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Types of Fungal Vaccines

Nada Fadhil Abbas*[1], ALdhahi Hasan Issa*[2]
[1]Dept. of Biology/ College of Science/ Univ. of Misan /Iraq
[2]College of Dentistry, University of Misan

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ABSTRACT

Fungal infections considered a very important disease in recent years, especially among immunocompromised patients. Several types of vaccines have been developed and tested against differenttypes of pathogenic fungi such as Aspergillus, Candida, Coccidomyces, and others, to test their advantages and disadvantages of each vaccine and the beneficiary group from people. There are special vaccines for each pathogen, such as attenuated and recombinant (subunit) vaccines, nucleic acid and nanotechnology-based vaccines. There are broad-spectrum vaccines that are composed of molecules common to the cellular structure of most types of fungi e.g. β-glucan molecules.

Keywords: Fungal infections, Vaccination, Immunotherapy

I. INTRODUCTION

Vaccine isan antigen suspension obtained from a pathogen.Vaccines are frequently given to healthy people in order to boost their immune system's response to infectious diseases.Therefore, vaccination is a type of immunoprophylaxis, or immunization-based disease prevention. Due to their enormous impact on lowering the incidence of illness and mortality from several illnesses that once had devastating consequences on civilization, vaccines have had a huge positive impact on public health (Jenni et al., 2019).Patients with weakened immune systems were more prevalent within the last few decades. The main causes of this are longer hospital stays, improvements in medical care, acquired immunodeficiency (such as HIV infection), at-risk patient preventive treatments, or treatment-induced immunodeficiency in patients receiving solid organ transplants, anticancer therapy, or hematopoietic stem cell transplants (Pappas et al., 2010). Due to the intricate underlying immunological dysfunction, these patients are highly vulnerable to serious infections, ranging from invasive deep-seated infections (Brown et al., 2012). Various mycoses still have unacceptablely low success rates, even with the newest antifungal drug additions to our arsenal, and anti-fungal drug therapy canusually be limited by high cost, toxicity and resistance. Alternative methods of treatment and prevention, such as vaccinations and passive immunotherapy, are being explored to get around these challenges (Tesfahuneygn and Gebreegziabher, 2018).Vaccination has been of the most significant advances in the field of public health over the last century, which improved and protected people's quality of life everywhere. According to reports based on analyses of several vaccines against infectious agents, vaccinations are said to avert 6 million deaths globally each year(Leibovitch and Jacobson, 2016). The significance of the fungal infection treatments and methods of prevention is underscored by the increase in the number of high-risk groups who are under the exposure ofIFIs (i.e. invasive fungal infections) those days, which include bone marrow transplant recipients, patients with AIDS, cancer patients who undergo chemotherapy, and patients with all other diseases that lead to immune deficiencies after extended stays at the hospitals (Edwards et al., 2012; Amorim et al., 2013). IFIs could be given to the patients who undergo intra-arterial or intravenous catheter treatment procedures besidesvarious antibiotics (De Amorim et al., 2013). Taking under consideration that different invasive mycoses prefer infectingimmune-compromised people, identifying target group for fungus vaccination is amongst the earliest and most complex problems in this field (Lorena et al., 2021). The increased rate of fungal infection incidence and prevalence worldwide, with the opportunistic infection agents being specifically concerning, is the main reason behind the need for fungal vaccines. As a significant global health danger, fungal infections are responsible for about 1.50 million death cases each year. This almost equals the number of the death cases that result from tuberculosis and HIV and more than the number of the death cases that result from malaria (Bongomin et al., 2017).

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II. HOW TO USE VACCINES TO PREVENT FUNGAL INFECTIONS

Inactivated and Live-Attenuated Vaccines

This approach that includes the use of heat, radiation, or chemical materials for the elimination of etiological organisms, has been utilized originally for generating the inactivated vaccination. Radiation-induced vaccinefrom *P. brasiliensiscan* be considered as one of the good examples of fungal inactivated vaccination; it was shown to produce protection as well as reducing fungemia and clinical symptoms in mice (do Nascimento etal., 2009). Based on Liu etal. (2012), a new approachthat utilizes heat-killed Saccharomycescerevisiae (HKY) vaccination for induction of protection from non-specific fungal infections can be considered as distinctive pan-fungal vaccination example.

