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Antifungal immunity in selected fungal infections

Odporność przeciwgrzybiczna w wybranych infekcjach grzybiczych

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Summary

Fungi are omnipresent in the environment; hence they are frequent factors causing infections in humans and animals even if their immune system works correctly. These facts stimulated interest in and the will to understand the antifungal immunity mechanisms. It has been, however, evidenced that the immunological response to mycotic pathogens is related to the species and morphological form of the fungus. Nevertheless, it is assumed that always in the antifungal response, there are mechanisms of innate and adaptive immunity that cooperate with one another to eliminate such pathogens. It has been evidenced that the main elements of antifungal immunity are physical barriers of the organism, phagocytosis, cytotoxicity, and possibly trogocytosis of PMN and MN cells, as well as T-cells, and to a smaller extent B-cells, the proportion of which is principally related to their products activating the processes of PMN and MN cells. An important role in this immunity also belongs to PRR, which activate the main processes of phagocytosis and cytotoxicity of PMN, MN, NK and DC cells.

Key words: **antifungal immunity • cytotoxicity • phagocytosis • PRR.**

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Abbreviations: **CARD** – caspase recruitment domain, **CLR** – C-type lectin receptor, **DAMP** – damage-associated molecular pattern molecules, **DC** – dendritic cell, **DC-SIGN** – dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, **GM-CSF** – granulocyte-macrophage colony-stimulating factor, **IFN** – interferon, **IL** – interleukin, **ILC** – innate lymphoid cells, **IRF** – interferon regulatory factor, **Lf** – lactoferrin, **LTi** – lymphoid tissue inducer T cells, **LZM** – lysozyme, **MAIT** – mucosal-associated invariant T, **MBL** – mannose-binding lectin, **MINCLE** – monocyte-inducible C-type lectin, **MIP** – macrophage inflammatory proteins, **MN** – monomorphonuclear leukocytes, **MR** – mannose receptor, **MR1** – major histocompatibility complex class I- related protein 1, **NET** – neutrophil extracellular trap, **NF** – nuclear factor kappa-light-chain-enhancer of activated B cells, **NF-AT** – nuclear factor of activated T-cells, **NK** – natural killer, **NLR –** NOD-like receptor, **PMN** – polymorphonuclear leukocytes, **PRR** – pattern recognition receptor, **PTX3** – pentraxin-related protein 3, **Syk** – spleen tyrosine kinase, **TGF** – transforming growth factor, **TLR** – Toll-like receptor, **TNF** – tumour necrosis factor.

Fungi are omnipresent in the environment; hence they are frequent factors causing infections in humans and animals even if their immune system works correctly, although there are some among them that cause high morbidity in individuals with immunological defects [3,4]. These facts induced interest in and the will to understand the antifungal immunity mechanisms [3,4]. For a long time, and possibly still, there has been a dispute over which of the immunity types is the most important in the immunological response against such pathogens. The studies from recent years confirm the share of both non-specific and specific mechanisms, both cellular and humoral, presently referred to as innate and adaptive immunity, which cooperate to eliminate such pathogens [3,16].

