Research Progress of Talaromyces Marneffei

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***Abstract*—Talaromyces marneffei has a very high mortality rate and is prone to devastating effects on immunocompromised people, but there is far less attention paid to diseases caused by Talaromyces marneffei are globally. Diseases that caused by Talaromyces marneffei may present with fever, anemia, emaciation, respiratory symptoms, hepatosplenomegaly, lymph node enlargement, and osteolytic destruction. The treatment of Talaromyces marneffei infection is limited, and the commonly used drugs are amphotericin B, itraconazole and voriconazole. In this paper, the biological characteristics, epidemiology, infection and pathogenic mechanism of Talaromyces marneffei were systematically discussed in order to provide theoretical basis for the clinical treatment of Talaromycosis.**

***Keywords*—Talaromyces marneffei, virulence factor, bidirectional fungus, immune system**

I. Introduction

Fungi are everywhere in our lives, and it is astonishing how easily humans can get fungal infections without even recognizing it [1]. We can unwittingly expose ourselves to the possible dangers they carry through consumption or casual contact. Talaromyces, a specific bacterium, has long piqued the interest of medical specialists. Though it was identified in 1959 by Doctor Segretain and initially discovered in China in 1984, its actual nature was not fully known until 2011, when it was isolated from Penicillium through scientific research [2]. Talaromyces contains a wide range of species, including the conditionally pathogenic fungus Talaromyces marneffei. Talaromyces marneffei is the only temperature dimorphic fungus among more than 200 Talaromyces species [3]. Talaromycosis is a dangerous fungal disease that is mostly found in tropical and subtropical Asia. The Talaromyces marneffei causes the disease, which affects approximately 17,000 people per year. Unfortunately, Talaromycosis has a very high death rate [4]. Despite the significant impact of Talaromycosis on immunocompromised persons, particularly HIV-positive people, and the increasing prevalence of non-HIV infected people, the diagnosis and treatment of Talaromycosis remains underfunded globally [5].

Herein, we originally reviewed the biological properties of Talaromyces marneffei in the literature review section. We know that Talaromyces marneffei is the pathogen of epidemic infectious disease, so we'd like to talk about the epidemiological aspects of Talaromyces marneffei, such as the route of transmission among susceptible hosts, and the susceptible population, as well as the clinical aspects, such as the different symptoms of different body systems infected by Talaromyces marneffei, particularly in HIV patients. We explored three main problems in the discussion section: how does Talaromyces marneffei transition from the mycelial phase to the yeast phase, and how does Talaromyces marneffei survive in macrophages, and how these two questions relate to existing Talaromyces marneffei therapeutic techniques.

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II. Biological Characteristics of Talaromyces Marneffei

A. Temperature Dependent Bidirectional Fungi

Talaromyces marneffei is a member of the genus Talaromyces and the only pathogen in the genus Talaromyces capable of biphasic transformation [6]. Biphasic fungi are characterized by different forms under different environments and can transform each other.

Temperature is the core factor to induce the morphological transformation of Talaromyces marneffei, which takes the form of hyphal phase at room temperature and yeast phase at 37°C [7]. At room temperature, Talaromyces marneffei grows in mold form and mycelium differentiates to produce conidium, which is recognized and phagocytic by host macrophages and neutrophils after being inhaled into the lung of the patient. In this process, Talaromyces marneffei biphasic conversion is a response mechanism to evade giant cell immunity. This phase conversion of Talaromyces marneffei is different from other truly characteristic pathogenic mechanisms, and identifying the mechanism of Talaromyces marneffei biphasic conversion is the key to the prevention of Talaromyces marneffei infection.

