys initiatives significantly limits our understanding of the epidemiological surveillance of fungal candidiasis worldwide (Lamoth et al. 2018). The incidence of *Candida* species observed in females diagnosed with vaginal candidiasis exhibits significant variability across different geographic locations and studied populations. Characteristically, a single *Candida* species is described. However, in a small proportion of women (approximately 2% to 5%) with both complicated and uncomplicated vulvovaginal candidiasis, more than one species has been detected within the self-similar vaginal culture (Richter et al. 2005). Examining Australia, Europe and the United States of America, *C. albicans* is the most prevalent pathogens defined in patients with vulvovaginal candidiasis, accounting for approximately 76% to 89% of cases. This is followed by *C. glabrata,* which represents approximately 7% to 16% of cases. Non-*C. albicans* species collectively constitute 11% to 24% of vulvovaginal candidiasis cases within these countries and regions (Spinillo et al. 1997; Holland et al. 2003; Richter et al. 2005).

Numerous studies have indicated an upward trend in the incidence of invasive candidiasis within the United States of America when compared to Australia, Latin America, Europe and Canada. Population-based studies in the United States of America have reported incidences ranging from 9.5 to 26.2 cases of invasive candidiasis per 100,000 participants (Cleveland et al. 2015).

In contrast, most European countries including Iceland (Asmundsdottir et al. 2013), France (Bitar et al. 2014), Sweden (Ericsson et al. 2013), Norwegian (Hesstvedt et al. 2015) and Finland (Poikonen et al. 2010), have reported lower incidences of 2.9 to 5.7 cases per 100,000 population. Interestingly, Spain and Denmark have both reported incidences exceeding 8 cases of candidemia per 100,000 populations (Arendrup et al. 2011; Puig-Asensio et al. 2014). Australia and Canada exhibit candidemia rates that are similar to those observed in European surveillance, with incidences of nearly 3 cases per 100,000 participants (St-Germain et al. 2008; Chapman et al. 2017). Furthermore, certain Asian and African countries have indicated a higher prevalence of fungal species, particularly *C. glabrata*, in cases of vulvovaginal candidiasis. The distribution of *Candida* sp. in China closely resembles that observed in the United States. (Holland et al. 2003; Richter et al. 2005). Higher rates of non-*C. albicans* species have also been observed in specific populations such as HIV-infected women (Spinillo et al. 1997), postmenopausal women, and women with uncontrolled diabetes, regardless of HIV infection (de Leon et al. 2002). Interestingly, an association has been observed between increasing age and a higher proportion of other *Candida* species in females with vulvovaginal candidiasis (Holland et al. 2003). *C. glabrata* is the most commonly isolated among all species. These findings underscore the prominence of identifying *Candida* species and their sensibilities in high-risk females with both *C. albicans* and non-*C. albicans* vulvovaginal candidiasis in order to ensure influential treatment strategies.

2.3. Antifungal Resistance of *Candida* species from Vaginal Candidiasis

The treatment of *Candida* species presents a distinct challenge due to their inherent resistance mechanisms, necessitating substantially higher concentrations of antifungal drugs compared to planktonic cells (Barantsevich and Barantsevich 2022). These species have developed resistance through various mechanisms, including nutrient sensing, glucose starvation, and heightened oxidative stress responses, enabling their survival in the presence of antifungal components that trigger the concentration of reactive oxygen species (ROS) (Lopes and Lionakis 2022; Brown 2023). *Candida* isolates obtained from vaginal samples exhibit some resistance patterns that are resilient to antifungal agents in patients with candidiasis. Specially, a remarkable proportion of *C. glabrata* strains display resistance to fluconazole, particularly in cases where patients have indwelling catheters, resulting in fungal infections characterized by *C. glabrata* embedded in biofilms. Instead of the resistance to fluconazole *Candida* cells related

to biofilm often illustrate a high level of resistance to azoles, including amphotericin B (AmB) (Sobel et al. 2000).