At present, it is assumed that the first defence mechanism of innate immunity (actually non-specific) involves physical barriers that separate the organism by skin and mucous membranes of the respiratory, digestive and urinary-genital system from the external environment [3]. It has been evidenced that mucous membranes feature such compounds as lysozyme (LZM), lactoferrin (Lf), calprotectin, peroxidase, and defensins, which, by blocking access to nutrients, distort metabolism and thus lead to destruction of structures of such pathogens. For example, LZM present in granularities of granulocytes and lysozymes of monocytes and macrophages, as well as in blood serum, has the capacity of killing or inhibition of growth of such fungi as *Candida* sp., *Cryptococcus* sp., *Histoplasma* sp., *Aspergillus* sp. and *Paracoccidioides* sp. [4,11]. Such action is related to its hydrolytic properties as regards the cellular wall and membrane of fungi [4]. In turn, Lf acts by limiting fungi's access to nutrient in the form of iron, as by binding it, it hinders growth of fungi and thus conditions control of mycotic infections [4]. Another effective mechanism distorting fungi's metabolism is calprotectin – a protein that binds zinc [4]. Another very important element limiting fungal infection is the occurrence on the surface of skin and mucous membranes of physiological microflora, which makes it difficult for pathogenic microorganisms, including fungi, to colonise such places [3,16]. Moreover, in mucous membranes, as a result of infection with fungi capable of producing riboflavin (*Saccharomyces cerevisiae*, *Candida glabrata* and *Candida albicans*), activation of a special subpopulation of T-cells was recorded, as related to mucosal-associated invariant T (MAIT), which belong to the group of natural cells (ILC) within which one can differentiate NK, LTi (lymphoid tissue inducer T cells), ILC22, ILC17, and ILC2 cells [6,17]. MAIT cells recognise fungal infection among others by presentation of riboflavin antigen by the MR1 receptor (major histocompatibility complex class I-related protein 1) of hematopoietic cells, which leads to expansion of MAIT cells in mucosa at the infection site, where they intensively synthesise for example IFN-gamma and TNF, which contributes to destruction of infected cells and accelerates maturation of DC cells, specific subpopulations of which can have the properties of NK cells, and thus form part of ILC cells [2,6,17]. In the event that fungi still manage to cross that barrier, they meet on their path cells with the capacity of phagocytosis, cytotoxicity and probably trogocytosis, namely: PMN cells (polymorphonuclear) and MN (mononuclear), dendritic, NK cells, but also T-cells and B-cells, as well as non-hematopoietic epithelial and endothelial cells showing properties of defence elements [1,3]. The cells recognise pathogen-associated molecular patterns (PAMP), which in fungi are beta-glucan, chitin, manganese, or zymosan, by PRR (pattern recognition receptors). Among major PRR receptors of the immune system that participate in antifungal immunity and in mycotic structure recognition (table 1), there are Toll-like receptors (TLR) and C-type lectin receptors (CLR), as well as NOD-like receptors (NLR) [4,15,20,21,22].

Among TLR receptors with major importance for fungal recognition, there are TLR 4, 9 and 2, which as a result of ligand binding lead to kinase cascade activation in mammal cells, and migration of transcription factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB), nuclear factor of activated T-cells (NF-AT) and interferon regulatory factor 3 (IRF3) to the nucleus, which induces gene expression for many cytokines, including interleukins and pro-inflammatory chemokines that have antifungal action [4,15,21,22]. It was evidenced that polymorphism within TLR4 is related to increased sensitivity to pulmonary aspergillosis and vascular blastomycosis, while polymorphism within TLR9 is related to bronchopulmonary aspergillosis [5,15,21,22]. It was evidenced that, in the case of infection with *Candida albicans*, lack of TLR2 leads to reduced production of TNF, IL-1 and macrophage inflammatory protein MIP-2, which results in increased possibility of infection with this pathogen [5,15,21,22]. Nevertheless, it was demonstrated that activation of phagocytosis of PMN and MN cells by TLR receptors is related to the type of phagocytes and the fungal species, as in the case of infection with *Aspergillus* sp. macrophage activation occurs via TLR2, while neutrophil activation occurs via TLR4 [4].

Another group of important receptors taking part in recognition of fungal infections is the CLR family, including dectin 1 (also referred to as CLEC7A), dectin 2 (CLEC6A), monocyte-inducible C-type lectin (MINCLE), DC-specific ICAM3 grabbing non-integrin (DC-SIGN), mannose receptor (MR) and mannose-binding lectin (MBL) [4,14,15]. It was recorded that dectin 1 reveals capacity of recognising ligands of fungi from the genera of *Candida*, *Coccidioides*, *Pneumocystis* and *Aspergillus* [20]. As a result of such recognition, the paths related to spleen tyrosine kinase (Syk) and cytosolic adapter caspase recruitment domain, member 9 (CARD9) are activated [14,20]. Activation of these paths induces synthesis of many cytokines, including GM-CSF, TNF and IL 1,2,6,10,23, and CXCL2 chemokines [7,14,20,23]. Furthermore, it was evidenced that the signal path related to adaptor protein CARD19 additionally induces maturation of DC cells, and regardless of TLR receptors affects the response of Th17 lymphocytes, which proves that in fungal infections dectin 1 is an important marker conditioning the effectiveness of adaptive antifungal immunity [23]. Additionally, it was evidenced