B. Two Forms of Yeast and Penicilliform

When they were selectively culture the samples of Talaromyces marneffei, they inoculate the mycelial colonies of 1,270 strains into a new culture plate under the temperature of 37°C. During this process, only a portion of the transformed seeds grow colonies. We know that Talaromyces marneffei grows in the mycelial phase at 25°C and transforms into the yeast phase at 37°C [8]. In this transfer culture, only a part of the yeast phase Talaromyces marneffei grows in the 37°C environment. One possible reason is that the gene controlling the transformation of Talaromyces marneffei from the

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mycelial phase to the yeast phase affects the speed of its transformation. The yeast phase takes longer to transition to the mycelium phase, and therefore the rate of colony formation is slower, which means that Talaromyces marneffei does not normally develop colonies at 37°C. In the study of gene editing, it was found that a single gene could affect different forms of Talaromyces marneffei in different environments at the same time. The edited Talaromyces marneffei changed into yeast form with chaotic mycelia at 25°C when it should have been hyphal form. At 37°C, it becomes rhabdoid form, and the edited Talaromyces marneffei also has different morphological changes, such as bleaching, colony thickening and more folds, which can affect the survival of Talaromyces marneffei in organisms. Therefore, we can conclude that the biphasic morphological changes of Talaromyces marneffei are affected by temperature under the regulation of genes, and different morphologies will affect the survival of Talaromyces marneffei in vivo.

C. Long Incubation Period of Talaromyces Marneffei

The incubation period of Talaromyces marneffei varies from individual to individual and is usually a few days to a few weeks. During its survival in the human body, Marneffei first enters the skin or soft tissue through trauma, stab wounds, or contact with damaged skin. Infection with Talaromyces marneffei begins with the inhalation of fungal conidia. During infection, mononuclear phagocytes of the innate immune system, such as macrophages and Dendritic Cells (DCS), play a crucial role. Phagocytosis of Talaromyces marneffei conidia by macrophages promotes its survival within macrophages, thereby allowing it to spread throughout the body [9]. In addition, Talaromyces marneffei has shown the ability to induce macrophages towards M2-like polarization to evade immune responses [10]. Although Talaromyces marneffei has certain means to avoid being destroyed by macrophages, the immune system also responds to Talaromyces marneffei in a number of ways to defeat them. Neutrophils have amazing antifungal activity against Talaromyces marneffei, producing the key neutrophil enzyme myeloperoxidase, which is important for the effective production of antibacterial free radicals [11]. In addition, Talaromyces marneffei has been reported to induce protective autophagy in primary human DC [12]. This series of mechanisms allows Talaromyces marneffei to survive longer in the human body and delay detection by immune cells in the human body as long as possible, thus achieving a long incubation period.

III. Epidemiological Characteristics of Talaromyces Marneffei

Marneffei is an endemic pathogenic bacterium, mainly prevalent in Southeast Asian countries and southern China in addition, in Japan, Australia, Belgium, France, Germany, the Netherlands, Sweden, Switzerland, the United Kingdom, Oman and the United States also have HIV-positive cases of Marneffei disease, most of these patients have a history of travel to Southeast Asia [13]. In areas with high prevalence of the disease, the infection rate of Talaromyces marneffei in hospitalized HIV-positive patients is 4% to 16%. In China, the largest number of cases have been reported in Guangxi and Guangdong, while cases have also been reported in Yunnan, Fujian, Hubei, Chongqing and Hong Kong [14].

A. Hosts and the Transmission Routes

In 1956, researchers first discovered Talaromyces marneffei in the diseased livers of bamboo rats in Vietnam. Several bamboo rat species in southern China, central and northern Thailand, and India, including the Chinese bamboo rat, the silver star bamboo rat, the great bamboo rat, and the small bamboo rat, are also natural hosts of Talaromyces marneffei [4]. A large number of studies have shown that Talaromyces marneffei exists in the soil where bamboo rats live, and the infection of humans, bamboo rats, and even dogs may come from this. Some studies on the genotyping of Talaromyces marneffei strains have found that bamboo mouse isolates have the same genotype as human isolates, but whether exposure to or consumption of bamboo mice is a risk factor for disease remains controversial.