Fluconazole is commonly preferred as a first-choice antifungal therapy to combat mucosal candidiasis, caused by *Candida albicans* and *Candida parapsilosis*. However, resistance to fluconazole is widely distributed among various *Candida* species, such as *Candida auris, Candida krusei* and *Candida glabrata*. These strains display high level of minimum inhibitory concentrations (MICs) for fluconazole ($\geq$64mg/L), indicating resistance to the antifungal agents (Chowdhary et al. 2016). Besides, these species can also exhibit resistance to other antifungal classes, including azoles, amphotericin B and even echinocandins (Arendrup and Patterson 2017; Chowdhary et al. 2018). The progress of antifungal resistance in *Candida* species is subject to various molecular mechanisms, depending on target gene mutation, enhancement of target expression, impaired intracellular conversion of drugs, increased activity of efflux pumps and decreased uptake of antifungal drugs (Jensen et al. 2015; D. Sanglard 2016). These alternatives may support the improvement of novel antifungal drugs, the identification of new applications for established drugs, the synergistic combination of existing drugs, or the advancement of biological therapies targeting virulence factors on *Candida* metabolism (McCarthy and Walsh 2017).

It is pivotal to address the growing challenge posed by candidiasis, which has infectious agents to exhibit resistance to conventional anti-fungal drugs. Despite the development in understanding of the mechanisms and treatment strategies against *candida* infections, there is still a need to develop effective alternative strategies to combat fungal pathogens (McCarthy and Walsh 2017). In this context, MSCs and their anti-fungal activity could provide emerging evidence as a therapeutic option for the treatment of vaginal candidiasis.

3. MSCs and Their Anti-fungal Activity

MSCs can be obtained from a variety of origins such as placenta, adipose tissue, Wharton's jelly, bone marrow, uterus, umbilical cord, dermis, amniotic fluid, peripheral blood, periosteum, skeletal muscle and dental pulp (Vizoso et al. 2017). In accordance with the "International Society for Cellular Therapy" , it has been defined that MSCs exhibit the following characteristics: (i) adherence to plastic surfaces (ii) expression of specific stem cell markers (e.g., CD29, CD44, CD73, CD90 and CD105), while lacking expression for hematopoietic markers (CD45 and CD14), endothelial markers (CD31 and CD34) and also HLA-DR surface

molecules, and (iii) the ability to be speciliazed in vitro into chondroblastic, osteoblastic and adipocytic cells (Dominici et al. 2006). MSCs have a specific talent for differentiating into multiple cell lineages and displaying widely immunomodulatory characteristics towards the congenital and acquired immune system. These properties are modulated by the release of soluble factors, including interleukins (IL) and interferons (IFN) (Zhang et al. 2020; Oh et al. 2021). Both clinical and experimental studies have supported the immunosuppressive capabilities of MSCs to treat a variety of invasive autoimmune illnesses. MSCs have been shown to downregulate the immune cells, such as B and T lymphocytes, natural killer (NK) cells and dendritic cells (Aggarwal and Pittenger 2005). MSCs can also secrete soluble proteins including interleukin-10 (IL-10), tumor necrosis factor- α (TNF-α), prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), and interleukin-17, by which these proteins potentiate their antimicrobial effects (Yang et al. 2013; Alcayaga-Miranda et al. 2017).