Table 1. Receptors recognising fungi

PRRs recognize fungi	Fungal species	References
TLR	*Candida albicans* *Aspergillus sp.*	[4,5,21,22]
Dectin 1	*Candida sp.* *Coccidioides sp.* *Pneumocystis sp.* *Aspergillus sp.*	[20]
Dectin 2	*Candida albicans* *Trichophyton rubrum* *Microsporum audouinii* *Histoplasma capsulatum*	[4,23]
MINCLE	*Candida albicans* *Malassezia sp.*	[21,24]
DC-SIGN	*Candida sp.*	[4,9]
MR	*Pneumocystic sp.* *Cryptococcus neoformans*	[23]
MBL	*Candida albicans* *Aspergillus fumigatus*	[21]
NLR	*Candida albicans*	[15]

that dectin 1 takes part in activation of lymphocytes by calcineurin (protein phosphatase), which is an important element of the signal path leading to lymphocyte activation [7,20]. In turn, dectin 2 is characterised by the capacity of recognising mannose-rich mycotic structures and activation of the Syk-CARD9 path, which leads to release of cytokines such as TNF and IL-2, -10, -6, -1, -12, -22 and -23 [15]. Dectin 2 is also considered as a typical receptor for infections caused by fungi, such as *Candida albicans*, *Trichophyton rubrum*, *Microsporum audouinii*, as well as *Histoplasma capsulatum* [4,23]. In turn, the MINCLE receptor participates among others in recognition of *Candida albicans* and *Malassezia* sp. by macrophages, but it was demonstrated that it is not involved in induction of phagocytosis of such cells [20,21,24]. In the case of the DC-SIGN receptor, it was recorded that it is mainly present on DC cells, and its role comprises calcium-dependent recognition of mannose-rich fungal structures [4]. It was evidenced that the marker induces signal paths related to Raf kinase by modulating the response related to TLR receptors, and stimulates anti-inflammatory activity of IL-10, which is due to its nature inhibiting the immunological response in fungal infections [23]. In turn, the mannose receptor (MR) recognises oligosaccharides, such as chitin, fucose and mannose, while its role and participation were proven in infection with *Pneumocystis* sp. and *Cryptococcus neoformans* [23]. After recognising fungal antigens, the MR receptor induces activation of NF-kappaB transcription factor, by which it increases synthesis of such cytokines as IL-12, IL-8, IL-1beta, IL-6 and GM-CSF [23]. In infection with *Pneumocystis* sp., similarly as the DC-SIGN receptor, the marker also reveals an immunosuppressive impact on the synthesis of proinflammatory cytokines – principally TNF [25]. In turn, mannose-binding lectin (MBL), as a soluble protein synthesised by the liver, has capacity of binding to *Candida albicans* and *Aspergillus fumigatus* [21]. Furthermore, recognition of fungal particles by the receptor leads to activation of complement components, in particular C3b, which, by opsonising fungal particles, facilitates and increases the activity of phagocytosis of PMN and MN cells against them [23]. It must also be added that some of the listed CLR receptors can directly induce signal paths, activating NF-kappaB, whereas others, as mentioned before, act via TLR 2, 4 and 9 [4,15]. It was demonstrated that some fungal species can be recognised by receptor "sets" on various phagocytising cells, depending on morphology of the fungus. It was evidenced that *Candida* sp. mannans recognition by macrophages occurs principally with the aid of mannose receptor (MR), while in the case of DC cells it occurs via three receptors, namely MR, dectin-2 and DC-SIGN. In turn, mannans in other morphological form of the fungus, e.g. hyphae, are recognised by dectin-2 receptor, both on macrophages and DC cells [4,9]. When analysing the role of CLR receptors, it must be stated that their activation contributes to production of many cytokines, including IL-1, -2, -6, -10 and -23, and mycotic antigen presentation by dendritic cells to T-cells, which leads to very effective T-cell differentiation in their subpopulations Th1, Th2, Th17 and T_{reg} [4,9,15,19,21].

In turn, participation of the aforementioned NLR receptors in antifungal immunity is related to the NLRP3 receptor, which, after prior recognition of a ligand, e.g. damage-associated molecular pattern (DAMP) formed for example after cell damage as a result of fungal action, induces IL-1beta and IL-18, which contributes to formation of a protein complex referred to as inflammasome – a very important element of the immunological response [15]. It was evidenced that ligand recognition by NLR leads to caspase 1 activation by way of autoproteolysis, as a result of which synthesis of pro-inflammatory cytokines, such as IL-1, IL-18 and IL-33, is induced [12].

