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Review Article

Dendritic Cells Trained Immunity: A Revolutionary Therapy in Genitourinary Tract infections

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Abstract:

Genitourinary Tract infections (GTI), including both vulvovaginal candidiasis (VVC) and urinary tract infections (UTIs), represent a significant burden on public health, affecting millions of women worldwide. These conditions not only impact the quality of life of patients but also incur high healthcare costs due to the need for recurrent treatment and management of complications. The mainstay of treatment for these conditions has traditionally been antibiotics and antifungals. However, overuse of these medications is linked to antibiotic resistance and adverse effects. Dendritic cell trained immunity is an innovative, state-of-the-art reprogramming therapy that offers a revolutionary approach, especially when conventional vaccines are unavailable or for individuals experiencing recurrent infections. Novel studies have demonstrated that these glycoconjugates induce long-lasting epigenetic changes in dendritic cells (DCs), initiating a trained immunity effect that extends protection against subsequent microbial exposures. The aim of this study is to present the latest evidence on the treatment of recurrent genitourinary tract infections, highlighting the potential of dendritic cell trained immunity as a significant breakthrough in gynecological care. This innovative approach not only represents a shift from traditional treatment methods but also offers hope for more effective and sustainable management of recurrent infections, ultimately improving patient outcomes and reducing the burden on healthcare systems.

Keywords: genitourinary tract infections; urinary tract infections; dendritic cells; trained immunity; immunotherapy

1.Introduction

Vulvovaginal candidiasis (VVC) remains one of the most frequent infections in women, predominantly caused by Candida albicans [1] RVVC affects approximately 138 million women annually (range 103–172 million) worldwide [1]. It is estimated that up to 75% of women of childbearing age will experience a VVC episode in their lifetime. Of these, about 5 to 20% will face recurrent episodes, defined as three or more infections per year. The highest attack rates are observed in women aged 25 to 34." [2]. This often results in physical discomfort, emotional distress, and high medical costs due to frequent consultations and treatments. The morbidity associated with RVVC can negatively affect women's personal and professional lives, harming their relationships and work performance. Apart from clinical suffering or morbidity, both sporadic and RVVC impose an enormous cost on individual patients and healthcare systems. In high-income countries, the economic burden from lost productivity exceeds $14 billion annually [1].

Similarly, urinary tract infections (UTIs) are bacterial infections that primarily affect the bladder and urethra, and are especially prevalent among women due to the anatomy of the female urinary tract. About 60% of women will have at least one UTI during their lifetime, with 30% to 40% experiencing recurrent rUTIs.

Recurrent UTIs represent a considerable burden for both patients and healthcare systems, potentially leading to severe complications, including pyelonephritis and kidney damage if not properly treated [5]. The indiscriminate use of antibiotics to treat asymptomatic bacteriuria in individuals without risk factors contributes to the emerging crisis of antimicrobial resistance, highlighting the need for more judicious treatment practices [5].

Hundreds of millions of women worldwide suffer from UTIs annually, with significant costs associated with treatment, including medications,

laboratory tests, and hospitalizations. Effective prevention and management of these infections are crucial to reducing economic impact and improving patients' quality of life [5].

This article provides a comprehensive overview of genitourinary tract infections, highlighting their epidemiology, economic impact, and current treatment approach limitations. It also discusses advances in trained immunity. A deeper understanding of these aspects is essential for developing effective trained immunity immunotherapy strategies for the prevention and management of genitourinary infections, contributing to the improvement of women's health globally.

1.1 Applications and limitations of antibiotics and antifungals in prophylaxis

The main pathogen remains Candida albicans as the dominant pathogenic species, but the less frequent and the most common being Candida glabrata.

Although not life-threatening, VVC causes severe itching, soreness, vaginal irritation, and interferes with normal sexual relations. These symptoms and manifestations are considerably magnified when attacks are frequent, recurrent, and particularly when the disease is refractory to conventional therapy.

C. albicans or VVC, both as topical and systemic agents [1, 3]. Regimens are available as single-dose and multidose, both by prescription and over the counter.