B. Propagation and Growth Conditions

The route of transmission of Talaromyces marneffei is still unclear, and inhalation of airborne conidia and direct inoculation are considered possible modes of transmission [15]. There have been cases of HIV-positive patients infected with Talaromyces marneffei after learning morphological identification of Talaromyces marneffei in non-endemic areas, but no pathogens were found in air samples collected in the teaching building. There have also been reports of local infection caused by direct inoculation with contaminated sharp objects, and cases of Talaromycosis transmitted through organ transplantation.

C. Susceptible Population

Talaromyces marneffei is mainly parasitic in the cell, which has a strong resistance to non-specific phagocytosis, multiple infections in patients with cellular immune dysfunction, such as HIV patients, recipients of organ transplants, patients with hematological malignant, and long-term treatment with steroid hormones or cytotoxic drugs [16]. In HIV-positive patients, most patients with Marneffei have CD4+T-lymphocyte counts of less than 100/μl. Our research group found that HIV patients with CD4+T-lymphocyte count less than 200/μL had a higher risk of infection with Marneffei. Therefore, in Marneffei endemic areas, screening for Marneffei should not be neglected in HIV patients with CD4+T-lymphocyte counts less than 200/μl. The main immune susceptibility factors include: (1) HIV/HIV-positive patients, especially CD4 count <100 cells/mm^3; (2) Acquired adult immunodeficiency syndrome caused by γ-interferon autoantibodies is the most important immune susceptibility factor for non-HIV Talaromyce Marneffei disease in endemic areas of Marneffei in China; (3) Primary immunodeficiency: common in children, including idiopathic CD4 lymphocytopenia, infection

with immune-related genes such as CYBB, CD40L, STAT1/STAT3 GOF mutations caused by immunodeficiency; (4) Secondary immune deficiency factors other than HIV: autoimmune diseases treated with hormones, immunosuppressants, malignant tumors, solid organs or hematopoietic stem cell transplantation.

IV. Clinical Characteristics of Talaromyces Marneffei

A. Classified by Affecting Body Parts

According to the location and characteristics of the disease, it can be divided into boundedness type and disseminated type.

1) Restrictive type

Talaromyces marneffei is confined to the invasion site and causes disease in individual organs. The localized disease is more insidious, and the clinical manifestations are often dominated by the primary symptoms [17]. Localized infections of the skin and subcutaneous tissue often occur in localized subcutaneous nodules, subcutaneous abscesses, or lymph node enlargement. Localized infections of Talaromyces marneffei can easily be misdiagnosed as other infections, such as tuberculosis, histoplasmosis, cryptococcus, and malignant tumors.

2) Disseminated type

The main clinical manifestations of Talaromyces marneffei disease are disseminated type, without specificity. Patients present fever, anemia, emaciation, respiratory symptoms, hepatosplenomegaly, lymph node enlargement and osteolytic destruction [18].

B. Classified by Symptoms

1) Skin and mucosal manifestations

About 40% to 80% of HIV-positive patients with Talaromyces marneffei disease have skin lesions, including umbilical concave rash, papules, nodules, necrotizing papules, acne-like lesions, folliculitis and ulcers, of which umbilical concave rash is more common, similar to molluscum contagiosum, often involving the face, ears and limbs, and occasionally involving the genitals [19]. Mucosal lesions are similar to skin lesions and often involve the mouth, throat, digestive system and genitals.

2) Digestive system manifestation

When Talaromyces marneffei invades the digestive system, the lesions can reach up to the esophagus and down to the colon. Gastrointestinal symptoms are relatively common, and about 10% to 30% of HIV-positive patients with Talaromyces marneffei bacteria have gastrointestinal symptoms [20]. Common gastrointestinal symptoms include abdominal pain, abdominal distension and diarrhea. Some patients have bloody or tarry stools. In addition, systemic symptoms such as fever, anemia, and weight loss may be associated. A physical examination showed mild abdominal tenderness. When Talaromyces marneffei invades the liver, patients may have fever, abdominal bloating, and hepatomegaly, some of which may be combined with liver insufficiency, including mild to moderate elevations in serum AST, ALT, ALP, and total bilirubin levels. Some scholars have made pathological classification of Talaromyces marneffei liver disease, which is divided into diffuse type, granulomatous type and mixed type. Patients with granulomatous type have better cellular immune function, patients with diffuse type have worse cellular immune function, and mixed type is between the two.

