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Spontaneous Prematurity, Innate Immune System, and Oxidative Stress at the Maternal-Fetal Interface: An Overview

Natália Prearo Moço, Bruna Ribeiro de Andrade Ramos, Mariana de Castro Silva, Jossimara Polettini, Ramkumar Menon and Márcia Guimarães da Silva

Abstract

Despite the multifactorial etiology of prematurity, intra-amniotic infection is present in 25–40% of preterm pregnancies. Bacteria in amniotic cavity synthesize phospholipases associated with the production of prostaglandins that leads to rupture of fetal membranes and uterine contractions. Bacterial pathogen-associated molecular patterns (PAMPs) activate pattern recognition receptors (PRRs) such as Toll-like (TLRs) and NOD-like receptors (NLRs), triggering pathways that culminate in the production of cytokines that further increase prostaglandin release. Importantly, endogenous molecules called damage-associated molecular patterns (DAMPs) released under stressful conditions can also activate PRRs. Risk factors for both preterm labor (PTL) and preterm premature rupture of membranes (PPROM), including infection-induced inflammation, may cause an increase of ROS release and depletion of antioxidant defenses. In spite of the similarity between the pathophysiology of PTL and PPRM, there are significant differences regarding molecular mediators, degree of tissue damage, and oxidative stress present in these two conditions. PPRM seems to be a consequence of notable tissue damage resulting from chronic oxidative stress, while PTL is associated with minimal tissue degradation resulting from acute exposure and greater antioxidant status. A better understanding of prematurity pathophysiology and the differences between PTL and PPRM can benefit therapeutic approaches to prevent these important inflammatory syndromes.

Keywords: prematurity, innate immune system, oxidative stress

1. Introduction

Innate immune responses play a critical role at different stages of gestation, and a successful pregnancy depends on the balance between anti- and pro-inflammatory molecules. In addition, normal pregnancy is marked by increased oxidative stress, due to increased fetal metabolism, decreased maternal antioxidant reserves,

or maternal supply of substrate. Disruption of these two major mechanisms, inflammation and oxidative stress, is closely linked to spontaneous prematurity.

2. Innate immunity and pattern recognition receptors (PRRs)

Innate immunity is a primordial defense system implicated in the identification and eradication of infectious agents that also recognizes products from damaged cells and works to eliminate them. The innate immune system acts through the recognition of molecular structures common to microorganisms, called pathogen-associated molecular patterns (PAMPs) and endogenous molecules called damage-associated molecular patterns (DAMPs) [1], which are passively released from damaged and dying cells, or actively secreted by immune cells or severely stressed cells [2].

PAMPs and DAMPs are recognized by pattern recognition receptors (PRRs) expressed by several cell types [1, 3]. Their ubiquitous localization in cells enables PRRs to recognize microorganisms present in distinct compartments. Membrane-bound PRRs are located in the plasma membrane, endosomal and lysosomal membranes, while cytosolic PRRs are located in the cytoplasm of cells [1, 3].

Toll-like receptors (TLR) are PRRs coupled to the cell membrane [4], composed of type I integral membrane glycoproteins, comprised of an ectodomain with a leucine-rich repeat domain (LRR), an endodomain with Toll/IL-1 receptor (TIR), that shares a 200-amino acid conserved region with interleukin-1 (IL-1) and IL-18 receptors, and a short transmembrane domain [1, 5]. The ectodomain recognizes specific PAMPs, while the endodomain recruits adaptor molecules, enabling the intracellular cascade [5].

The first group of TLRs is responsible for the recognition of structural components of microorganisms and comprises receptors expressed on the cell surface, including TLR-1, TLR-2, TLR-4, TLR-5, TLR-6, and TLR-11 [4]. The second group includes receptors exclusively expressed in intracellular vesicles, TLR-3, TLR-7, and TLR-9, which recognize nucleic acids from microorganisms [4, 6].

PAMPs' recognition by TLRs activates intracellular pathways that lead to the activation of transcription factors responsible for the expression of genes involved in inflammatory and antiviral responses [1, 5, 6]. Among the transcription factors activated by TLR signaling, the most common factors are nuclear factor kappa-B (NF- κ B), activating protein 1 (AP-1), interferon regulatory factor 3 (IRF3), and IRF7 [1]. Activation of NF- κ B and AP-1 results in the transcription of several genes of pro-inflammatory effector molecules, such as cytokines and chemokines, while the activation of IRF3 and IRF7 leads to the production of type I interferons that are involved in antiviral immunity [1, 3].