When assessing and analysing activation of the presented PRR receptors of the immune system as a result of binding to fungi, it must be stated that it leads to strong activation of phagocytising cells, namely PMN and MN cells, which results in stimulation of phagocytosis, although some also claim that it also stimulates cytotoxicity, the NET network, and hypothetically also trogocytosis, as a result of which fungi are eliminated [1,4]. In the case of phagocytosis, in both bacterial and viral infections, it is characterised by the fact that the phagosome binds to lysozymes forming a phagolysosome where intercellular killing and digestion occur [4]. The degradation process in phagocytosis occurs with participation of mechanisms of oxygen toxicity, namely toxic compounds of oxygen and nitrogen as a result of oxygen explosion, or with the participation of mechanisms independent of oxygen – principally hydrolases and anti-pathogenic peptides [4]. It was evidenced that activation of PMN and MN cells and their effector mechanisms participating in antifungal immunity are affected by cytokines and many other soluble factors that strengthen the process, such as IFN-gamma, or inhibiting it, as in the case of IL-10 [4]. It was demonstrated that PMN, MN and DC cells have a different capacity of killing fungal cells depending on the species [4]. It was recorded that neutrophils have a stronger fungicidal potential in respect of *Candida albicans* than monocytes, macrophages and DC cells [4]. In turn, DC cells show greater fungicidal activity in respect of *Histoplasma capsulatum*, which is not observed for PMN cells [4]. Furthermore, various phagocytising cells respond to fungal infections in a different order; for example, macrophages are the first and main cells participating in immunity against *Cryptococcus* sp. and *Pneumocystis* sp., whereas PMN cells are the principal effector cells taking part in infections caused by *Candida albicans* and *Aspergillus fumigatus* [3,19]. It was demonstrated that PMN and MN cells can also destroy e.g. fungal hyphae that are too large to be phagocytised, by secretion of free radicals (reactive forms of oxygen and nitrogen) and cidal compounds independent of oxygen, e.g. lysozyme, defensin, or proteolytic enzymes, to the extracellular space [8,15,20,22]. Moreover, it was observed that killing of *Candida albicans* occurs using the neutrophil extracellular trap (NET) – an extracellular antimicrobial structure comprising chromatin and granule proteins released from PMN cells [4]. It was evidenced that the NET network also contains pentraxin-related protein 3 (PTX3) and soluble PRR receptors, stored in neutrophil granules, which are the basic element in the mechanism of recognition and killing of *Aspergillus fumigatus* [4]. Furthermore, as a result of activation of PMN cells, monocytes and macrophages, many cytokines are secreted, including TNF-alpha, IL-1, IL-6, IL-12, which are engaged and activated in the process of forming "new" PMN and MN cells, which yields the effect of their inflow and intensification of infection. It was demonstrated that presentation of mycotic antigens to adaptive immunity cells – T-cells and partly B-cells – principally occurs by DC cells, although also by activated MN and PMN cells. Such professional antigen presenting cells, namely DC cells, apart from migration to surrounding lymph nodes, where they present mycotic antigens to virgin and memory T-cells, secrete such cytokines as IL-12, IL-18 and INF-gamma, which strengthen the "pro-inflammatory environment" [4,15,20]. It was evidenced that, depending on the recognised morphological form, DC cells can indicate different profiles of cytokine synthesis (predominance of IL-12 or IL-4/IL-10) and affect the response of T-cells in two ways. In the case of absorption of a yeast form of *Candida albicans*, DC cells are activated towards IL-12 synthesis, which leads to activation of the Th1 cell response, whereas absorption of hyphae of the fungus leads to inhibition of IL-12 production and induction of IL-4, which results in development of a Th2-dependent response [10]. Most frequently, however, while degrading the cells of such fungus as *Histoplasma capsulatum* or *Aspergillus fumigatus*, DC cells stimulate T- and B-cell proliferation [10]. The result is intensive secretion of IL-2 by T-cells, which activates proliferation of T-cells (CD4+ and CD8+), as well as B-cells. The activated T-cells migrate to the focus of infection, where CD4+ Th cells polarise in the direction of Th1 lymphocytes producing IFN-gamma or IL22, which leads to stimulation of migration, adherence and absorption of PMN and MN cells in the case of IFN-gamma, and activation of local immunity of mucous membranes in the case of IL-22 [15]. Such an image of domination of Th1 cells intensively supports the process of phagocytosis, by which it strengthens antifungal immunity.