In BALB/c and CD1 mice, HKY vaccine is effective in the prevention of systemic mycosis that is caused by *A. fumigatus, Candida albicans*,and Coccidioides (Liu et al., 2012). In addition to that, it could play the role of therapeutic immunization. Due to the fact that polysaccharide epitopes of *S. cerevisiae* resemble the polysaccharide epitopes of several types of fungus, it appears that fungus can present protection fromvarious other fungus types. Those epitopes are present in its cell walls. FKS (i.e., Formalin-killed *Coccidioides immitis* spherules) vaccination is one of the fungal vaccines in the group. It was the first to provide protection against coccidioidomycosis. It is important to note that such vaccination has shown encouraging outcomes in trials. In instance, the FKS vaccination showed complete protection against a fatal challenge with *C. immitis* in the case when administered intramuscularly to CD-1 mice. However, it was unable to significantly reduce the disease's severity or incidence in phase 3 clinical trials (Inácio et al., 2023).

Comparing the FKS and HKY vaccinations with regard to protection against *C. immitis* challenges in CD1 mice, it was shown that the former produced 100% and 70% protection, respectively (Capilla et al., 2012). Those outcomes are comparable to a live-attenuated *C. posadasiistrain* (Δcts2/ard1/cts3 or ΔT) that has been treated with triple-attenuated vaccine but was unable to endosporulate because two chitinase genes were disrupted. This vaccination, given as two subcutaneous injections separated by 14 days, protected 75–100% of the rats exposed to the pathogenic *C. posadasii* strain C735. (Xue et al., 2009).

According to Xue et al. (2009), the groups emphasized that attenuated strain's live spores have shown less reactogenicity than the mice that received the FKS vaccination. Notable for its capacity to protect against an otherwise deadly *Coccidioides posadasii* intranasal infection, the avirulent strain Coccidioides posadasii CPS1 deletion mutant results in mean residual lung fungal burdens of fewer than 1000 CFU and over 95% survival. (Narra et al., 2016). A new study deserves notice for its groundbreaking work regarding a vaccination against coccidioidomycosis. Mendel et al. (2022) had eliminated Ryp1, a conserved transcription factor in the Coccidioides that is crucial in the formation of both spherules and hyphal. Although immunizing C57BL/6 mice with live Δryp-1 spores didn't appear to provide any protections against deadly *C. posadasii* intranasal infections, our study revealed the first factor of transcription which produces full virulence and spherulation in the Coccidioides (Mendel et al., 2022). Indeed, live-attenuated vaccines are widely employed because, like the impacts of the infectious pathogen itself, they stimulate a strong and persistent immune response. Many studies are currently being carried out in this field to evaluate the application of different strategies using both inactivated and live fungus. Nonetheless, live-attenuated vaccinations have a typically favorable safety profile in the immune-competent people. Yet, they might still result in a dysregulated inflammatory response or an infection in the immune-suppressed people, who are more vulnerable to the fungal infections (Levitz and Santos, 2014) (Inácio et al., 2023).

The reason for this encouraging discovery is that CD8+ T cells independently mediate efficient immunity against antifungal vaccinations and make up for the deficiency of CD4+ cells (Wang et al., 2001). MHC class I restricted CD8+ T cell immunity, which was subsequently mediated through cytokines, like TNF, IFN-γ, and GM-CSF. The present work suggests that CD8+ T cells could be a target for the robust vaccination-induced immunity from the experimental fungal lung infections that result from *H. capsulatum* and Blastomyces dermatitidis(Wuthrich etal., 2003).

