Brazilian Journal of Biology®

ISSN 1519-6984 (Print)
ISSN 1678-4375 (Online)

Review Article

Neonatal innate immunity response in invasive candidiasis

Resposta imune inata em neonatos frente à candidíase invasiva

J. A. G. Suárez[a], R. J. N. Calumby[b], D. P. Silva[b], V. T. Barbosa[b], F. C. A. Maranhão[b], I. F. Moreira[b], M. S. C. Melhem[c] and R. T. F. Moreira[b,c*]

[a] Universidade Federal de Ouro Preto – UFOP, Ouro Preto, MG, Brasil

[b] Universidade Federal de Alagoas – UFAL, Campus A. C. Simões, Maceió, AL, Brasil

[c] Universidade Federal de Mato Grosso do Sul – UFMS, Faculdade de Medicina, Programa de Pós Graduação em Doenças Infecciosas, Campo Grande, MS, Brasil

Abstract

Infections caused by *Candida* spp. are frequent in critically hospitalized patients, especially among premature neonates, representing one of the most common healthcare-related infections. Although there is considerable production of current knowledge about the mechanisms of immune response, aspects involved in the newborn's innate defense are not fully understood. The aim of this study was to describe the innate immune mechanisms involved in the defense of neonates against invasive candidiasis. This is an integrative literature review from the Scopus, Scifinder, Medline, Web of Science databases and the electronic libraries ScienceDirect and Scielo, in the period between 2002 and 2020, with rescue based on primary descriptor Immunity Innate plus secondary descriptors Candidiasis Invasive AND Infant Newborn. We have observed the involvement of various mechanisms in the neonatal response against invasive candidiasis, including the recognition, signaling, recruitment, and initiation of an effective immune response. These mechanisms encompass the presence of antimicrobial peptides, phagocytosis, synthesis of reactive oxygen species, inflammatory mediators, and complex cell signaling systems mediated by Pattern Recognition Receptors (PRRs). With this study, it is expected to contribute to the expansion of knowledge about the immunological mechanisms involved in the innate immune response of the newborn against disseminated infections caused by *Candida* species, and in the same sense, highlight the importance of this knowledge as a reflex in the decrease in mortality in the neonatal period.

Keywords: immunity innate, candidiasis invasive, infant newborn, neonatal infections, immune defense.

Resumo

As infecções causadas por *Candida* spp. são frequentes em pacientes hospitalizados em estado crítico, especialmente entre neonatos prematuros, representando uma das infecções relacionadas à assistência à saúde mais comuns. Embora haja considerável produção de conhecimento atual sobre os mecanismos de resposta imune, os aspectos envolvidos na defesa inata do recém-nascido não são totalmente compreendidos. O objetivo deste estudo foi descrever os mecanismos imunes inatos envolvidos na defesa dos neonatos contra a candidíase invasiva. Trata-se de uma revisão integrativa da literatura a partir das bases de dados *Scopus*, *Scifinder*, *Medline*, *Web of Science* e nas bibliotecas eletrônicas *ScienceDirect* e *Scielo*, no período de 2002 a 2020, com resgate baseado no descritor primário "Imunidade Inata" e descritores secundários "Candidíase Invasiva" e "Recém-Nascido". Observamos o envolvimento de vários mecanismos na resposta neonatal contra a candidíase invasiva, incluindo o reconhecimento, sinalização, recrutamento e início de uma resposta imune efetiva. Esses mecanismos englobam a presença de peptídeos antimicrobianos, fagocitose, síntese de espécies reativas de oxigênio, mediadores inflamatórios e sistemas complexos de sinalização celular mediados por Receptores de Reconhecimento de Padrões (PRRs). Com este estudo, espera-se contribuir para a expansão do conhecimento sobre os mecanismos imunológicos envolvidos na resposta imune inata do recém-nascido contra infecções disseminadas causadas por espécies de *Candida* e, da mesma forma, destacar a importância desse conhecimento como reflexo na redução da mortalidade no período neonatal.

Palavras-chave: imunidade inata, candidíase invasiva, recém-nascido, infecções neonatais, defesa imune.

1. Introduction

During pregnancy, the components of the immune system responsible for activating an inflammatory response in the baby are suppressed (Sharma et al., 2012). The immune cells responsible for inducing the effector response and its regulation does not fully develop in the first years of life, which is necessary to prevent maternal-fetal halogen rejection and, at the same time, leaves the newborn vulnerable to infections, especially when

*e-mail: rossana.moreira@eenf.ufal.br
Received: July 2, 2023 – Accepted: March 18, 2024

premature, due to incomplete maturation of immune cells (Michalski et al., 2017). On the other hand, the newborn's immune system has some tools to protect itself from the multiple threats to which it is exposed (Sharma et al., 2012), although deficient.

The epidermis, still under development, can result in a barrier function, and the lower the gestational age, the greater the permeability of the skin, which is an important source of infection (Visscher et al., 2015). Taking into consideration that the newborn's skin is in the process of colonization by fungi, the factors that determine this colonization, in addition to physicochemical processes, include components of innate immunity, such as Pattern Recognition Receptors (PRRs), which mediate responses immune (Carvalho et al., 2010).

The relationship between PRRs and immunity to bacterial infections is described in the literature, but few studies associate these receptors with antifungal immunity. In adults, single nucleotide polymorphism (SNPs) in PRRs, such as toll-like receptor protein 4 (TLR4), were associated with increased susceptibility to *Aspergillus* and *Candida* infections, and defective TLR4 in mice, also was associated with increased susceptibility to *Candida* infection (Netea et al., 2002; Carvalho et al., 2010; Paul et al., 2020). However, the fungal microbiota of neonates is not well known.

Yeasts of the genus *Candida* cause frequent infections in critically hospitalized patients, such as premature neonates, being one of the most common healthcare-associated fungal infections (Chow et al., 2012; Kumar et al., 2015). *Candida albicans* is the species responsible for the largest number of fungal infections and commonly colonizes skin and mucous membranes after vertical transmission during vaginal birth, and the correct activation of the innate immune response results in prevention of the excessive spread of this microorganism and, consequently, of an infectious state (Manzoni et al., 2007; Arsenault and Bliss, 2015; Paul et al., 2020).

Multiple resistance strategies undertaken by *Candida* hinder the recognition, recruitment and initiation of an effective response against this pathogen (Chow et al., 2012; Arsenault and Bliss, 2015). In addition, the functional and structural limitations of the main cell types involved in the newborn's defense may allow the installation of *Candida* spp. as an opportunistic microorganism in clinically compromised infants, commonly undergoing antibiotics and under inadequate antifungal therapy (Kumar et al., 2015). There are several risk factors associated with physiological, immunological and clinical conditions culminating in the newborn's susceptibility to invasive candidiasis, such as prematurity, low birth weight, invasive procedures and prolonged hospitalization in the Neonatal Intensive Care Unit (NICU) (Manzoni et al., 2007; Chow et al., 2012; Arsenault and Bliss, 2015).

Research on the functional characteristics of the immune system in newborns has progressed very recently, while few studies have focused on fungi in experimental models. Therefore, this study aimed to characterize the mechanisms of the innate immune response of newborns to invasive *Candida* spp. infections, based on the study of the specialized literature.