Intracellular signaling through NF- κ B and AP-1 is very well characterized [4, 7], and TLR-4 and TLR-9 are shown as examples of TLRs on the cell surface and in endosomes, respectively, in **Figure 1**. The activation of TLRs by PAMPs and DAMPs triggers the formation of a signaling complex, a myddosome, composed of protein MyD88 and interleukin-1 receptor-associated kinase 1 (IRAK1) and IRAK4, leading to activation of pro-inflammatory transcription factors, NF- κ B and AP-1.

Although infection is the main stimulus for inflammation, it can also be induced in sterile conditions [8]. Therefore, DAMPs are as important to sterile inflammation as PAMPs are to innate response to microorganisms. DAMPs are endogenous factors that in physiologic conditions are protected from cellular receptors. During

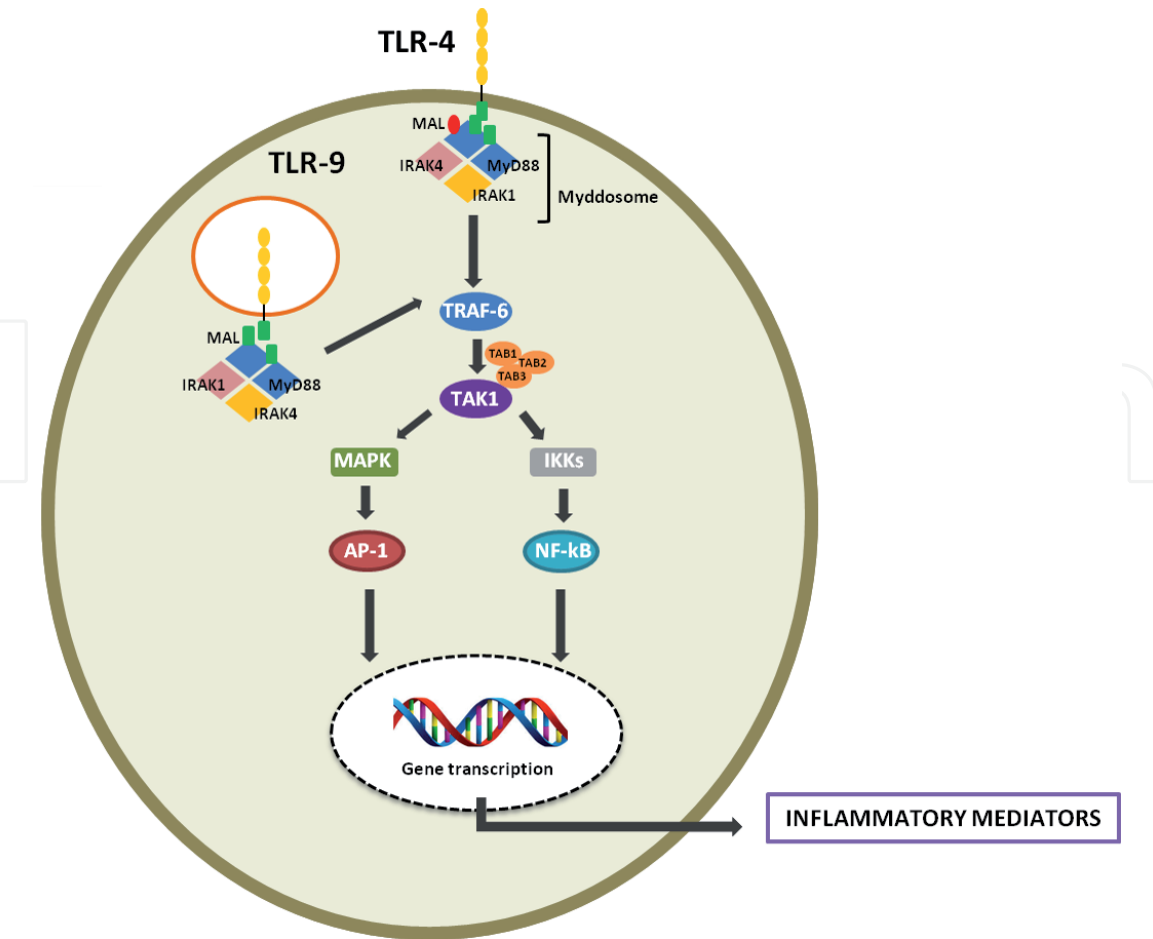


Figure 1.
Overview of TLR signaling pathways. Activation of TLRs on the cell surface or endosomal membranes and formation of myddosome complex, leading to activation of pro-inflammatory transcription factors NF- κ B and AP-1. Communication between TLR and the myddosome occurs through interaction of the TIR domain of the Toll-like receptor with the TIR domain of MyD88 and depends on the adapter molecule called MAL, allowing the myddosome to form a helical structure. IRAK-4 activates IRAK-1, which undergoes autophosphorylation. Phosphorylated IRAK-1 then binds to TRAF-6, resulting in the activation of the TAK-1, which results in activation of the cascade of Ks that phosphorylate the inhibitory protein of NF- κ B, leading to activation of NF- κ B. Additionally, the activation of TAK-1 protein also results in activation of MAPKs, leading to activation of the transcription factor AP-1. AP-1, activator protein 1; IKK, I κ B kinase; IRAK, interleukin-1 receptor-associated kinase; MAL, MyD88-adapter-like protein; MAPK, mitogen-activated protein kinase; MYD88, myeloid differentiation primary response protein 88; TAB, TAK1-binding protein; TAK1, transforming growth factor β (TGF- β)-activated kinase 1; TRAF6, tumor necrosis factor receptor-associated factor 6. Adapted from Kawasaki and Kawai [4].

tissue damage, DAMPs are liberated from cells and are recognized by immune cells [9]. DAMPs can also be actively secreted by immune and severely stressed cells [2]. Evidence shows that PAMPs and DAMPs act in different ways to stimulate innate immunity. Antigen-presenting cells that are unresponsive to lipopolysaccharide (LPS) can be activated by necrotic cells, indicating that TLR-4 activation, regardless of LPS, occurs in response to endogenous ligands [10]. Similarly, TLR-3 recognizes cells that undergo necrosis during acute inflammatory events, independently of the presence of viral PAMPs [11].