Up to the present, stem cell-based therapy has shown promise in the treatment of immune diseases. While significant progress has been made in utilizing MSCs to address infectious diseases and their associated complications, there is limited research focusing on their potential as a host response against fungal infections (Keshtkar et al. 2022). Several cytokines that are expressed at high levels have been identified to possess antifungal potentials, including Chemokine (C-C motif) ligand (CCL- 5 and CCL-6), IL-6, IL-8 and IL-17. Among them, IL-17 plays an important role in mucocutaneous syndrome to tackle *Candida albicans* (Ling et al. 2015). Although the conventional mechanism of cytokine action involves cell signaling based on immune system, supporting document suggests that cytokines can be directly exerted to disrupt fungal pathogens. Notably, a study has shown that IL-17 can attach to the receptor of *Candida albicans,* leading to the prevention of fungal growth (Zelante et al. 2012). Moreover, Li et al. have observed that IL-17 exhibits a direct inhibitory effect on the proliferation of various eukaryotic cells, including neural stem cells, leading to a significant decrease in the number of neural precursor cells. Although purely and simply hypothesis, it is plausible that same inhibitory effect may occur against *Candida* cells. Thus, apart from its known proinflammatory function through immune system activation, IL-17 might also be exerted to restrain the proliferation of *Candida* cell (Li et al. 2013). In the context of adipose stem cells, specifically human umbilical cord-derived MSCs (hUCESCs), studies have shown elevated levels of IL-17. This heightened interleukin production with antifungal properties is not a characteristic observed in all MSCs, but rather a distinct feature of hUCESCs, likely

developed as an evolutionary response to *Candida* strains in the vagina, particularly in the conversion part of the cervix (Schneider et al. 2016). Consequently, the use of stem cells other than conventional drugs for the treatment of vaginal candidiasis may potentially be quite effective.

4. The Therapeutic Applications of MSCs against Vaginal Candidiasis

The NIH Clinical Trial Database currently contains over 1000 registered clinical trials focused on MSC therapy. Among these trials, approximately 47.1% (491 trials) are specifically targeting immune disorders. Within this subgroup, there are 2 trials focused on fungal infections and 5 trials conducted on infected individuals with vaginal diseases (source: https://ClinicalTrials.gov/ ; accessed on 8 June 2023). The trials addressing fungal and vaginal diseases primarily involve the transplantation of autologous or allogeneic MSC through local injection to treat some diseases including fistulas, rectovaginal fistulas, and Crohn's disease of vulva. Allogeneic MSC are more commonly used due to their ability to be expanded in large quantities and fully characterized before administration, offering greater convenience in terms of cell dose availability. MSCs possess the capability to react to immune response in the host and also release various soluble factors, leading to immunomodulatory properties. As a result, the therapeutic potential of MSCs has evolved from primarily focusing on their regenerative effects to encompassing their anti-inflammatory properties, as well as other notable attributes such as angiogenesis promotion, anti-oxidative stress effects, anti-tumoral and antimicrobial activities (Fernández-Francos et al. 2021).

Certain sources of MSC have gained attention for their potential in specific therapeutic indications. For instance, MSC sourced from reproductive tissues have shown promise in terms of their anti-tumor activity (Schneider et al. 2016). hUCESCs have been recognized for their immunomodulatory properties (Eiró et al. 2014), while MSC derived from dental pulp have demonstrated potential in addressing neurological disorders (Apel et al. 2009). The regenerative effects of MSC have been primarily attributed to paracrine signaling (Bluguermann et al. 2013), whereby MSCs also release a range of growth factors, which comprise vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor as well as transforming growth factor (TGF-β1 and TGF-α), among others. These factors contribute to the increased proliferation of endothelial cells as well as their proliferation (Park et al. 2018; Ahangar et al. 2020). In addition to, MSCs have been reported to encourage the survival and reinforce the

regeneration of epithelial cells in the colon, by means of EVs including growth factors and cytokines (Shi et al. 2019; Sendon-Lago et al. 2021).