2. Methodology

This study is an integrative review of the scientific literature as an investigation method for analysis of the mechanisms of the newborn's innate immune response against *Candida* species in invasive infection, synthesizing species, synthesizing the results in a critical and orderly manner for evidence-based practice (EBP) in order to guarantee rigor methodological and contribute to the building of scientific knowledge on the studied topic. Thus, the following steps were performed: 1) definition of the guiding question; 2) database search; 3) categorization of studies; 4) analysis of the selected studies; 5) results interpretation and discussion; and 6) synthesis of the evidence.

2.1. Search strategy

The research question that guides the search was formulated in the PICO strategy (Population, Interest/Phenomenon of interest and Context) (Cardoso et al., 2019): What are the innate immune response mechanisms (I) of neonates (P) against yeasts of the genus *Candida* (C)?

From April to May 2021 was performed an electronic search in the PubMed, Embase, SCOPUS, Scifinder, Web of Science, Medline, Lilacs, Science Direct, and SCIELO databases for scientific articles published.

The studies were retrieved using the primary descriptor "Immunity Innate", combined with the following secondary descriptors: "Candidiasis Invasive" and "Infant Newborn". These descriptors composed the search strategy based on its combination in English using the Boolean logical operator AND.

2.2. Study selection, data collection and analysis

The inclusion criteria for our review were: (i) National and international articles published in English, Portuguese and Spanish; (ii) Published between January 2002 and December 2020; (iii) Available online in the indicated databases. Studies corresponding to editorials, conference abstracts, annals, opinions, comments and articles repeated in more than one database were excluded. After the inclusion and exclusion criteria application, the remaining studies were subjected to fluctuating reading of titles, abstracts and the full text available. A data collection instrument developed by the authors was used to organize the selected studies by title, journal, type of study, country, language, year of publication, authors, title, objective, result and study type/design. Each study was further classified according to the level of evidence, and the synthesis of the evidence occurred through thematic categories.

3. Results

In the critical literature review, a total of 40 (100%) articles were identified, followed by the exclusion of 26 (65,0%) for not meeting the inclusion criteria, resulting in a final sample of 14 (35.0%) publications.

All studies were published in English and had as original countries: the United States of America (35.7%), United Kingdom (35.7%) and Netherlands (28.6%). For the period

of publication, two (14.3%) articles were published in 2015 and two (14.3%) in 2020, followed by the other years (2002, 2003, 2005, 2007, 2008, 2009, 2010, 2011, 2013 and 2016) with one (7.1%) single article each.

Regarding the impact factor, whose reference corresponded to the year 2019, the articles varied between 1.9690 and 13.4220. An article from 2015 did not have an impact factor identified, using as a criterion the Journal Citation Reports (JCR) statistical database from Clarivate Analytics. Regarding the type of the study and level of evidence, all studies were experimental type with level of evidence II (Souza et al., 2010), as shown in Table 1.

Table 1. General characterization of the selected studies, indicating main results (n = 14).

Nº	Title/Periodic/Impact factor	Type of study/ evidence level	Authors (Year)	Country	Objective	Main results
1	The role of Toll-like Receptor (TLR) 2 and TLR4 in the host defense against disseminated candidiasis / Journal of the Pediatric Infectious Diseases Society / 2.2120(2019).	Experimental/II	Netea et al. (2002)	United Kingdom	To evaluate the TLR4 role in the host defense in *C. albicans* infections.	Mice with genetic defects that alter the TLR4-mediated response are more susceptible to infections caused by *C. albicans*.
2	Expression and function of Toll-like receptors 2 and 4 in human keratinocytes / International Immunology / 3.5190(2019).	Experimental/II	Pivarcsi et al. (2003)	United Kingdom	To study the expression and function of TLR2 and TLR4 in human keratinocytes.	NF-kB nuclear activation and transcription occurs in keratinocytes in response to microbial stimulation. This activation is necessary for the death of *C. albicans*.
3	Dectin-1 mediates macrophage recognition of *Candida albicans* yeast but not filaments / The EMBO Journal / 9.8890(2019).	Experimental/II	Gantner et al. (2005)	United States	To determine the relevance of Dectin-1 in host defense against infections caused by *Candida* species.	Dectin-1 is a receptor responsible for the identification and recognition of fungal PAMPs (B-glucan).
4	Early-onset neutropenia is a risk factor for *Candida* colonization in very low-birth-weight neonates / Diagnostic Microbiology and Infectious Disease / 2.4990(2019).	Experimental/II	Manzoni et al. (2007)	Netherlands	To assess the role of early-onset neutropenia in the development of *Candida* colonization in preterm and low birth weight infants admitted to the NICU.	Colonization in the first month of life was significantly higher in newborns with early-onset neutropenia, but sepsis rates did not differ compared to those without neutropenia.
5	Developmental expression of Toll-like receptors-2 and -4 in preterm baboon lung / Developmental and Comparative Immunology / 3.1920(2019).	Experimental/II	Awasthi et al. (2008)	United Kingdom	To study the expression of TLR2 and TLR4 mRNA and proteins in lung tissue of premature baboons	It has been observed that the expression of TLR2 and TLR4 is altered in cases of respiratory infection in premature baboons.
6	Oxidative burst and phagocytosis of neonatal neutrophils confronting *Candida albicans* and *Candida parapsilosis* / Early Human Development / 1.9690(2019).	Experimental/II	Destin et al. (2009)	Netherlands	To compare the immunological capacity of neonatal neutrophils and adult neutrophils in the generation of an oxidative response against *Candida* species	The oxidative response mediated by neonatal neutrophils exposed to *C. albicans* hyphae was similar to the response generated by adult neutrophils.
7	Innate immune mechanisms for rw2ecognition and uptake of *Candida* species / Trends in Immunology / 13.4220(2019).	Experimental/II	Netea and Maródi (2010)	Netherlands	Describe the molecular basis of the receptors involved in the recognition and death of *C. albicans* and the role of these receptors in the development of the inflammatory response	Different PRRs are involved in the recognition, signaling, expression of proinflammatory cytokines and death of *C. albicans*, including TLRs, CLRs, NLRs, among others.

Table 1. Continued...