Physicians have increasingly tolerated and often encouraged self-treatment; a growing practice facilitated by the availability of over-the-counter drugs. Over the past two decades, oral fluconazole has progressively dominated azole consumption due to its efficacy, safety, and availability as a generic product. Additionally, several maintenance regimens of fluconazole are widely used for recurrent vulvovaginal candidiasis (RVVC). For three decades, fluconazole has been the favored drug of choice for treating oral and vaginal (i.e., superficial or mucosal) candidiasis [1].

However, concerns about fluconazole-resistant VVC continue to grow, particularly as resistance to fluconazole is widely recognized in Candida species, notably C. glabrata and C. albicans, though fewer epidemiological studies have addressed this issue [6–8]. Reports indicate that fluconazole resistance is becoming an increasingly significant clinical problem, especially in women with RVVC [8–11].

The implications of refractory vaginitis caused by fluconazole-resistant C. albicans are numerous, leading to chronic and often severe vulvovaginal symptoms, exacerbated by the limited availability of alternative therapeutic options. Although suppressive therapy with fluconazole and antibiotics can maintain control of RVVCs, achieving effective results has become increasingly difficult due to the high levels of resistance to this drug [12].

However, the use of ketoconazole and itraconazole are good options for occasional episodes or suppression; they are not indicated for maintenance treatment due to significant side effects [13].

Urinary tract infections (UTIs) are among the most common health issues globally, particularly impacting women.Often these women rely on long-term antibiotic prophylaxis; however, with the alarming global rise in antibiotic resistance, there is a growing urgency to find alternative antibiotic-free treatment options. The problem is such that the WHO implemented a global action plan in 2015 to tackle antimicrobial resistance [3,4]

1.2 Importance of Innate and Adaptative Immunity

The innate immune response is a crucial factor in the defense against Candida infection. It is responsible for the destruction of the pathogen and functions as a physical barrier against this microorganism. Through morphological alterations, yeasts transform into hyphae and penetrate epithelial cells by two mechanisms: induced endocytosis and active penetration [14].

In addition, macrophages display potent candidacidal activity, producing inflammatory cytokines and chemokines that recruit immune cells to the site of infection. Among the recruited cells, the most important and most potent for the elimination of Candida are neutrophils, which are the only cells capable of successfully inhibiting the germination of yeasts into hyphae [15].

The recognition of pathogen-associated molecular patterns (PAMPs) is a crucial stage in the activation of the rapid immune response. These molecular patterns are recognized by receptors such as the mannose receptor, Toll-like receptors (TLRs), and the dectin-1 receptor. The main TLRs responsible for the recognition of Candida are TLR2 and TLR4, which are bound to the membrane and recognize the constituents of the fungal cell wall [15].

The cell wall of C. albicans is composed of two layers: the outer layer presents mainly O- and N-linked glycoproteins that consist of 80-90% mannose, the inner layer contains skeletal polysaccharides of chitin, β-1,3-glucan, and β-1,6-glucan, which strengthen and model cells. These polysaccharides represent the main PAMPs that are recognized by host receptors (PRRs) [15].

In this process, the C-type lectin receptors (CLRs) are very important as they are responsible for the recognition of β-1,3- glucan and β-1,6-glucan. The most studied β-glucan receptor is dectin-1, which is expressed by monocytes and macrophages. In addition to inducing direct cell activation, dectin-1 also broadens the response by binding to TLR2 and TLR4 [16].

When the infection is not controlled by innate immunity, adaptive immunity begins to act. Dendritic cells (DCs) carry out the presentation of fungal antigens to activate the response of Th cells. The most important cytokines in the evolution of Candida-specific Th cells are IL-17 and IFNγ [16]. Furthermore, the production of IL-17 by Th17 cells is important for host defense. These cells are responsible for recruiting and activating neutrophils, as well as activating epithelial cells and releasing antifungal β-defensins [17].

1.3 β-glucans as Innate and Adaptative Immunity Training Driver

In addition to the benefits observed in the treatment of candidiasis, the application of β-glucan also shows promise in recurrent UTI.