The immune response of the human body includes innated and acquired immune responses to combat infections. Within the scope of innate immunity, antimicrobial peptides (AMPs) play a crucial role by exerting antimicrobial effects and modulating the immune system, thereby reducing pathogen virulence (de Oca 2013). MSC have been found to directly contribute to antimicrobial activity through the release of AMPs. These peptides can induce the destruction of membrane integrity in microbial cells and interact with peculiar intracellular adhesion molecules to combat microbial agents (Alcayaga-Miranda et al. 2017; Marrazzo et al. 2019; Yagi et al. 2020). Several AMPs have been identified as effective against *Candida*, including human beta-Defensins (HBD), histatins, cathelicidin LL-37 Peptide (Edgerton et al. 1998; Joly et al. 2004; López-García et al. 2005). LL-37, in particular, exhibits a wide range of antimicrobial effect against both bacterial and fungal diversity as well as viral diseases (López-García et al. 2005; Peter et al. 2007; Wang et al. 2019). Multiple investigations have demonstrated the talent of LL-37 to disrupt the cellular membrane and lipid vesicles of certain bacteria (Henzler-Wildman et al. 2004). LL-37 has also been demonstrated to interact with the cell wall of *C. albicans* (Tsai et al. 2011). These findings match a study by den Hertog et al., which indicated that LL-37 can interfere in planktonic *C. albicans* to disrupt the plasma membrane and the cell wall of fungal cells (Hertog et al. 2006). Another study showed an efficient antifungal activity of LL-37 against *C. albicans* (López-García et al. 2005). HBD also possess fungicidal activity against *C. albicans* (Joly et al. 2004). In the presence of *C. albicans,* an increase in HBD-2 level was observed in the female genital tract (Kotani et al. 2020). These findings have shown a positive correlation between the presence of Lactobacillus and *Candida* spp., and the activity of HBD-2. Moreover, HBD-2 has shown efficacy in decreasing the amount of fungus in a mouse model of vaginal candidiasis (Liao et al. 2017).

Emerging clinical research has indicated the significant involvement of MSCs in antimicrobial activity. MSC therapy has also shown efficacy in facilitating prompt control in patients with invasive Aspergilllus infections, under the favour of hematopoietic stem cell transplantation (Ozdoğu et al. 2014). Investigations have indicated the efficiency of human cathelicidin LL-37 and its parts LL13-37 and LL17-37, in which this AMP displays comparable potency to restrain the growth of C. albicans. However, the death of C. albicans cells may also be attributed to other intracellular targets as well as LL13-37 fragments (Wong et al. 2011). In the case of patients

with agonising neutrophilic bronchial asthma, implementation of MSCs has been shown as a promising treatment by reducing Aspergillus-induced inflammation and improving diseases symptoms with the help of detention of the Th_{17} signaling pathway (Lathrop et al. 2014). Collectively, subsets of MSCs displaying the aforementioned characteristics hold potential to be valuable *candida*tes for addressing and combating infectious diseases. Further validations of these findings through additional research may open new avenues for innovative therapeutic strategies aimed at addressing vaginal candidiasis.

5. Conclusion

Vaginal candidiasis is a type of infectious diseases that is closely associated with the pathogenic mechanism of microorganism and is susceptible to a wide range of infectious pathogens due to its unique microbiome. Within this context, the follow-up of MSC-based therapy has the potential to influence the development, progression, prevention and containment of the disease. MSCs also play a remarkable role in regulating the host immune system in microbial infections. Furthermore, MSCs can be employed in the diagnosis of infectious diseases. Considering the significance of addressing vaginal infectious diseases and the convenience of using cell-based therapies, MSCs can be regarded as a viable and accessible option for the treatment of vaginal candidiasis. However, further extensive studies are needed in the future to explore their full potential and efficacy in this context.

The pathogenesis of *Candida* species is complex, posing challenges in finding an effective therapeutic strategy that comprehensively deals with various clinical applications. The therapeutic potential of MSCs has evolved over time, transitioning from autologous to allogeneic MSC applications and from the initial focus on their remedial effects to encompass anti-inflammatory, anti-tumor, antimicrobial and anti-oxidative stress properties. These advancements in understanding open up new possibilities for developing therapeutic strategies for vaginal candidiasis. MSCs have demonstrated the ability to counteract fungal infections, suggesting their potential as a defence mechanism against vaginal infections. Incorporating nanotechnology-based advancements can further optimize MSC-based therapeutic applications in clinical practice. These advancements pave the way for designing innovative therapeutic approaches against the diverse and intricate therapeutic targets associated with vaginal candidiasis using cell-based therapies.

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