Nº	Title/Periodic/Impact factor	Type of study/ evidence level	Authors (Year)	Country	Objective	Main results
8	Fungal recognition is mediated by the association of dectin-1 and galectin-3 in macrophages / Proceedings of the National Academy of Sciences / 9.4120(2019).	Experimental/II	Esteban et al. (2011)	United States	Evaluate the interaction between Dectin-1 and galactin-3 in *Candida* species recognition.	The association between Dectin-1 and galactin-3 facilitates the initiation of the inflammatory response from the synthesis and expression of inflammatory mediators such as TNF.
9	Galectin-3 plays an important role in protection against disseminated candidiasis /Medical mycology / 2.8220(2019).	Experimental/II	Linden et al. (2013)	United Kingdom	It was demonstrated that the association between these two receptors facilitates the initiation of the inflammatory response from the synthesis and expression of inflammatory mediators such as TNF.	Mice deficient in galectin-3 (gal3 -/-) - compared to Wistar mice - were more susceptible to infection, died significantly faster, exhibited a trend of increased fungal load, increased abscess formation in brains and kidneys.
10	Candidemia-induced pediatric sepsis and its association with free radicals, nitric oxide, and cytokine level in host / Journal of Critical Care / 2.6850(2019).	Experimental/II	Kumar et al. (2015)	United Kingdom	To describe epidemiological data related to the susceptibility of sepsis induced by *Candida* species, non-albicans, in neonates hospitalized in the NICU, and the role of inflammatory mediators and reactive oxygen species in the neonatal immune response against these pathogens.	The polymorphonuclear-mediated oxidative response and the role of inflammatory mediators such as nitric oxide, hydrogen peroxide, among others, were proven in this study.
11	Galectin-3 binding protein in human preterm infant umbilical cord plasma/ Journal of Neonatal-Perinatal Medicine.	Experimental/II	Chan et al. (2015)	Netherlands	Compare Gal3BP concentrations from samples obtained from umbilical cord blood from preterm and full-term neonates.	Gal3BP concentrations are higher in preterms, in cases of gestational diabetes, prenatal steroid exposure, and increased maternal parity; and decreased in cases of chorioamnionitis.
12	Reduced PICD in monocytes mounts altered neonate immune response to *Candida albicans* / PLoS ONE / 2.7400(2019).	Experimental/II	Dreschers et al. (2016)	United States	Determine whether TLR2 is involved in monocyte recognition of *C. albicans.*	TLR-2 has been shown to be a receptor implicated in the recognition of PAMPs (phospholipomannans) found in the cell wall in *Candida albicans*.
13	Pretreatment with antibiotics impairs Th17-mediated antifungical immunity in newborns rats / Inflammation / 3.2120(2019).	Experimental/II	Wang et al. (2020)	United States	Using an animal model to demonstrate how the use of antibiotics affects the antifungal immune function and promotes susceptibility.	The use of antibiotics significantly decreased the ability of newborn rats to develop an effective antifungal response.
14	Fungal cutaneous microbiome and host determinants in preterm and term neonates / Pediatric Research / 2.7470(2019).	Experimental/II	Paul et al. (2020)	United States	To characterize the skin microbiota of preterm newborns and compare it with the microbiota of full-term newborns to describe the clinical and host determinants that influence its diversity.	The alpha microbiota diversity was influenced by exposure to antibiotics and the environment of the Intensive Care Unit; The diversity of the beta microbiota varied according to mode of delivery, diet and location in the body.

With regard to the objectives, nine articles directed their studies to the expression, function and involvement of PRRs, describing the main immunological mechanisms of the innate and adaptive immune response of the newborn against fungi. Four publications addressed risk factors such as neutropenia, low birth weight and prematurity, antibiotic therapy and colonization of the skin microbiota and one article compared the immunological capacity of neonatal neutrophils to adults in generating an oxidative response against *Candida* species.

Thus, the results of these studies provide general explanations about aspects of the immune response against *Candida* spp. infections. This evidence is limited by the experimental approach *in vitro* and *in vivo*, remaining a little explored gap in the knowledge about how this process behaves in the newborn.

For a better didactic description, this review began by addressing neonatal infections caused by *Candida* in general, comparing characteristics of preterm newborns with full-term newborns, followed by the mechanisms involved in the innate immune response, with emphasis on antimicrobial peptides, phagocytosis and oxidative stress, cell signaling and reactive oxygen species.

4. Discussion

4.1. Neonatal Candida infections

Candida species are commonly found colonizing the skin and mucous membranes of humans as commensal organisms, but they are also important causes of infections, particularly among those with immunological compromise (Vazquez and Sobel, 2002). This process starts even before birth and, depending on homeostasis, it can become a predisposing factor to infections (Manzoni et al., 2012).

At birth, newborns generally have a low fungal load, with colonization due to vertical (mother to child) or horizontal (nosocomial) transmission (Pinhat et al., 2012; Leibovitz et al., 2013) and most invasive *Candida* infections occur between the second and sixth week of postnatal age (Manzoni et al., 2012). *C. albicans* is the most frequently isolated species in newborns with candidemia, but other species, particularly *Candida parapsilosis*, as well as *Candida tropicalis*, *Candida glabrata* and *Candida krusei* are increasing in frequency (Michalski et al., 2017).

Newborns are a subset of patients who are susceptible to fungal infections and their complications. Healthy, full-term newborns can usually develop superficial (mucocutaneous) infection in the form of oral candidiasis and diaper dermatitis, while preterm infants have a higher risk of disseminated infection, due in part to immaturity and modulation of the immune system in the developing fetus that tends to ripen after delivery (Gladstone et al., 1990; Witek-Janusek and Cusack, 1994). Thus, candidiasis in neonates represents a unique pathogen-host interface, in which the fungal virulence mechanisms and the neonate's response to infection may differ from other clinical settings of candidiasis (Arsenault and Bliss, 2015)

In hospitalized neonates, whose defenses are normally altered, secondary to their own clinical condition, diseases or invasive procedures, as well as the prolonged use of antibiotics, *Candida* can cause serious and disseminated infections, including candidemia, as well as infection of more deep organs, and this condition is associated with high morbidity and mortality (Weimer et al., 2022).

4.2. Innate immune responses

4.2.1. Antimicrobial peptides and caseous vernix

One of the main defense mechanisms of innate immunity, acting in the prevention and combat of infections in the newborn, are represented by broad-spectrum biological molecules called antimicrobial peptides (AMPs), such as LL-37 (Dürr et al., 2006). AMPs are made up of chains with approximately 150 - 200 amino acids, produced and expressed by different cell types, such as neutrophils, Paneth cells in the small intestine or epithelial cells, with antifungal, antibacterial, antiviral and antitumor activities of these molecules having been demonstrated (Wang et al., 2022). In neonates, these components represent the first defense mechanism in the prevention of infectious diseases, such as molecules present in the vernix, such as the LL-37 peptide, which directly destroy microorganisms (Dürr et al., 2006). Furthermore, AMPs have the ability to recruit and promote other elements of the immune response (polymorphonuclear cells and T-CD4 lymphocytes), interacting with other non-protein molecules to increase the microbicidal potential of peptides (Yoshio et al., 2003; Tollin et al., 2005; Dürr et al., 2006).

Using chromatographic techniques, Yoshio et al. (2003) evaluated the antimicrobial activity through the disk diffusion method to demonstrate that extracts, protein and peptide fractions present in the vernix of healthy newborns present activity against *Bacillus megaterium* and *C. albicans* isolates, including α-defensins, LL-37 and lysozyme. Protein fractions that contained higher content of α-defensins exhibited greater antimicrobial action, evidencing the main role they play in defending the newborn against infections.

Nevertheless, defensins are not the only peptides involved in host defense. Lysozymes, which are microbicidal proteins located in different types of tissues, are recognized for their synergistic role with other antimicrobial peptides such as LL-37 and lactoferrin (Tollin et al., 2005). Lactoferrin is present in low concentrations in neonates, as is elastase in neutrophils; however, defensin levels are comparable to those found in adults (Koenig and Yoder, 2004). This allows us to deduce that AMPs are part of the antimicrobial defense of the vernix, and some of these molecules can interact with other chemotactic components to promote and stimulate the neonatal cutaneous immune response (Yoshio et al., 2003; Tollin et al., 2005).