A different type of live-attenuated vaccination that produced immunity against Cryptococcosis in mice involved the use of a strain of *Cryptococcus neoformans* that produced gamma interferon. For the first time, a pathogenic fungus was altered genetically to produce a cytokine which has in vivo biological impacts and

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was shown to be protective against the resolution of illness. Owing to protection that is provided by IFN-γ producing CD4+ Th-1 cells against a pathogenic *C. neoformans* strain, "immune-deficient" A/Jcr mice that are infected by IFN-γexpressing *C. neoformans* H-99 strain not just recovered from primary infection, yet demonstrated total resistance against it afterwards (Wozniak et al., 2011).

One of the recent studies has shown that using heat-inactivated or live cryptococcal cells that overexpress ZNF-2, a transcription factor that is associated with *C. neoformans* filamentation, in vaccination can protect the host against a consequent challenge through otherwise deadly wild-type H-99 strain (Lin et al., 2022). In an independent study, mice devoid of CD4+ T cells—a disorder most frequently related to cryptococcosis have been protected against heat-killed *Cryptococcus neoformans* Δsg-l1 mutant which was accumulating steryl-glucosides. Additionally, suchvaccination has been able to lower lung fungal burden and had strong therapeutic benefit, according to Normanile et al. (2022). *A. fumigatus* has been the subject of a similar investigation. Immunocompromised mice were vaccinated against the deadly wild-type *A. fumigatus* strain through administering vaccinations against ΔsglA strain, which lacks sterylglucosidase gene (Fernandes et al., 2022).

It is important to stress that there are problems with administering this vaccination to humans because it is live. In particular, in immunocompromised hosts, it is impossible to guarantee the safety and profitability of attenuated vaccines.. Nonetheless, a number a variety of strategies could be considered for immunizing those who do not have CD4+ T cells, particularly those who are HIV/AIDS patients.

Attenuated vaccinations from viral infections had shown excellent efficacy in immunocompetent patients. An attenuated vaccination from endemic fungal infection could aid in eradicating such illnesses in areas where they have a high prevalence (Levitz and Santos, 2014).

III. TYPES OF FUNGAL VACCINES:

3.1. Live-attenuated vaccines:

The first vaccination to be created with this method which involves destroying etiological organisms with radiation, heat, or chemicals was the inactivated vaccine. The radiation-induced vaccination against *P. brasiliensis* is an excellent illustration of a fungal inactivated vaccine; it was shown to be capable of generating protection and reducing clinical signs and fungemia of mice (do Nascimento et al., 2009). Another notable example of a fungal vaccine which has shown promise in experimental investigations is the FKS vaccine, which was the first vaccination against coccidioidomycosis. In the future, people with good immune system, living in the endemic regions can find such immunizations beneficial in the revention of the endemic fungal illnesses. (Xue etal., 2009; Capilla etal., 2009).

HKS (i.e., heat-killed *Saccharomyces cerevisiae)* vaccinationrepresents a valuable finding serving as pan-fungal vaccination and offering defense from different fungal infections (Liu etal., 2011; Liu etal., 2012). It was observed that the immunization from virulent strains of the endemic fungus with the subcutaneous HKS administration provides some protection. *C.posadasii* (i.e., *Coccidioides posadasii*) (Xue et al., 2009),*C. albicans* and *A. fumigates* (Liu etal., 2012). Additionally, a review of the clinical researches has been performed in order to specify whether fully recombinant *S. cerevisiae*-based therapeutic methods can be created for treating cancer and some viral diseases while boosting the clinical responses, besides the cytotoxic drugs (Ardiani et al., 2009). One major issue with the vaccination is its specificity, which limits the breadth of its effects (Do Nascimento et al., 2010). According to Pirofski & Casadevall (1998), attenuated live vaccinations usually have strong records of safety in the immune-competent individuals. However, in immunocompromised individuals, they could still produce dysregulated inflammatory responses or an infection. Consequently, since immunocompetent people could get endemic fungus, this approach might work best for them. The CDC had recommend that specific live vaccinations be given to a subpopulation of individuals who are immune-compromised. This advice has several exceptions, based on how severe the immunosuppression is.