3) Lymphatic system manifestation

HIV-positive patients with Talaromyces marneffei infection may appear lymph node enlargement, including superficial lymph node enlargement, abdominal lymph node enlargement, hilar or mediastinal lymph node enlargement [21]. Among them, about 26.0% to 67.2% of HIV-positive patients with Talaromyces marneffei infection have superficial lymph node enlargement. The size of the enlarged lymph nodes is about 5~34mm, the node texture is hard, and there is no adhesion or tenderness. Up to 58.0% of HIV-positive patients with Talaromyces marneffei infection have abdominal lymph node enlargement, and the enlarged lymph nodes are widely distributed. Intraperitoneal and retroperitoneal areas can be extensively involved, mainly around the mesenteric branch blood vessels and mesenteric roots, can cause abdominal pain, diarrhea and other gastrointestinal symptoms about 40.9%~81.3%.

C. Clinical Characteristics of HIV-Negative and HIV-Positive Talaromyces Marneffei Infection

There are few reports of nervous system involvement in HIV-positive patients with Talaromyces marneffei disease, which can be manifested as insanity, agitation and depression [22]. Skeletal system involvement is rare in HIV-positive patients, and once skeletal system involvement leads to osteolysis, it may indicate serious systemic disease with poor prognosis and high recurrence rate. The disease most commonly affects the flat and long bones, and most patients also experience swelling and tenderness of the soft tissues and joints around the bone. Skeletal system involvement is relatively common in HIV-negative patients. A study in northern Thailand compared 116 HIV-positive patients with 34 HIV-negative patients and found that HIV-negative patients were more likely to develop bone and joint infections. One study found this symptom in 21 Vietnamese patients, all of whom were isolated the cerebrospinal fluid and found with an overall case fatality rate of 81%. HIV-positive patients with Talaromyces marneffei infection have mediastinal or hilar lymph node enlargement. The enlarged lymph nodes are mainly between 1 and 2cm in diameter, and no obvious necrotic changes have been seen. It needs to be distinguished from tuberculosis, lymphoma and other diseases.

V. Treatments of Talaromyces Marneffei

Induction therapy with amphotericin B is clinically recommended for 10–14 days, followed by consolidation therapy with itraconazole for 10 weeks [23]. Voriconazole may be selected in patients who cannot tolerate amphotericin B induction therapy. Studies have shown that Talaromyce Marneffei bacteria have low

sensitivity to fluconazole and are easy to resist, so fluconazole is generally not recommended.

VI. The Virulence Factor of Bacteria

The substances constituting bacterial virulence are called virulence factors, which are mainly invasive and toxic, and some virulence factors are still unclear [24]. Recent studies have found that the secretion of many important virulence factors in bacteria is related to the secretion system of bacteria.

A. What Is Virulence Factor?

1) Invasiveness

The first step of bacterial infection is colonization in the body, and the premise of colonization is that the bacteria should adhere to the host digestive tract, respiratory tract, reproductive tract, urethra and eye conjunctiva, so as to avoid being cleared by intestinal peristalsis, mucus secretion, respiratory cilia movement and other functions [25]. A crucial element in the colonization process is adhesins, which are all the structural components of the bacteria that have adhesion, usually some macromolecular structural component on the surface of the bacteria, such as the pili of Gram-negative bacteria. Most bacterial adhesins have host specificity and tissue tropism.

The second step in bacterial infection is to overcome the immune clearance of the colonized area, so as not to be cleared by the host, in order to achieve subsequent infection [26].