In this sense, preterm infants born with little or no vernix caseous are more susceptible to infections than those who born at term (Yoshio et al., 2003). Furthermore, the skin, which serves as a physical barrier, is underdeveloped and immature, including its microbiota (Capone et al., 2011; Paul et al., 2020).

Tollin et al. (2005) identified and characterized AMPs and lipid components present in the vernix, demonstrating

the synergism between these components and catalecin LL-37, in relation to its antimicrobial potential. Among the identified peptides, the highlight was the presence of compounds with great antimicrobial potential, such as ubiquitin, psoriasin and calgranulin A, B and C. These proteins add protective functions to the vernix, such as antifungal activity, opsonization capacity, protease inhibition and inactivation of microorganisms.

4.2.2. Phagocytosis and oxidative stress

The role of neutrophils in the innate immune response against fungal infections is well known for their performance through phagocytosis and production of reactive oxygen species (Koenig and Yoder, 2004; Destin et al., 2009; Kumar et al., 2015; Dreschers et al., 2016; Kan et al., 2016; Michalski et al., 2017; Silvestre-Roig et al., 2019). The increase in the susceptibility of premature infants to infectious diseases is related to deficiencies in the production or functional alteration of the neutrophil, defects in adherence and endothelial migration, opsonization and phagocytosis, expression of cytokines and recognition of surface antigens, limiting the neonatal immune response (Koenig and Yoder, 2004; Manzoni et al., 2007; Netea et al., 2015; Silvestre-Roig et al., 2019).

Destin et al. (2009) carried out a study in order to compare the differences between the phagocytosis of adult and neonatal neutrophils in defense against *C. albicans* and *C. parapsilosis*, and thus evaluate the basic phagocytic response, without the participation of opsonins. For this purpose, samples of neutrophils from adults and from the umbilical cord of term and preterm newborns (22-27 weeks of gestation) were collected for *in vitro* phagocytosis assay. Results were analyzed with fluorescence microscopy to assess differences in neutrophil staining. From these findings, it was possible to evidence that there was no difference in the response mediated by adult neutrophils and premature or term neonates, suggesting that neutrophil-mediated phagocytosis did not significantly contribute to the increase in the newborn's susceptibility to acquire infectious diseases caused by yeasts of the genus *Candida* (Destin et al., 2009). Normal or complete phagocytic response is facilitated by the appropriate opsonization of microorganisms, being directly related to the presence of serum and tissue opsonins (Katsifa et al., 2001; Cockram et al., 2019).

Opsonins, protein molecules that are part of a complex molecular process of identifying and alerting innate immunity, are used by monocytes/macrophages and neutrophils to facilitate antigen recognition and trigger an effective immune response (Cockram et al., 2019). Immunoglobulins, especially IgG, fibronectin and some complement proteins (C3b and C4b) are considered opsonins, and premature neonates have lower levels of these proteins, especially those with very low birth weight and extremely low birth weight, constituting a disadvantage in relation to the macrophage and neutrophil-mediated phagocytic response to *Candida* (Koenig and Yoder, 2004; Cockram et al., 2019).

A different perspective was presented in a retrospective study conducted by Manzoni et al. (2007), wherein neonates with very low birth weight (VLBW) were compared regarding early neutropenia in the first week of life with neonates without neutropenia. The study revealed that early neutropenia serves as an independent and predisposing risk factor for colonization by Candida species, thereby increasing the prevalence of invasive candidiasis in VLBW infants. Thus, colonization by *Candida* is a predictive factor with broad clinical relevance for neonatal candidemia, and it is easy to establish a negative relationship between neutropenia and this disease (Manzoni et al., 2007).

Gioulekas et al. (2001) assessed the impact of recombinant macrophage colony-stimulating factor (M-CSF) on the antifungal activity of monocytes derived from both healthy adults and neonates against *C. albicans*. Interestingly, no discernible disparity in antifungal activity was observed between neonatal and adult monocytes. Additionally, there was no significant alteration in the antifungal activity of neonatal monocytes following treatment with M-CSF compared to untreated monocyte controls.

4.2.3. Cell signaling

Monocytes, as well as macrophages and neutrophils, are important components of the innate immune response for pathogen recognition (Awasthi et al., 2008; Bhattarai et al., 2018), through PRRs comprising a diverse family of Toll-like (TLR), NOD-like (NLR), RIG-1-like (RLR) and C-type lectin receptors (CLR) (Wang et al., 2019). These receptors, in turn, recognize molecular patterns associated with pathogens (PAMPs), such as mannans and glucans in the yeast cell wall, lipopolysaccharides in Gram-negative bacteria, and peptidoglycan in Gram-positive bacteria. This recognition initiates the development of intracellular and extracellular mechanisms that facilitate the control of microbial spread (Pivarcsi et al., 2003; Møller et al., 2005; Zhou et al., 2014; Bhattarai et al., 2018).

TLRs are part of a complex system of receptors that play an important role in the identification of microorganisms, modulation of the immune response and initiation of the effector response (Zhang et al., 2010). Furthermore, these receptors are part of a group of transmembrane proteins, responsible for effecting and participating in the differentiation of effector cells (Fleer and Krediet, 2007). There are several studies on the relationship between TLRs and recognition of *C. albicans*, however, there are few studies aimed at the expression and recognition of this microorganism in neonates (Netea et al., 2006; Seider et al., 2010; Pinke et al., 2016).

In their investigation of the susceptibility of TLR-4-deficient C3H/HeJ mice to *C. albicans* infection, Netea et al. (2002) demonstrated that the lack of TLR-mediated immune response resulted in enhanced dissemination of *Candida* spp. within the kidney tissue of these animals. Although, initially, TLR-4 was related to LPS recognition in Gram-negative bacteria, it is known that one of the greatest virtues of signaling mediated by TLRs is its ability to associate with other receptors, such as PRRs. Consequently, multiple intracellular and extracellular signaling pathways mediated by PRRs are used to generate an effector and differentiated response against

all types of microorganisms (Fleer and Krediet, 2007; Esteban et al., 2011; Kollmann et al., 2012). Other studies have demonstrated this existing cooperation between TLRs and other PRRs, resulting in a beneficial symbiosis for the distinction of pathogens, such as the participation of TLR-4 and mannose receptors in the recognition of *C. albicans* residues, while wall-associated glucans *Candida* spp. are recognized by the Dectin-1 complex, TLR-2 and TLR-6 (Netea et al., 2006; Esteban et al., 2011).

In another study, Awasthi et al. (2008) investigated the expression of TLR-2 and TLR-4 mRNA and proteins in fetal lung tissue of baboons at different gestational ages and found that the expression of these receptors increases proportionally with the time of gestation. From this research, it was observed that the expression of TLR-2 and TLR-4 is differentially regulated in response to infectious stimuli, as TLR-2 has bacterial and fungal ligands, while TLR-4 has specific ligands for recognition from Gram-negative bacteria (Roeder et al., 2004; Fleer and Krediet, 2007; Awasthi et al., 2008; Netea and Maródi, 2010).