3.2. Recombinant (subunit) vaccines:

Subunit vaccines consist of one or more pathogen components which can trigger an immune response and have been isolated. Common subunit vaccination types include toxoids, capsular polysaccharides, pure proteins, and recombinant protein antigens. Subunit vaccines, which include one or more pure recombinant proteins or polysaccharides from fungus, are the most researched kind of fungal vaccines. Scientific developments in immunology, microbial pathogenesis, and genetic engineering make it

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easier to create subunit vaccinations that work. This approach's scientific foundation is the production and transfer of a gene which generates immunogenic antigen so as to elicit the intended immune response. Actually, in such process, an inherited gene encodes a portion that is linked to pathogenicity and virulence of the species. To boost immunity and extend immunization, such protein antigens are frequently mixed with some suitable protein carrier or adjuvant, majorly bacterial toxoids. (Olafsdottir et al., 2015; Levitz and Santos, 2014; Cassione, 2008). Adjuvants that cause robust antibody responses are commonly used in this field; these include alum (or aluminum salts, like aluminum phosphate and aluminum hydroxide) (Levitz and Golenbock, 2012;Leroux. 2010).As technology has developed, the production of recombinant DNA vaccines has increased in popularity. This has made it possible to manufacture vaccines in a safer, more economical manner that doesn't require the culture of highly pathogenic organisms and has fewer adverse effects on recipients. Recombinant subunit vaccines have a number of benefits, including the removal of the pathogenic agent, which makes their administration safer overall and especially for individuals with impaired immune systems (Santos and Levitz, 2014). Highly specialized antigens were engineered through the meticulous design, production, and purification of vaccines through the integration of DNA engineering and recombination technologies (Zepp, 2016; Cunningham et al., 2016). With encouraging outcomes, two recombinant Candida vaccines are moving forward with human clinical studies. Initially, PEV7 is composed of virosomes made from recombinant aspartyl-proteinase 2 (Sap-2), which is a protein that is secreted through *C. albicans*. (2018) De Bernardis et al. A phase 1 clinical trial evaluating the immunogenicity and safety of PEV7 was carried out in healthy female participants following the demonstration of protective effects in rats challenged with *C. albicans*. Following vaccination, the 48 women showed varying B-cell memory responses. The immunogenicity and safety of PEV7 were assessed in a phase 1 clinical trial with healthy female participants after the drug's protective benefits against *C. albicans* infected rats were shown. The B-cell memory responses of the 48 women differed after vaccination. Preclinical studies demonstrated that the immunization elicited an immune response and protected mice against species of Candida. Interestingly, animals that were challenged with Staphylococcus aureus did not become infected. This is most likely because of structural similarities between the surface proteins of *S. aureus* and Als3p. NDV-3 induced higher antigen-specific IgA1 and IgG titers as well as enhanced IFN-γ and IL-17A cytokine production in comparison to placebo recipients in phase 1 clinical intervention involving 40 volunteers (Schmidt et al., 2012). A multi-center double-blind placebo-controlled phase 1b/2a trial had been conducted in order to evaluate the efficacy and immunogenicity of NDV-3A vaccination in 188 adult females with RVVC (i.e., recurrent vulvovaginal candidiasis) in light of such results and a positive safety profile(Edwards et al., 2018).

3.3-Conjugate vaccines

A strong antigen, such as a protein, is covalently attached to a weak antigen, typically a polysaccharide, to create a conjugate vaccination. Initiating a strong immunological response is the aim here (Davis and Furman, 2015). The term "T-independent immunity" describes how B cells can produce antibody responses in response to polysaccharide antigens without the help of T cells. Actually, polysaccharide epitopes can be recognized through B cell receptors. However, before antigens can be presented to T cells, they need to bind to peptides (hapten-carrier system), and the peptide needs to be transported by the MHC complexes that are expressed by antigen-presenting cells (APCs). Immunity that is induced by T cells is strong and persistent. T cell responses are elicited by MHC molecules attaching proteins by conjugating a poly-saccharide to protein carrier (Levitz and Lionakis, 2018).