The first way is to break through the body's defensive barriers. Bacteria have a defense mechanism to interfere with or escape the host. Once the pathogen attaches to the surface of cells or tissues, it must overcome the local defense mechanism of the body, especially to interfere with or escape the local phagocytosis and secreting antibody-mediated immunity, in order to establish infection. At the same time, anti-phagocytosis also plays a role in protecting bacteria from being cleaned by the host. Anti-phagocytosis consists of four key processes. First, it is not in contact with phagocytes, such as destroying the cytoskeleton through exotoxins to inhibit the role of phagocytes. Second, it inhibits the uptake of phagocytes, such as M-proteins from capsules, pili and streptococcus. Third is the survival in phagocytic cells, such as Salmonella certain components can inhibit the lysosome and phagosome fusion; For example, after Listeria is phagocytic, it quickly escapes from the phagosome and enters the cytoplasm directly. Staphylococcus aureus, on the other hand, produces large amounts of catalase, which neutralizes oxygen free radicals in phagocytes. Fourth is to kill or damage phagocytes, bacteria destroy the cell membrane of phagocytes by secreting exotoxins or proteases, or induce cell apoptosis, or directly kill phagocytes.

The second method is the anti-humoral immune mechanism. Bacteria escape bodily fluids to avoid being detected by the immune system and to avoid being harmed by bodily fluids secreted by the immune system. Bacteria escape humoral immunity mainly through three methods, first, antigen camouflage or antigen mutation, the former is mainly on the surface of the bacteria to bind body tissue components, such as Staphylococcus aureus through cell-binding coagulase to bind blood fibrin, or through SPA to bind immunoglobulin. Second, secrete protease to degrade immunoglobulin, and Hemophilus can secrete IgA protease to destroy IgA on mucosal surface. Third, through the action of LPS, OMP, capsule and S-layer, it escapes complement and inhibits antibody production.

The third method is internalization, which refers to the process by which certain bacteria can enter phagocytes or non-phagocytes after adhering to the cell surface. Once bacteria lose the ability to enter cells, virulence decreases significantly. The significance of internalization for bacteria is that through this translocation, bacteria enter deep tissues or enter the blood circulation, so that bacteria can spread from the primary focus of infection to the whole body or more distant target organs. Host cells provide a small environment and shelter for bacteria to proliferate, allowing bacteria to escape the killing of the host immune mechanism.

The third step is to proliferate in the body. After successfully avoiding elimination from the immune system, how bacteria proliferate in the host is the core problem of infection. The rate of proliferation is extremely important for pathogenicity. If the proliferation is fast, bacteria can overcome the body's defense mechanism at the beginning of infection and easily survive in the body. On the contrary, if the proliferation is slow, it is easy to be cleared by the body.

2) Toxin

Exotoxins are toxins produced by bacteria. Exotoxins can cause damage to the host by destroying cells or disrupting normal cellular metabolism. Exotoxin is not heat resistant, unstable, strong antigenic, can stimulate the body to produce antitoxin, can neutralize exotoxin, used as treatment. It can be detoxicated by formaldehyde treatment, made into toxoid, and used as immunoprophylactic agent. Endotoxin is a general term for toxic substances present in Gram-negative bacteria. It is the cell wall component of a variety of gram-negative bacteria, and the toxin released by the cell after lysis is also called "pyrogen". Its chemical composition consists of phospholipid polysaccharide – protein complex, and its toxic component is mainly dactyloid A. Endotoxins are located in the outermost layer of the cell wall, covering the mucopeptide of the cell wall. Exotoxins play a major role in the spread of bacteria through the host and are a key factor. Proteases secreted by bacteria are called extracellular proteases, which have a variety of pathogenic effects, such as activating exotoxins, inactivating complement in serum, etc., and some proteases themselves are exotoxins. In addition, the most important effect is to act on the tissue matrix or cell membrane, causing their damage, increasing their permeability, and conducive to the spread of bacteria in the body. Such common are: 1. Hyaluronidase, formerly known as diffusion factor, breaks down connective tissue hyaluronic acid; 2. Collagenase mainly breaks down

collagen in ECM; 3. Neuraminidase mainly breaks down the intercellular substance of intestinal mucosal epithelial cells; 4. Phospholipase (alpha toxin), which hydrolyzes the phospholipids of cell membranes; 5. Lecithinase, which breaks down the lecithin of cell membranes; 6. Kinases activate plasminogen to fibrinolytic enzyme to break down fibrin and prevent the formation of blood clots; 7. Coagulase, the spread of bacteria in the body can also be accomplished through internalization. In particular, cell-binding coagulase can provide antigenic camouflage for bacteria, so that they are not recognized by phagocytosis or the body's immune mechanism.