Cytokines released after TLR stimulation have a potent regulatory effect on innate immune cells and differ depending on gestational age (Kasturi et al., 2011). For example, the production of innate anti-inflammatory cytokines (IL-10) is greater in preterm infants, while the production of Th17 cell-promoting cytokines (IL-6 and IL-23) predominates in full-term infants. During childhood, there is a decrease in the production of IL-10, IL-6 and IL-23 and an increase in the production of pro-inflammatory cytokines TNFα, IL-1β in whole blood, monocytes and dendritic cells. As a result, full-term infants show differences in immune response compared to adults, as they have a greater number of Th17 cells, resulting in increased function (Kollmann et al., 2012). On the other hand, this lower production of Th17 polarizing cytokines by the neonatal antigen-presenting cells of very prematurely newborns may partly explain their greater susceptibility to infections caused by *Candida* (Kan et al., 2016). According to Wang et al. (2020), when the body is infected by fungi, β-glucan, the main component of the fungal cell wall, binds to receptors and induces the differentiation of immature CD4+ T lymphocytes into Th17 cells through the secretion of related cytokines. In this pathway, there is an increase in cytokines that promote Th17 differentiation, such as IL-6 and IL-23, while the Th1-related stimulating cytokine, IL-12, decreases. Thus, the lack of Th17 response and low levels of IL-17 increase susceptibility to fungi and worsen the phenotype of fungal infection.

Netea et al. (2002) observed the effects of the absence of TLR receptors and demonstrated that without TLR-4 mediated signaling, there is no direct intervention on the production of pro-inflammatory cytokines or on the development of antifungal mechanisms, however, it directly interfered with the recruitment of neutrophils due to defective synthesis of cytokine KC (CXCL1) and macrophage inhibitor protein MIP-2 (CXCL2), responsible for promoting the recruitment of this cell type.

Other types of receptors involved in pathogen recognition are CLRs, which play an important role in host defense against *C. albicans* (Netea and Maródi, 2010). Dectin-1 is a CLR expressed mainly in phagocytic cells such as macrophages and dendritic cells, being responsible for the recognition of β-glucans in the *Candida* cell wall (Gantner et al., 2005).

Esteban et al. (2011) showed that fungal recognition is mediated by the association of dectin-1 and the PRR galectin-3 in macrophages. Galectin-3 is able to recognize β-1,2 oligomannans present in the cell wall of *C. albicans*, triggering a specific response against this pathogen and playing an important role in the differentiation between pathogenic and non-pathogenic fungi. Furthermore, this dectin-1/galectin-3 association modulates TNF-α induction in such a way that a reduction in galectin-3 levels decreases TNF-α induction. Therefore, the decreased levels of galectin-3 in macrophages may have a significant impact on recruitment and immune regulation during *Candida* infections.

Galectin-3 also plays a crucial role in the effector functions of neutrophils, such as the production of reactive oxygen species, degranulation, and increased phagocytosis (Farnworth et al., 2008; Linden et al., 2013; Chan et al., 2015). Therefore, the absence of galectin-3 can also negatively affect the function of neutrophils during infection. Additionally, Linden et al. (2013) observed that serum levels of galectin-3 are considerably lower in newborns compared to healthy adults. The finding of reduced serum galectin-3 levels in a population at risk for mucocutaneous and/or disseminated candidiasis leads to speculation that galectin-3 deficiency contributes to susceptibility to this condition. However, further studies are needed to establish a definitive relationship between them.

4.2.4. Reactive oxygen species

Regarding the production of Reactive Oxygen Species (ROS), these are also significantly reduced in neonates (Chang et al., 2011). On the other hand, the response to oxygen radicals is increased, favoring a reduction in the clearance of these radicals, and a consequent increase in tissue damage (Kollmann et al., 2012). This can be seen in the production of hyphae and oxygen radicals that end up signaling the TLR-2 pathway that induces an increase in the sensitivity of TLR-8 and TLR-4 due to the signaling of phospholipid membranes oxidized by oxygen radicals, thus promoting increased inflammatory response. Avoiding a more complex response, cytokine expression occurs solely mediated by TLR-2, which facilitates the spread and occurrence of infectious diseases caused by *C. albicans* (Gantner et al., 2005; van der Graaf et al., 2005; Kollmann et al., 2012).

Gantner et al. (2003) demonstrated that in macrophages and dendritic cells, Dectin-1 and TLR-2 collaborate to coordinate inflammatory responses, including cytokine secretion and ROS production, in response to particles containing β-glucan. In a separate investigation, Gantner et al. (2005) observed that Dectin-1 can readily bind to β-glucans present in specific regions of the *C. albicans* blastoconidia cell wall but does not interact with pseudohyphae.

In line with these findings, Pinke et al. (2016) also observed the involvement of TLR-2 and Dectin-1 in protective responses developed by mast cells against

C. albicans, through the production of nitric oxide. However, this process is impaired in the presence of high percentages of internalization of *C. albicans*, and there may be a dangerous fungal reservoir mechanism, which would protect these pathogens from extracellular immune mechanisms, in addition to allowing their replication. This hypothesis is supported by evidence suggesting that *C. albicans* can disrupt phagosome-lysosome fusion and impede nitric oxide detoxification, enabling its intracellular persistence (Seider et al., 2010).

5. Final Considerations

From this review, mechanisms involved in the recognition, signaling, recruitment, and effector response of neonates against invasive candidiasis were identified and discussed. These mechanisms include the presence of antimicrobial peptides, phagocytosis, synthesis of reactive oxygen species, inflammatory mediators, and complex cell signaling systems mediated by PRRs. In addition to these mechanisms, the importance of the presence of caseous vernix on the skin of newborns, which does not exist in preterm infants, and can affect the balance of the newborn's microbiota, making it more susceptible to infections.

More research is necessary to elucidate the molecular mechanisms involved in the neonate's defense, especially on TRLs, against invasive candidiasis. With this study, it is expected to contribute to the expansion of knowledge about the immunological mechanisms involved in the innate immune response of the neonate against disseminated infections caused by *Candida* species, and in the same sense, highlight the importance of this knowledge as a reflex in the reduction of mortality child, especially in the neonatal phase.

References

ARSENAULT, A.B. and BLISS, J.M., 2015. Neonatal candidiasis: new insights into an old problem at a unique host-pathogen interface. *Current Fungal Infection Reports*, vol. 9, no. 4, pp. 246-252. http://dx.doi.org/10.1007/s12281-015-0238-x. PMid:26779297.

AWASTHI, S., CROPPER, J. and BROWN, K.M., 2008. Developmental expression of Toll-like receptors-2 and -4 in preterm baboon lung. *Developmental and Comparative Immunology*, vol. 32, no. 9, pp. 1088-1098. http://dx.doi.org/10.1016/j.dci.2008.02.005. PMid:18377992.