3.4. Nucleic acids vaccines:

The most recent development in vaccine formulation techniques is the use of nucleic acid-based vaccinations. Based on the nucleic acid utilized in the formulation of vaccine, vaccinations based on nucleic acids could be either DNA- or mRNA-based. Pfizer and Moderna's COVID-19 vaccines are the best example of mRNA-based vaccinations (Kumar and Srivastava, 2023).

3.5. Nanotechnology:

Using nanotechnology to develop vaccines is a relatively recent strategy. A target immunogen is attached to or coated on a nanomaterial (beads or nanoparticles). This method works better to increase immunological response than soluble protein immunogen due to its particulate nature. Applying plasma beads coated with cytoplasmic proteins from Candida albicans, for instance,

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stimulates the immune system for fighting Candida infection(Ahmad et al., 2012).

3.6. Pan fungal vaccines:

A vaccination that targets multiple clinically relevant fungi and has broad range activity would be excellent. None of such vaccination candidates have progressed to a point of clinical trials, despite promising preclinical data demonstrating the viability regarding such pan-fungal vaccines. Recent research in mouse as well as nonhuman primate models has shown that the recombinant peptide vaccination NXT2, which is based upon a conserved KEX-1 sequence that is present on several pathogenic fungi, is effective in protecting against pneumocystosis, invasive aspergillosis, and systemic candidiasis (Rayens et al., 2022). The β-glucan-based vaccination CRM-197 has been able to produce protective responses in mice challenged to *C. albicans* and A. fumigates (Torosantucci etal., 2005; Bromuro et al., 2010). Remarkably, beta glucans are strong trained immunity inducers, which suggests that these vaccines might also provide nonspecifically advantageous protection against other pathogenic pathogens including Mycobacterium tuberculosis(Netea et al., 2020).

IV. CONCLUSION

Fungal infections are a global problem, and their prevalence and spread vary depending on local factors like climate, topography, and socioeconomic developments. In their 1st Fungal Priority Pathogens List, WHO had made a rank of a number of fungal pathogens on the basis of their epidemiology, like fatality, annual incidence, global distribution, and treatment effectiveness. The critical group was defined as *C. albicans, A. fumigatus, C. auris, and C. neoformans*. Several Candida species, including *C. glabrata, C. parapsilosis*, and *C. tropicalis,* have been identified as causal agents of Eumycetoma, Fusarium spp., Histoplasma spp., and Murorales in the high priority group. Researchers have lately turned to developing vaccines with the use of molecular approaches in an effort to reduce the incidence regarding such diseases as well as control endemic fungal infections. Other fungi associated with pulmonary infections, like Paracoccidioides spp. and *Pneumocystis jirovecii*, have been placed in the medium group. Patients with compromised immune systems and those with active immune systems are the most susceptible to infection. Despite the efforts of numerous research groups to create vaccines, particularly for the mycoses that the WHO has highlighted in the FPPL, no human fungal vaccine is currently on the market. The development of vaccines is further complicated by the fact that various mycoses are opportunistic and primarily attack people with impaired immune systems. It is also critical to acknowledge that there is still a commercial motivation to produce vaccines against fungi that are restricted in space or for a smaller target group. Developing effective vaccinations against commensal organisms like Candida spp. is a challenging task in vaccine development. In spite of such challenges, vaccinations remain one of the optimal solutions for preventing and treating infectious diseases, such as mycoses, especially in the case when multi-fungal vaccinations are created. In conclusion, the extensive and continuous research being done on fungal vaccinations suggests that the creation of fungal vaccine isn't just feasible, yet also getting closer to reality.

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