Among the cytosolic PRRs, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are of great importance [1]. The NLR family is a class of intracellular receptors that lead to intracellular signaling associated to inflammation, after recognition of PAMPs and DAMPs [1]. Members of the NLR family are characterized by at least three domains: the first one is an LRR domain, responsible for the recognition of the ligand; the second is a NACHT domain that allows the formation of oligomers of NLRs; and the third is the effector domain, usually a

caspace recruitment domain (CARD), responsible for the recruitment of accessory proteins [12].

The first NLRs described were NOD-1 and NOD-2 [13], which recognize peptides from degradation of peptidoglycan (PG) that occurs during bacterial growth or destruction. Recognition of PGs by NOD-1 and NOD-2 leads to activation of intracellular pathways, which activate the transcription factor NF- κ B, and results in the synthesis of several inflammatory cytokines [14, 15].

Members of the NLR family known as NLRP are capable of responding to cytoplasmic PAMPs and DAMPs through the formation of intracellular signaling complexes, termed inflammasomes [1]. Inflammasomes activate proteases from the caspase family during immune regulation in physiologic and pathologic conditions [16]. The typical structure of the inflammasome consists of NLRP, adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC; also known as PYCARD), and pro-caspase [17]. This transient oligomer starts a cascade that culminates with activation of caspase-1 and production of the active form of IL-1 β [18] and IL-18 [19].

The inflammasome NLRP3 is activated in response to several PAMPs, such as flagellin, muramyl dipeptide, LPS, and pore-formation toxins [1]. Moreover, it can be activated by DAMPs, reactive oxygen species (ROS), and environmental signals [16, 20]. Three models describing mechanisms of NLRP3 inflammasome activation have been suggested, which may not be mutually exclusive [21–23] (**Figure 2**). In the absence of activation mechanisms, NLRP3 inflammasome complex is autorepressed, owing to an interaction between NATCH domains and LRRs. When one or