3) What are the virulence factors of common bacteria?

Common bacterial virulence factors are first extracellular enzymes, that is, a series of extracellular enzymes headed by hyaluronidase, collagenase, neuraminidase, lecithinase, phospholipase, kinase and coagulase. In addition to extracellular enzymes, bacterial endotoxins can also cause different pathological symptoms in the host, so as to activate the immune system in the host, thereby reducing the harm of the immune system to bacteria. For example, in febrile reaction, endotoxin is used as an exogenous thermogenic source for granulocytes and monocytes to release endogenous pyrogens and cause fever. Glucose metabolism disorder, the first occurrence of hyperglycemia, turned to hypoglycemia, a large amount of glycogen consumption, may be related to the secretion of adrenaline. Vasomotor dysfunction, endotoxin activates the release of vasoactive substances such as 5-hydroxytryptamine, kallikrein and kinin. Peripheral blood vessels dilate, permeability increases, venous return decreases, cardiac output decreases, leading to hypotension and shock may occur. Metabolic acidosis occurs when vital organs, such as the kidneys, heart, liver, lungs, and brain, are starved of oxygen due to insufficient blood supply, and organic acids accumulate. Disseminated Intravascular Coagulation (DIC), endotoxin XII factors can activate blood coagulation system, when the blood coagulation function after the start, make fibrinogen to fibrin, caused by DIC. Due to the large consumption of platelets and fibrinogen, the breakdown of fibrin, and then the bleeding tendency. Shwartzman phenomenon: A particular form of DIC that may be caused by endotoxins. The endotoxin was injected into the skin of the animal, then intravenously the next day, and a few hours later, local skin necrosis appeared after the first injection. DIC may occur if the endotoxin is injected intravenously both times. It is thought that the first dose of endotoxin blocks the mononuclear phagocytic cell system, so that the second injection of endotoxin cannot be eliminated, and this reaction occurs. The same results can also be obtained by replacing the first endotoxin dose with carbon granules to block the mononuclear phagocytic system, or by treating with adrenocorticoids.

B. Talaromyces Marneffei's Virulence Factor

The main virulence factors of Talaromyces marneffei include melanin, phospholipase, MP1p protein and other polyketides [3].

1) Melanin

Talaromyces marneffei secretes melanin and plays an important role in the pathogenicity and survival of Talaromyces marneffei [27]. Studies have found that melanin has the role of resisting various non-specific pressures, such as ultraviolet light, oxidizing enzyme cleavage at extreme high and low temperatures, scavenging oxygen free radicals to protect fungi from oxygen or nitrogen-derived free radical mediated damage, regulating immune cytokine levels and enhancing fungal resistance to drugs. The study found that the melanin synthesized by Talaromyces marneffei after gene editing knocked out the melanin synthesis site gene was significantly reduced, and its infectivity was decreased, so that the survival time of infected mice was significantly increased compared with that of mice infected with wild strains, indicating that the melanin secreted by Talaromyces marneffei has a lethal effect on the host, which can effectively lower the host's resistance to Talaromyces marneffei and reduce the host's activity.