As stated, these carbohydrates play crucial roles in physiology and pathophysiology, such as cell interaction and signaling, inflammation, and pathogen-host adhesion/recognition. Therefore, glycoconjugated polysaccharides are being used as adjuvants, carriers for antigens, and as targets for vaccines and immunostimulants for RVVC and a large spectrum of rUTIs patogens.

An improved understanding of the immune system and identification of specific and relevant polysaccharide structures have led to the development of glycoconjugated vaccines and immunostimulants. Resistance to antibiotics and chemotherapeutics has increased scientific interest in such preventive and therapeutic strategies [18].

One of the most important phases in the development of these strategies is the creation of alternatives to using aluminum- based adjuvants. Among the numerous categories of particulate antigen delivery systems, such as immune-stimulating complexes, liposomes, micro- and nanoparticles, and virus-like particles, Saccharomyces cerevisiae-derived β- glucan holds major relevance. β-1,3- glucans are structurally complex carbohydrates, usually isolated from yeast (Saccharomyces cerevisiae) cell walls. This yeast is characterized by a high glucan content (85% β-1,3-D-glucan polymers) [19].

Polysaccharides such as β-glucan can serve both as immunostimulants and as vector systems for efficient antigen delivery to immune cells. The major β-glucan receptors in mammals are dectin-1 and complement receptor 3 (CR3, CD11b/CD18). It has been reported that stimulation via dectin-1 primes Th1, Th17, and cytotoxic T lymphocyte responses, upregulates cell surface presentation of MHC molecules and co-stimulation molecules, and induces the production of inflammatory cytokines [20].

β-glucans, as smart antigen carriers, enhance immunostimulant responses. An antigen delivery system using antigen- loaded glucan particles has shown strong humoral and cytotoxic T cell immune responses and activation of dendritic cells. Subcutaneous administrations of β-glucan microparticulate formulations produce strong antigen-specific antibody production and T cell responses, including cytokine production (IFN-γ and IL-17a) by CD4+ Th1 and Th17 cells [20].

A Brazilian study showed through several assays that β-glucan may be considered an efficient immunomodulator that triggers an increase in the microbicidal response of neutrophils for both species, Candida albicans and Candida glabrata, isolated from vulvovaginal candidiasis [21].

This effect of β-glucan is consistent with several other studies that reported β-glucan as an immunomodulator that improves the human response to infections [22,23]. Recently, this ability to boost innate immunity as well as enhance adaptive responses has been termed "Trained Immunity", a new concept that open a new horizon for immunostimulants [24]

1.4 Trained Immunity as a New Horizon for Immunostimulants

Trained immunity is an emerging concept linked to the capacity of the innate immune system to develop immunological memory. Repeated encounters between a pathogen and classical innate immune cells trigger cellular changes at epigenetic, transcriptional, and functional levels that accelerate future defense against the same or an unrelated pathogen [24].

Trained immunity enables the immune system with the ability to 'remember' and 'train' cells through metabolic and transcriptional reprogramming, allowing them to provide a faster, more robust, and nonspecific defense against a wide array of pathogens during subsequent encounters. [23].

The efficient regulation of immune homeostasis and the promotion or inhibition of immune responses are required for a balanced response. Trained immunity- based vaccines can serve as potent immune stimuli, helping to clear pathogens from the body through multiple or heterologous effects and conferring protection against both nonspecific and specific pathogens [25].

The concept of trained immunity has been used to guide the development of vaccines and immunostimulants aimed at promoting host resistance against a wide spectrum of pathogens. Trained immunity aims to stimulate broader responses, increasing the nonspecific effector response of innate immune cells (e.g., monocytes/macrophages) to pathogens and harnessing the activation state of dendritic cells to enhance adaptive T cell responses to both specific and unrelated (bystander) antigens [24].

As trained immunity is triggered by pattern recognition receptors (PRRs), these formulations include microbial structures containing suitable PRR-ligands, such as whole inactivated bacteria, bacterial lysates, and organelles. The concept of trained immunity is emerging, and several current anti-infectious vaccines, immunostimulants, and adjuvants already fall into this category [24].