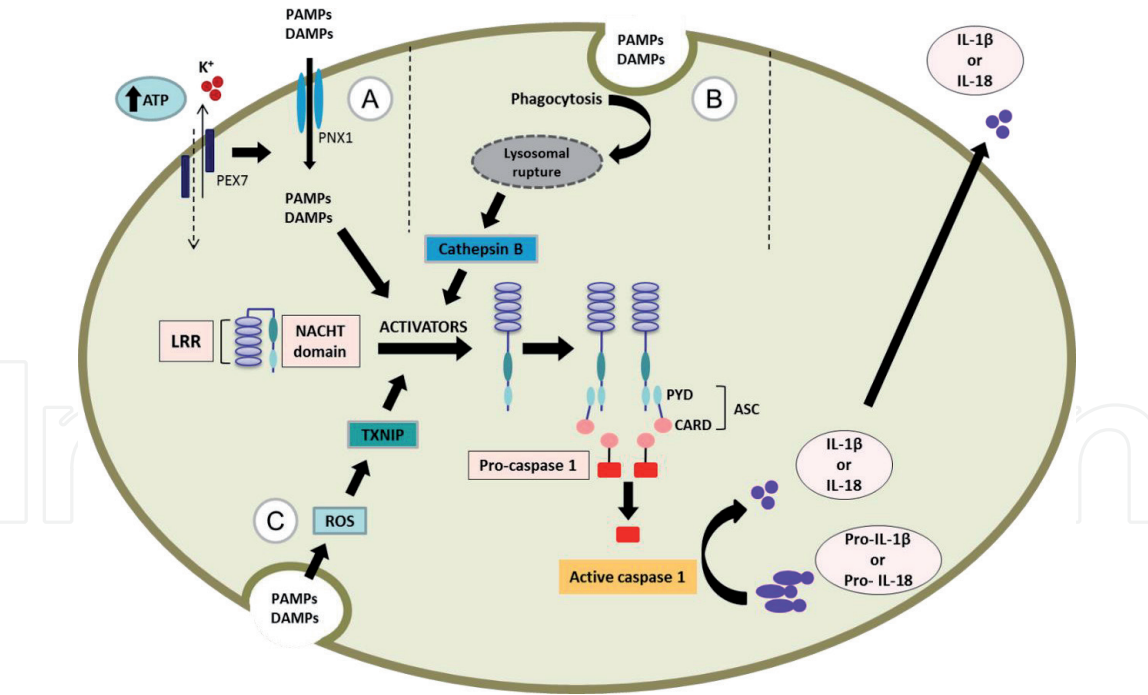


Figure 2. Mechanisms of NLRP3 inflammasome activation. PAMPs and DAMPs are able to induce the activation of the NLRP3 inflammasome by three principal mechanisms: (A) high concentrations of extracellular ATP lead to opening of PANX1 channels by binding to the P2X7 receptor, which results in K⁺ efflux and influx of PAMPs and DAMPs; (B) phagocytosis of PAMPs and DAMPs leads to disruption of the lysosomal membrane and consequent release of a putative NLRP3-activating molecule, such as cathepsin B; and (C) PAMPs and DAMPs can induce the production of ROS, which may activate TXNIP to trigger NLRP3 activation. Activation of the NLRP3 inflammasome results in maturation of caspase-1 and release of mature forms of IL-1 and IL-18. ATP, adenosine triphosphate; DAMPs, damage-associated molecular patterns; LRR, leucine-rich repeat domain; PAMPs, pathogen-associated molecular patterns; PANX1, pannexin-1; ROS, reactive oxygen species; TXNIP, thioredoxin-interacting protein. Adapted from Tschopp and Schroder [23].

more activation mechanism is present, this autorepression is removed, resulting in NATCH domain exposure. After this exposure, NLRP3 oligomerizes and recruits ASC and pro-caspase 1, leading to activation of caspase 1 and, consequently, maturation and secretion of IL-1 β and IL-18 [21, 22]. The immune response initiated by inflammasome activation shows a close relationship with both physiologic and pathologic processes, as immunological defense and development of inflammatory diseases [20].

3. Pregnancy, maternal immunity, and oxidative stress

During pregnancy, a tightly regulated immune system allows for fetal survival and its adequate development. Among the several modifications made by the maternal immune system to raise tolerance to the allograft fetus, changes in cytokine profiles at the maternal-fetal interface are of great importance [24].