2) Phospholipase

Extracellular phospholipase is a class of enzyme that can effectively decompose lipid components of cell membranes and lysate cell membranes, has been widely proved to be a universal virulence factor for pathogenic bacteria [28]. Phospholipases hydrolyze one or more bonds in glycerol phospholipids. Scientists divide phospholipases into phospholipases ABC and D according to their ability to hydrolyze different vinegar bonds. Since cell membrane is the first line of defense, in the process of microbial invasion into the host cell, cracking the host cell membrane and destroying the function of the host cell membrane is a necessary step. Phospholipase decompose the lipid components of the cell membrane effectively, leading to the damage and fragmentation of the cell membrane. Therefore, the presence of phospholipase can effectively increase the infection rate for Talaromyces marneffei since it helps a lot during breaking the host cell membrane. Studies have shown that the expression of intracellular phospholipase B in the yeast phase of Marneffei is significantly higher than that in the mycelium phase, that is, in the case that Talaromyces marneffei can cause disease, intracellular phospholipase B plays a positive role, so it is also an important factor affecting the pathogenicity of Talaromyces marneffei.

3) MP1p protein

MP1p is an abundant yeast glycoprotein on the cell wall encoded by the MP1 gene, which has been used as an immune antigen in the detection of Marneffei basket infection [29]. However, with the in-depth understanding of Talaromyces marneffei, researchers found that MP1p protein can be counted as a new virulence factor of Talaromyces marneffei. It was found that MP1P-LBD2, one of the Mp1p proteins, is a 5-helical bundle of monomers with a long hydrophobic center and has a high affinity for Arachidonic Acid (A.A). It can trap and block 1–2 A.A, reduce the level of intracellular A.A, and then inhibit the release of downstream A.A metabolites and pro-inflammatory factors IL-6 and TNF-a, and ultimately

reduce the inflammatory response of the body. Thus, the presence of MP1p protein can low down the ability of reporting the appearance of Talaromyces marneffei to the immune system and cause inflammation, which helps Talaromyces marneffei to survive longer.

C. How Talaromyces Marneffei Survive in Macrophages

1) Binding

First, Talaromyces marneffei enters the human body and binds to the surface of epithelial cells through adhesion factors (such as C-C-dependent adhesion factors) on respiratory mucosal epithelial cells. They then penetrate further into host cells by damaging the surface of epithelial cells and affecting adhesion related signaling pathways.

2) Endocytosis

After entering macrophages, Talaromyces marneffei is phagocytic by macrophages under the mediation of endocytosis [30]. Endocytosis is the process by which macrophages encase and ingest microorganisms by extending their pseudopods. This process relies on a class of receptor molecules on the cell surface, such as substitutive magnesium sulfate adhesion proteins, which we call recognition receptors, which are able to bind Talaromyces marneffei surface molecules such as binding proteins. Once Talaromyces marneffei is engulfed by macrophages, it enters the endocytic vesicle. However, Talaromyces marneffei has the ability to escape and kill the vesicles. This is achieved through escape mechanisms such as secreting proteases and affecting intracellular acidification. These mechanisms allow Talaromyces marneffei to escape the lethal acidic and enzymatic environment of the endocytic vesicle.

3) Granuloma formation

Meanwhile, an important mechanism by which Talaromyces marneffei survives in macrophages is the formation of granulomas. Granulomas are diseased structures made up of macrophages and other immune cells, such as lymphocytes and dendritic cells. During granuloma formation, Talaromyces marneffei still regulates macrophage activity and function by interfering with signaling pathways and the production of pro-inflammatory cytokines.

4) Manipulating the immune response

In addition, Talaromyces marneffei enhances the ability to survive in macrophages by manipulating the immune response of host cells [31]. Talaromyces marneffei interferes with macrophage signaling pathways, such as the nuclear transcription factor κB pathway and the type I interferon pathway, which regulate immune processes such as apoptosis, cytokine production, and inflammatory response. Talaromyces marneffei activates specific type I interferon signaling pathways that lead to increased production of anti-inflammatory cytokines, such as -γ and IL-10. This series of interferon-induced gene expression and cell apoptosis pathway changes help regulate the immune response of host cells, inhibit macrophage activity, and provide favorable conditions for Talaromyces marneffei survival; It also inhibits the production of pro-inflammatory cytokines such as tumor necrosis factor-α and IL-12. This balanced cytokine secretion pattern can inhibit the activity of macrophages, reduce the killing of Talaromyces marneffei, and also help Talaromyces marneffei evade the immune response of clearance in macrophages.