BHATTARAI, D., WORKU, T., DAD, R., REHMAN, Z.U., GONG, X. and ZHANG, S., 2018. Mechanism of pattern recognition receptors (PRRs) and host pathogen interplay in bovine mastitis. *Microbial Pathogenesis*, vol. 120, pp. 64-70. http://dx.doi.org/10.1016/j.micpath.2018.04.010. PMid:29635052.

CAPONE, K.A., DOWD, S.E., STAMATAS, G.N. and NIKOLOVSKI, J., 2011. Diversity of the human skin microbiome early in life. *The Journal of Investigative Dermatology*, vol. 131, no. 10, pp. 2026-2032. http://dx.doi.org/10.1038/jid.2011.168. PMid:21697884.

CARDOSO, V., TREVISAN, I., CICOLELLA, D.A. and WATERKEMPER, R., 2019. Systematic review of mixed methods: method of research for the incorporation of evidence in nursing. *Texto & Contexto Enfermagem*, vol. 28, e20170279. http://dx.doi.org/10.1590/1980-265x-tce-2017-0279.

CARVALHO, A., CUNHA, C., PASQUALOTTO, A.C., PITZURRA, L., DENNING, D.W. and ROMANI, L., 2010. Genetic variability of innate immunity impacts human susceptibility to fungal diseases. *International Journal of Infectious Diseases*, vol. 14, no. 6, pp. e460-e468. http://dx.doi.org/10.1016/j.ijid.2009.06.028. PMid:19828347.

CHAN, C., BODE, L. and KIM, J., 2015. Galectin-3 binding protein in human preterm infant umbilical cord plasma. *Journal of Neonatal-Perinatal Medicine*, vol. 8, no. 2, pp. 99-104. http://dx.doi.org/10.3233/NPM-15814055. PMid:26410432.

CHANG, B.A., HUANG, Q., QUAN, J., CHAU, V., LADD, M., KWAN, E., MCFADDEN, D.E., LACAZE-MASMONTEIL, T., MILLER, S.P. and LAVOIE, P.M., 2011. Early inflammation in the absence of overt infection in preterm neonates exposed to intensive care. *Cytokine*, vol. 56, no. 3, pp. 621-626. http://dx.doi.org/10.1016/j.cyto.2011.08.028. PMid:21940177.

CHOW, B.D., LINDEN, J.R. and BLISS, J.M., 2012. *Candida parapsilosis* and the neonate: epidemiology, virulence and host defense in a unique patient setting. *Expert Review of Anti-Infective Therapy*, vol. 10, no. 8, pp. 935-946. http://dx.doi.org/10.1586/eri.12.74. PMid:23030332.

COCKRAM, T.O.J., PUIGDELLÍVOL, M. and BROWN, G.C., 2019. Calreticulin and galectin-3 opsonise bacteria for phagocytosis by microglia. *Frontiers in Immunology*, vol. 10, pp. 2647. http://dx.doi.org/10.3389/fimmu.2019.02647. PMid:31781126.

DESTIN, K.G., LINDEN, J.R., LAFORCE-NESBITT, S.S. and BLISS, J.M., 2009. Oxidative burst and phagocytosis of neonatal neutrophils confronting *Candida albicans* and *Candida parapsilosis*. *Early Human Development*, vol. 85, no. 8, pp. 531-535. http://dx.doi.org/10.1016/j.earlhumdev.2009.05.011. PMid:19481378.

DRESCHERS, S., SAUPP, P., HORNEF, M., PREHN, A., PLATEN, C., MORSCHHÄUSER, J. and ORLIKOWSKY, T.W., 2016. Reduced PICD in monocytes mounts altered neonate immune response to *Candida albicans*. *PLoS One*, vol. 11, no. 11, e0166648. http://dx.doi.org/10.1371/journal.pone.0166648. PMid:27870876.

DÜRR, U.H., SUDHEENDRA, U.S. and RAMAMOORTHY, A., 2006. LL-37, the only human member of the cathelicidin family of antimicrobial peptides. *Biochimica et Biophysica Acta*, vol. 1758, no. 9, pp. 1408-1425. http://dx.doi.org/10.1016/j.bbamem.2006.03.030. PMid:16716248.

ESTEBAN, A., POPP, M.W., VYAS, V.K., STRIJBIS, K., PLOEGH, H.L. and FINK, G.R., 2011. Fungal recognition is mediated by the association of dectin-1 and galectin-3 in macrophages. *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 34, pp. 14270-14275. http://dx.doi.org/10.1073/pnas.1111415108. PMid:21825168.

FARNWORTH, S.L., HENDERSON, N.C., MACKINNON, A.C., ATKINSON, K.M., WILKINSON, T., DHALIWAL, K., HAYASHI, K., SIMPSON, A.J., ROSSI, A.G., HASLETT, C. and SETHI, T., 2008. Galectin-3 reduces the severity of pneumococcal pneumonia by augmenting neutrophil function. *American Journal of Pathology*, vol. 172, no. 2, pp. 395-405. http://dx.doi.org/10.2353/ajpath.2008.070870. PMid:18202191.

FLEER, A. and KREDIET, T.G., 2007. Innate immunity: toll-like receptors and some more. A brief history, basic organization and relevance for the human newborn. *Neonatology*, vol. 92, no. 3, pp. 145-157. http://dx.doi.org/10.1159/000102054. PMid:17476116.

GANTNER, B.N., SIMMONS, R.M., CANAVERA, S.J., AKIRA, S. and UNDERHILL, D.M., 2003. Collaborative induction of inflammatory responses by dectin-1 and Toll-like receptor 2. *The Journal of Experimental Medicine*, vol. 197, no. 9, pp. 1107-1117. http://dx.doi.org/10.1084/jem.20021787. PMid:12719479.

GANTNER, B.N., SIMMONS, R.M. and UNDERHILL, D.M., 2005. Dectin-1 mediates macrophage recognition of Candida albicans yeast but not filaments. *The EMBO Journal*, vol. 24, no. 6, pp. 1277-1286. http://dx.doi.org/10.1038/sj.emboj.7600594. PMid:15729357.

GIOULEKAS, E., GOUTZIOULIS, M., FARMAKIS, C., DROSSOU, V., KREMENOPOULOS, G., TSIOURIS, J. and ROILIDES, E., 2001. Effects of macrophage colony-stimulating factor on antifungal activity of neonatal monocytes against *Candida albicans*. *Biology of the Neonate*, vol. 80, no. 4, pp. 251-256. http://dx.doi.org/10.1159/000047152. PMid:11641546.

GLADSTONE, I.M., EHRENKRANZ, R.A., EDBERG, S.C. and BALTIMORE, R.S., 1990. A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience. *The Pediatric Infectious Disease Journal*, vol. 9, no. 11, pp. 819-890. http://dx.doi.org/10.1097/00006454-199011000-00009. PMid:2263432.

KAN, B., RAZZAGHIAN, H.R. and LAVOIE, P.M., 2016. An immunological perspective on neonatal sepsis. *Trends in Molecular Medicine*, vol. 22, no. 4, pp. 290-302. http://dx.doi.org/10.1016/j.molmed.2016.02.001. PMid:26993220.