Many studies have been conducted with bacterial and fungal formulations. These formulations confer protection against a broad spectrum of pathogens, such as viruses, through a mechanism mediated by trained immunity. These findings open a new horizon in immunostimulants strategy to develop formulations that fit into the trained immunity category [23].

1.5 Trained Immunity" in genitourinary Tract infections

Dendritic Cells Trained Immunity is a novel, state-of-the-art reprogramming therapy that represents a revolutionary strategy. The capacity of trained immunity to promote responses beyond their nominal antigens is game-changing when conventional vaccines are not available or when recurrent infections arise in susceptible individuals [24].

Recurrent (RUTIs) and recurrent vulvovaginal candidiasis (RVVCs) are major healthcare problems.

with high socio-economic impact. Antibiotic and antifungal prophylaxis for RUTIs and RVVCs remain the gold standard treatments, contributing to the rise of antimicrobial resistance, microbiota alterations, and co-infections. Some progress has been made in the gynecological field. Currently, there are a few available trained immunity formulations. Spain and Brazil are at the forefront with "named patient preparations" [27].

E. coli, P. vulgaris, K. pneumoniae, and E. faecalis are considered to produce the major RUTIs. The development of trained immunity immunostimulants glycoconjugated with mixtures of these microorganisms, consisting of whole-cell heat-inactivated in equal proportions (Escherichia coli 25%, Klebsiella pneumoniae 25%, Proteus vulgaris 25%, and Enterococcus faecalis 25%) targeted to the dendritic cells, was evaluated. These formulations showed clinical efficacy for the prevention of RUTIs and promoted dendritic cells' trained immunity responses on Th1/Th17 and IL-10 immune responses.

Data showed remarkable clinical success for the management of RUTIs in young women and frail elderly. These trained immunity formulations emerge as valuable immunoprophylaxis, contributing to an improvement in patients' quality of life [27, 28,29,30].

Currently, studies show that glycoconjugates (Saccharomyces cerevisiae) target DCs, increasing allergen uptake, increasing IL-10 production and PD-L1 expression, and promoting the generation of functional allergen-specific Treg cells of FOXP3, both in vitro and in vivo. These tolerogenic features are impaired by aluminum-based adjuvants [26].

Combining the clinical efficacy of two trained immunity formulations, heat-inactivated Candida albicans was mixed with E. coli, P. vulgaris, K. pneumoniae, and E. faecalis in aluminum-freeglycoconjugated immunostimulants. Clinical evidence reports that these mixed formulations imprint human dendritic cells (DCs) with the capacity to polarize potent IFN-γ- and IL-17A-producing T cells and FOXP3+ regulatory T (Treg) cells and also promote metabolic and epigenetic reprogramming in human DCs, which are key molecular mechanisms involved in the induction of trained immunity. Clinical studies uncover immunological mechanisms underlying the potential mode of action of the mixed formulation, revealing its efficacy and clinical relevance as an efficient and suitable approach for concomitant genitourinary tract infections (GUTIs) aligned with the trained immunity immunostimulants strategy [27].

1.5 Conclusions and future perspectives

(rUTIs and recurrent RVVC pose significant healthcare challenges with substantial socio-economic impacts. Traditional antibiotic and antifungal prophylaxis, while standard, contribute to the escalating issues of antimicrobial resistance, microbiota disruption, and co-infections.

As recurrent genitourinary infections continue to account for a significant portion of global infections requiring antibiotics and antifungals, research in this field is intensifying. Recent reviews highlight the potential of new preventative measures in treating these infections, with a particular focus on immunostimulant immunotherapy.

Immunostimulant immunotherapy leverages the patient's own immune system through trained immunity, a groundbreaking approach that reprograms dendritic cells to enhance immune responses. This revolutionary concept promises to transform the management of recurrent infections by developing.

formulations that align with trained immunity principles.

Combining proven clinical efficacy with the ability to prevent recurrent infections, trained immunity immunostimulants mark a major advancement in the field. Future research should delve deeper into the mechanisms of trained immunity and innovate new immunostimulant formulations, aiming to significantly improve the quality of life for women battling recurrent genitourinary infections.

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