5) Affecting apoptosis regulation

Talaromyces marneffei can also affect apoptosis regulation of macrophages [32]. This inhibition is mainly achieved by interfering with apoptosis signaling pathways, such as activating intracellular anti-apoptotic proteins (such as Bcl-2, Bcl-xL) and inhibiting cysteine protease activity. Apoptosis of cells is regulated by the apoptotic signal and transmits instructions. After inhibiting the apoptotic signal, macrophages will remain active until receiving the apoptotic signal, thus giving Talaromyces marneffei a more stable living environment and improving the survival probability.

6) Interfering the lysosomal function

Talaromyces marneffei can also interfere with the lysosomal function of macrophages. Lysosomes are organelles within macrophages that contain bactericidal acidic enzymes and other digestive enzymes [33]. Interfere can evade the lysosomal bactericidal mechanism in macrophages by reducing lysosomal acidification and inhibiting enzyme activity. In addition, interfere produces a range of antioxidant enzymes and detoxifying enzymes to combat reactive oxygen species and reactive nitrogen substances produced in macrophages. These substances are essential to the survival of Interfere. In summary, the mechanism of Talaromyces marneffei survival in macrophages involves multiple levels of interaction, including adhesion, phagocytosis, escape of endocytic vesicles, formation of granuloma, regulation of cytokine production, inhibition of apoptosis, interference with lysosomal function, and production of antioxidant and detoxifying enzymes. These mechanisms work together to enable Talaromyces marneffei to survive in macrophages and trigger long-lasting infections.

D. The Bidirectional Properties of Talaromyces Marneffei

Talaromyces marneffei grows in the mycelial phase in the external environment, but changes to the yeast phase at the physiological temperature of mammals [34]. Yeast phase is the pathogenic phase of Talaromyces marneffei. The biphasic conversion mechanism of Talaromyces marneffei is related to the immune system and environmental factors of different animal hosts involved in survival and reproduction. It helps the fungus better adapt and survive in different environments, thus contributing to its long-term existence and reproduction in different hosts. When Talaromyces marneffei infects humans or other animals, it needs to adapt to different environments in the host body, including the host's body temperature, pH, and resilience, among other things. In the host, the fungus undergoes a morphological transition from hyphal form to bifurcated mycelium or yeast substrate, a polymorphism known as a "biphasic transition". At present, there is no clear study on how the bidirectional transformation of Talaromyces marneffei

helps it adapt to different environmental factors to better survive, but we can know by inference that after entering the host, the bifurcated mycelium can spread in the host lymphatic system and organs; The yeast substrate is more able to evade the attack of the host immune system and survive in the tissues where the host immune response is weak. In addition, the survival and reproduction of Talaromyces marneffei may also involve interactions with other microorganisms. For example, the fungus may compete with other microbes for nutrients and living space by producing some antibiotic-like chemicals while growing in the dirt.

VII. Conclusion

This literature review examines general statements about the current state of Talaromyces marneffei and raises some questions for discussion. It mainly describes the unique survival mechanism of Talaromyces marneffei, that is, two-way conversion, and its pathogenic mechanism, including but not limited to entering and paralyzing the human immune system, survival and reproduction in the human viable system. At the same time, it also discusses the virulence factors of Talaromyces marneffei and how to survive, and compares it with common viruses to get the difference of Talaromyces marneffei. In order to better treat diseases caused by Talaromyces marneffei in the future, people need to find some ways to inhibit its growth and block it from the root as much as possible. Therefore, the pathogenic ability of Talaromyces marneffei analyzed in this paper can provide help for treatment to a certain extent, and at the same time, this paper also analyzes and puts forward some methods that can be treated.

Conflict of Interest

The author has claimed that no conflict of interest exists.

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