KASTURI, S.P., SKOUNTZOU, I., ALBRECHT, R.A., KOUTSONANOS, D., HUA, T., NAKAYA, H.I., RAVINDRAN, R., STEWART, S., ALAM, M., KWISSA, M., VILLINGER, F., MURTHY, N., STEEL, J., JACOB, J., HOGAN, R.J., GARCÍA-SASTRE, A., COMPANS, R. and PULENDRAN, B., 2011. Programming the magnitude and persistence of antibody responses with innate immunity. *Nature*, vol. 470, no. 7335, pp. 543-547. http://dx.doi.org/10.1038/nature09737. PMid:21350488.

KATSIFA, H., TSAPARIDOU, S., DIZA, E., GIL-LAMAIGNERE, C., WALSH, T.J. and ROILIDES, E., 2001. Effects of interleukin-13 on antifungal activity of human monocytes against *Candida albicans*. *FEMS Immunology and Medical Microbiology*, vol. 31, no. 3, pp. 211-217. http://dx.doi.org/10.1111/j.1574-695X.2001.tb00522.x. PMid:11720817.

KOENIG, J.M. and YODER, M.C., 2004. Neonatal neutrophils: the good, the bad, and the ugly. *Clinics in Perinatology*, vol. 31, no. 1, pp. 39-51. http://dx.doi.org/10.1016/j.clp.2004.03.013. PMid:15183655.

KOLLMANN, T.R., LEVY, O., MONTGOMERY, R.R. and GORIELY, S., 2012. Innate immune function by Toll-like receptors: distinct responses in newborns and the elderly. *Immunity*, vol. 37, no. 5, pp. 771-783. http://dx.doi.org/10.1016/j.immuni.2012.10.014. PMid:23159225.

KUMAR, D., KUMAR, A., SINGH, S. and TILAK, R., 2015. Candidemia-induced pediatric sepsis and its association with free radicals, nitric oxide, and cytokine level in host. *Journal of Critical Care*, vol. 30, no. 2, pp. 296-303. http://dx.doi.org/10.1016/j.jcrc.2014.11.023. PMid:25634073.

LEIBOVITZ, E., LIVSHIZ-RIVEN, I., BORER, A., TARABOULOS-KLEIN, T., ZAMIR, O., SHANY, E., MELAMED, R., RIMON, O.F., BRADENSTEIN, R., CHODICK, G. and GOLAN, A., 2013. A prospective study of the patterns and dynamics of colonization with *Candida* spp. in very low birth weight neonates. *Scandinavian Journal of Infectious Diseases*, vol. 45, no. 11, pp. 842-848. http://dx.doi.org/10.3109/00365548.2013.814150. PMid:23919503.

LINDEN, J.R., DE PAEPE, M.E., LAFORCE-NESBITT, S.S. and BLISS, J.M., 2013. Galectin-3 plays an important role in protection against disseminated candidiasis. *Medical Mycology*, vol. 51, no. 6, pp. 641-651. http://dx.doi.org/10.3109/13693786.2013.770607. PMid:23488971.

MANZONI, P., FARINA, D., MONETTI, C., PRIOLO, C., LEONESSA, M., GIOVANNOZZI, C. and GOMIRATO, G., 2007. Early-onset neutropenia is a risk factor for *Candida* colonization in very low-birth-weight neonates. *Diagnostic Microbiology and Infectious Disease*, vol. 57, no. 1, pp. 77-83. http://dx.doi.org/10.1016/j.diagmicrobio.2006.10.018. PMid:17178299.

MANZONI, P., MOSTERT, M., JACQZ-AIGRAIN, E., STRONATI, M. and FARINA, D., 2012. *Candida* colonization in the nursery. *Jornal de Pediatria*, vol. 88, no. 3, pp. 187-190. http://dx.doi.org/10.2223/JPED.2201. PMid:22717783.

MICHALSKI, C., KAN, B. and LAVOIE, P.M., 2017. Antifungal immunological defenses in newborns. *Frontiers in Immunology*, vol. 8, pp. 281. http://dx.doi.org/10.3389/fimmu.2017.00281. PMid:28360910.

MØLLER, A.S., OVSTEBØ, R., HAUG, K.B., JOØ, G.B., WESTVIK, A.B. and KIERULF, P., 2005. Chemokine production and pattern recognition receptor (PRR) expression in whole blood stimulated with pathogen-associated molecular patterns (PAMPs). *Cytokine*, vol. 32, no. 6, pp. 304-315. http://dx.doi.org/10.1016/j.cyto.2005.11.008. PMid:16406558.

NETEA, M.G., GOW, N.A., MUNRO, C.A., BATES, S., COLLINS, C., FERWERDA, G., HOBSON, R.P., BERTRAM, G., HUGHES, H.B., JANSEN, T., JACOBS, L., BUURMAN, E.T., GIJZEN, K., WILLIAMS, D.L., TORENSMA, R., MCKINNON, A., MACCALLUM, D.M., ODDS, F.C., VAN DER MEER, J.W., BROWN, A.J. and KULLBERG, B.J., 2006. Immune sensing of *Candida albicans* requires cooperative recognition of mannans and glucans by lectin and Toll-like receptors. *The Journal of Clinical Investigation*, vol. 116, no. 6, pp. 1642-1650. http://dx.doi.org/10.1172/JCI27114. PMid:16710478.

NETEA, M.G., JOOSTEN, L.A., VAN DER MEER, J.W., KULLBERG, B.J. and VAN DE VEERDONK, F.L., 2015. Immune defence against *Candida* fungal infections. *Nature Reviews. Immunology*, vol. 15, no. 10, pp. 630-642. http://dx.doi.org/10.1038/nri3897. PMid:26388329.

NETEA, M.G. and MARÓDI, L., 2010. Innate immune mechanisms for recognition and uptake of *Candida* species. *Trends in Immunology*, vol. 31, no. 9, pp. 346-353. http://dx.doi.org/10.1016/j.it.2010.06.007. PMid:20705510.

NETEA, M.G., VAN DER GRAAF, C.A., VONK, A.G., VERSCHUEREN, I., VAN DER MEER, J.W. and KULLBERG, B.J., 2002. The role of toll-like receptor (TLR) 2 and TLR4 in the host defense against disseminated candidiasis. *The Journal of Infectious Diseases*, vol. 185, no. 10, pp. 1483-1489. http://dx.doi.org/10.1086/340511. PMid:11992285.

PAUL, A.A., HOFFMAN, K.L., HAGAN, J.L., SAMPATH, V., PETROSINO, J.F. and PAMMI, M., 2020. Fungal cutaneous microbiome and host determinants in preterm and term neonates. *Pediatric Research*, vol. 88, no. 2, pp. 225-233. http://dx.doi.org/10.1038/s41390-019-0719-7. PMid:31816621.

PINHAT, E.C., BORBA, M.G., FERREIRA, M.L., FERREIRA, M.A., FERNANDES, R.K., NICOLAOU, S.K., OKAMOTO, C.T. and OLDENBURG NETO, C.F., 2012. Fungal colonization in newborn babies of very low birth weight: a cohort study. *Jornal de Pediatria*, vol. 88, no. 3, pp. 211-216. http://dx.doi.org/10.2223/JPED.2192. PMid:22622625.