Recent data have shown that a successful pregnancy depends on a complex balance between anti- and pro-inflammatory molecules that changes throughout pregnancy [25, 26]. First trimester is characterized by prevalence of the T helper cell type 1 (Th1) profile. During this stage, an inflammatory micro-environment is necessary for repair and remodeling of the uterine epithelium damaged during implantation and for removal of cellular debris [27]. In the second trimester, there is a prevalence of a Th2 profile [28–30]. The increased anti-inflammatory activity is important for maintenance of gestation. During the third trimester and labor, the Th1 profile is again predominant systemically [31] in the placental tissue and amniotic fluid, supporting the theory that proinflammatory overload in the intrauterine environment is required for initiation and progression of labor [32, 33]. The final trimester is characterized by an influx of immune cells at the maternal-fetal interface and increased production of pro-inflammatory cytokines [34, 35]. This scenario is essential for the development of the physiologic processes of cervical remodeling, weakening and rupture of fetal membranes, and initiation of uterine contractility, which together culminate in labor [36, 37].

Recent studies have also demonstrated that normal pregnancy is marked by increased oxidative stress, due to increased fetal metabolism, decreased fetal antioxidant reserves, or maternal supply of substrate [38, 39]. Oxidative stress results from exacerbated production of ROS and/or decreased production of antioxidants. Increased oxidative stress has been described in the third trimester of normal pregnancies and labor [38]. During the process of labor, the intensity of uterine contractions increases uterus pressure and can cause interruption or reduction in the uteroplacental blood flow, causing cycles of cellular hypoxia and reoxygenation. These events of parturition are responsible for inducing increased oxidative stress in pregnant women, which must be controlled by their antioxidant system [40, 41].

3.1 Prematurity, inflammatory response, and oxidative stress

Prematurity is the leading cause of neonatal mortality and is also responsible for several short- and long-term morbidities. The risk for these complications is inversely proportional to gestational age at birth [42–44]. Preterm delivery (PTD) is defined as birth before 37 weeks of gestation, and the incidence of PTD among singleton pregnancies is 9.6% worldwide [45]. Spontaneous PTD can be divided into PTD, which is preceded by preterm labor (PTL) with intact membranes, or

by preterm premature rupture of membranes (PPROM) [43, 46]. The incidence of PTL is approximately 60 and 30–40% for PPRM [27, 35, 47].

The etiology of prematurity is multifactorial and includes maternal, paternal, and genetic risks [48–52], as summarized in **Table 1**. Despite this multifactorial etiology, studies show that intra-amniotic infections (IAI) are present in 25–40% of preterm pregnancies; however, these frequencies are believed to be underestimated [43, 53].

The main infection route into the amniotic cavity (AC) is the ascending of bacteria present in the lower genital tract through the endocervical canal. Ascending bacteria can then cross the membranes and invade the AC, with subsequent proliferation in the amniotic fluid. Once microorganisms reach this site, they may travel to the amnion, connective tissue, and even chorion and decidua [54]. The establishment of inflammation in the chorioamniotic membranes in response to bacteria is called chorioamnionitis. Clinical chorioamnionitis (cCAM) occurs in 1–2% of term labors and in 5–10% of PTLs, and this prevalence increases in case of PPRM due to

Maternal		
Sociodemographic characteristics		African-American ethnicity
		Extreme maternal ages
		Low socioeconomic index
		Smoking
		Drugs and alcohol abuse
Clinical and gynecological history		Previous prematurity
		Diabetes
		Hypertension
		Cervical cone biopsy
Gestational characteristics		Multiple gestation pregnancies
		Placenta previa
		Placenta abruption
		Preeclampsia
		Polyhydramnios or oligohydramnios
		Uterine and cervical anomalies
		Assisted conception
		Infections
		Bacterial vaginosis
		Periodontal infection
		Chlamydial infection
		Intrauterine infection
Paternal	High paternal age	
Genetics	Polymorphisms	IL-1R,IL-1β, IL-6, IL-10, MMP-1, MMP-9, TLR-4, TNF-α, HPS47

IL-1R, interleukin 1 receptor; IL-1β, interleukin 1 beta; IL-6, interleukin 6; IL-10, interleukin 10; MMP-1, matrix metalloproteinase 1; MMP-9, matrix metalloproteinase 9; TLR-4, Toll-like receptor 4; TNF-α, tumor necrosis factor alpha; HPS47, heat shock protein 47.