Also B-cells, forming adaptive immunity, after activation as a result of fungal infection, secrete immunoglobulins (Ig), principally of IgG type, which opsonise and render mycotic pathogens more 'tasty' to PMN and MN cells, by which they facilitate phagocytosis, as well as cytotoxicity [1,3,4,15,20]. It was also described that the occurring quantitative and functional disorders of PMN and MN cells render it difficult for the pro-inflammatory environment to develop by contributing to T-cell polarisation towards Th2 cells that synthesise IL-4, IL-5 and IL-10, -25 and -33, which consequently leads to B-cell activation and Ig synthesis, although also to inhibition of phagocytosis [15]. As a result of this, non-phagocytised forms of fungi, e.g. pseudo-hyphae, despite the high IgG level, can spread with blood through distant tissues and organs [15]. Furthermore, it was demonstrated that activation of CD4+ or CD8+ T-cells, or both such cells, is of key importance in 'alleviation' of many fungal infections, including infections

caused by *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis* and *Paracoccidioides brasiliensis* [10]. As a result of infection with such fungi, principally the response with domination of Th1 cells is generated, characterised by production of IL-12, IFN-gamma, TNF-alpha, and GM-CSF, which is necessary in antifungal immunity. The alternative response of Th2 cells, characterised by production of IL-4, IL-5 and IL-13, is often related to more acute and severe infections connected with such fungi. There is evidence demonstrating that the Th2 response can affect the development of the response related to Th1 cells [10]. In the case of *Cryptococcus neoformans*, the mechanism is not entirely clear, but it was evidenced that this antifungal response involves CD8+ T-cells, which directly inhibit the growth of this pathogen, probably through cytotoxicity reactions of such cells. In this case, it was recorded that the impact of IL-15 on such lymphocytes (CD8+) leads to overexpression of antimicrobial peptides and granulysins of such cells – elements important in the cytotoxicity process [1]. Furthermore, it was demonstrated that granulysin activation depends not only on the presence of IL-15, but also on the supporting operation of CD4+ T-cells, while it is not related to perforins [10]. It is assumed that among T-cells forming antifungal immunity, also subpopulations of Th17, Th23, and T_{reg} are important, which, depending on cooperation of such cells, can contribute to strengthening or weakening of immunity and tolerance of fungi [4,15]. Furthermore, it was evidenced that in some conditions Th17 cells can affect the function of T_{reg} cells, as it was recorded that due to the presence of IL-17 and absence of IL-23, by production of IL-6 and TGF-beta, Th17 cells can affect induction of IL-10 production by T_{reg} cells [8].

As mentioned previously, antifungal immunity is related to the action of B-cells, which are cells producing antibodies – immunoglobulins [3,4,15,20]. It was demonstrated that IgG, as very strongly opsonising substances, participate in the aforementioned process of rendering mycotic pathogens more 'tasty' to phagocytising cells, by which they facilitate phagocytosis, and possibly also the processes of cytotoxicity and trogocytosis [1,4,15,20]. Furthermore, Ig alone prevent fungal adhesion and neutralise their toxins, and, as mentioned before, are necessary for antibody-dependent cytotoxicity of PMN and MN cells, although the process is not very well recognised in fungal infections [3,13]. It was evidenced that the role of immunoglobulins in antifungal immunity largely depends on their isotypes and idiotypes, as well as their proportion, number, and specificity; hence the exact function of particular antibodies in such immunity is not entirely known, although it is actually assumed that the role is related to IgG, and in the case of mycoses of mucous membranes with IgA [3,13].

To conclude, the immunological response to fungal pathogens is largely related to the species and morphological form of the fungus, although it is also assumed that antifungal immunity always involves mechanisms of innate and adaptive immunity that cooperate with one another, but their participation in fungal infections is dominated by innate immunity. Therefore, it is presently assumed that the main elements of antifungal immunity are physical barriers of the organism, phagocytosis, cytotoxicity, and possibly trogocytosis of PMN and MN cells, as well as T-cells, and to a smaller extent B-cells, the proportion of which is principally related to their products activating the processes of PMN and MN cells. An important role in this immunity also belongs to PRR receptors, which activate the main processes of phagocytosis and cytotoxicity of PMN, MN, NK and DC cells.

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