PINKE, K.H., LIMA, H.G., CUNHA, F.Q. and LARA, V.S., 2016. Mast cells phagocyte *Candida albicans* and produce nitric oxide by mechanisms involving TLR2 and Dectin-1. *Immunobiology*, vol. 221, no. 2, pp. 220-227. http://dx.doi.org/10.1016/j.imbio.2015.09.004. PMid:26421959.

PIVARCSI, A., BODAI, L., RÉTHI, B., KENDERESSY-SZABÓ, A., KORECK, A., SZÉLL, M., BEER, Z., BATA-CSÖRGOO, Z., MAGÓCSI, M., RAJNAVÖLGYI, E., DOBOZY, A. and KEMÉNY, L., 2003. Expression and function of Toll-like receptors 2 and 4 in human keratinocytes. *International Immunology*, vol. 15, no. 6, pp. 721-730. http://dx.doi.org/10.1093/intimm/dxg068. PMid:12750356.

ROEDER, A., KIRSCHNING, C.J., RUPEC, R.A., SCHALLER, M. and KORTING, H.C., 2004. Toll-like receptors and innate antifungal responses. *Trends in Microbiology*, vol. 12, no. 1, pp. 44-49. http://dx.doi.org/10.1016/j.tim.2003.11.003. PMid:14700551.

SEIDER, K., HEYKEN, A., LÜTTICH, A., MIRAMÓN, P. and HUBE, B., 2010. Interaction of pathogenic yeasts with phagocytes: survival, persistence and escape. *Current Opinion in Microbiology*, vol. 13, no. 4, pp. 392-400. http://dx.doi.org/10.1016/j.mib.2010.05.001. PMid:20627672.

SHARMA, A.A., JEN, R., BUTLER, A. and LAVOIE, P.M., 2012. The developing human preterm neonatal immune system: a case for more research in this area. *Clinical Immunology*, vol. 145, no. 1, pp. 61-68. http://dx.doi.org/10.1016/j.clim.2012.08.006. PMid:22926079.

SILVESTRE-ROIG, C., FRIDLENDER, Z.G., GLOGAUER, M. and SCAPINI, P., 2019. Neutrophil diversity in health and disease. *Trends in Immunology*, vol. 40, no. 7, pp. 565-583. http://dx.doi.org/10.1016/j.it.2019.04.012. PMid:31160207.

SOUZA, M.T., SILVA, M.D. and CARVALHO, R., 2010. Revisão integrativa: o que é e como fazer. *Einstein*, vol. 8, no. 1, pp. 102-106. http://dx.doi.org/10.1590/s1679-45082010rw1134. PMid:26761761.

TOLLIN, M., BERGSSON, G., KAI-LARSEN, Y., LENGQVIST, J., SJÖVALL, J., GRIFFITHS, W., SKÚLADÓTTIR, G.V., HARALDSSON, A., JÖRNVALL, H., GUDMUNDSSON, G.H. and AGERBERTH, B., 2005. Vernix caseosa as a multi-component defence system based on polypeptides, lipids and their interactions. *Cellular and Molecular Life Sciences*, vol. 62, no. 19-20, pp. 2390-2399. http://dx.doi.org/10.1007/s00018-005-5260-7. PMid:16179970.

VAN DER GRAAF, C.A., NETEA, M.G., VERSCHUEREN, I., VAN DER MEER, J.W. and KULLBERG, B.J., 2005. Differential cytokine production and Toll-like receptor signaling pathways by *Candida albicans* blastoconidia and hyphae. *Infection and Immunity*, vol. 73, no. 11, pp. 7458-7464. http://dx.doi.org/10.1128/IAI.73.11.7458-7464.2005. PMid:16239547.

VAZQUEZ, J.A. and SOBEL, J.D., 2002. Mucosal candidiasis. *Infectious Disease Clinics of North America*, vol. 16, no. 4, pp. 793-820, v. http://dx.doi.org/10.1016/S0891-5520(02)00042-9. PMid:12512182.

VISSCHER, M.O., ADAM, R., BRINK, S. and ODIO, M., 2015. Newborn infant skin: physiology, development, and care. *Clinics in Dermatology*, vol. 33, no. 3, pp. 271-280. http://dx.doi.org/10.1016/j.clindermatol.2014.12.003. PMid:25889127.

WANG, P., YAO, J., DENG, L., YANG, X., LUO, W. and ZHOU, W., 2020. Pretreatment with antibiotics impairs Th17-mediated antifungal immunity in newborn rats. *Inflammation*, vol. 43, no. 6, pp. 2202-2208. http://dx.doi.org/10.1007/s10753-020-01287-w. PMid:32623554.

WANG, X., ZHANG, Y., ZHANG, R. and ZHANG, J., 2019. The diversity of pattern recognition receptors (PRRs) involved with insect defense against pathogens. *Current Opinion in Insect Science*, vol. 33, pp. 105-110. http://dx.doi.org/10.1016/j.cois.2019.05.004. PMid:31358188.

WITEK-JANUSEK, L. and CUSACK, C., 1994. Neonatal sepsis: confronting the challenge. *Critical Care Nursing Clinics of North America*, vol. 6, no. 2, pp. 405-419. http://dx.doi.org/10.1016/S0899-5885(18)30500-8. PMid:7946196.

YOSHIO, H., TOLLIN, M., GUDMUNDSSON, G.H., LAGERCRANTZ, H., JORNVALL, H., MARCHINI, G. and AGERBERTH, B., 2003. Antimicrobial polypeptides of human vernix caseosa and amniotic fluid: implications for newborn innate defense. *Pediatric Research*, vol. 53, no. 2, pp. 211-216. http://dx.doi.org/10.1203/00006450-200302000-00003. PMid:12538777.

ZHANG, J.P., YANG, Y., LEVY, O. and CHEN, C., 2010. Human neonatal peripheral blood leukocytes demonstrate pathogen-specific coordinate expression of TLR2, TLR4/MD2, and MyD88 during bacterial infection *in vivo*. *Pediatric Research*, vol. 68, no. 6, pp. 479-483. http://dx.doi.org/10.1203/PDR.0b013e3181f90810. PMid:20805788.

ZHOU, A., LI, S., WU, J., KHAN, F.A. and ZHANG, S., 2014. Interplay between microRNAs and host pathogen recognition receptors (PRRs) signaling pathways in response to viral infection. *Virus Research*, vol. 184, pp. 1-6. http://dx.doi.org/10.1016/j.virusres.2014.01.019. PMid:24480588.

WANG, L., QU, L., LIN, S., YANG, Q., ZHANG, X., JIN, L., DONG, H. and SUN, D., 2022. Biological functions and applications of antimicrobial peptides. *Current Protein & Peptide Science*, vol. 23, no. 4, pp. 226-247. http://dx.doi.org/10.2174/1389203723666220519155942. PMid:35598243.

WEIMER, K.E.D., SMITH, P.B., PUIA-DUMITRESCU, M. and ALEEM, S., 2022. Invasive fungal infections in neonates: a review. *Pediatric Research*, vol. 91, no. 2, pp. 404-412. http://dx.doi.org/10.1038/s41390-021-01842-7. PMid:34880444.