Table 1.
Risk factors for spontaneous prematurity.

the compromised immune status of the fetal membranes [55]. Histological chorioamnionitis (hCAM) is defined by the presence of polymorphonuclear cells (PMN) in the chorioamniotic membranes. Most cases of hCAM are not followed by clinical signals and symptoms of infection; however, the diagnosis is made in approximately 20% of term pregnancies and over 50% of PTLs [56–58].

The main microorganisms found in the AC of pregnant women with IAI are *Ureaplasma urealyticum*, *Mycoplasma hominis*, and *Fusobacterium* sp. Gram-negative bacilli such as *Bacteroides* sp. and *Prevotella* sp. are also occasionally found, along with *Escherichia coli*, *Gardnerella vaginalis*, and group B *Streptococcus* [59–61].

The main mechanism by which IAI leads to prematurity is through the production of prostaglandins. Bacteria present in amniotic fluid synthesize phospholipases that, in turn, activate the liberation of arachidonic acid that is metabolized via cyclooxygenase, culminating in the production of prostaglandins. Concomitantly, activation of TLRs and NLRs by PAMPs present in these bacteria initiates production and release of inflammatory cytokines, which increase the release of prostaglandins by macrophage, decidual, and amniotic cells [62, 63].

PTL and PPRM pathways are similar in etiology; however, according to Menon et al. [64], the major difference is the presence of molecular factors associated with infection, such as metalloproteinases and pro-apoptotic factors that are responsible for structural modifications and weakening of fetal membranes in patients undergoing PPRM. These same factors are absent or minimally expressed in PTL. Other differences between PTL and PPRM include the distinct response to microorganisms present in the AC [65–67] and the intensity of the inflammatory response [68].

Recently, new data have demonstrated the participation of oxidative stress in the physiopathology of PPRM [69, 70], suggesting that this pathology is similar to term pregnancies with regard to degradation, apoptotic signals, oxidative stress, and premature aging of fetal membranes [71, 72]. Increased levels of oxidative stress markers have been not only associated with the third trimester of normal pregnancy and labor [73] but also observed during second trimester pregnancy disorders, such as preeclampsia and low birth weight [74]. Hence, early senescence, a mechanism leading to fetal membrane aging and immunological dysfunction, is a feature of PPRM [72, 75, 76]. Risk factors for both PTL and PPRM, including infection-induced inflammation, may cause an increase of ROS release and depletion of antioxidant defenses [76, 77]. In this way, Menon suggests that PPRM is characterized by pronounced tissue damage resulting from oxidative stress and proteolysis, while PTL has minimal tissue damage [76]. The greater tissue damage present in PPRM may be a consequence of chronic exposure to oxidative stress risk factors. PTL, in turn, may result from acute oxidative stress associated with a better antioxidant status, a scenario in which the capacity of cell resistance is maintained, while the inflammatory response required for initiation of labor pathway is preserved. PPRM also differs from PTL in its molecular signature linked to senescence of fetal membranes, where premature aging and tissue injury cause DAMPs' release from fetal membranes, which can also contribute to rupture and secondary invasion of microbes due to an immunocompromised environment. Therefore, sterile inflammation by senescent fetal tissues is also a major contributor to PPRM pathology. We have reported differences in antioxidants, telomere length (marker of aging), F2-isoprostanes (markers of oxidative lipid peroxidation), and senescence-associated β -galactosidase (senescence) in fetal membranes and amniotic fluid between PPRM and spontaneous preterm births without PPRM, illustrating the molecular differences between the two phenotypes [75, 78, 79].

3.2 TLRs and NLRs at the maternal-fetal interface and pregnancy complicated by chorioamnionitis and prematurity

Regarding the maternal-fetal interface, expression of TLRs has mainly been investigated in chorioamniotic membranes and the placenta. TLR-2 and TLR-4 are able to recognize most PAMPs present in pathogens involved in AC infections, which are associated with precocious activation of inflammatory response in amniochorionic membranes. Due to this, they are evaluated in most studies concerning TLR expression at maternal-fetal interface.

TLR-2 recognizes microbial lipoproteins, peptidoglycans, and lipoteichoic acid from Gram-positive bacteria, lipoarabinomannan from mycobacteria, zymosan from fungi, and hemagglutinin from smallpox virus [80]. The large capacity of recognition shown by TLR-2 can be explained by its ability to form heterodimers with TLR-1 and TLR-6. The heterodimer TLR-1/TLR-2 recognizes tri-acetylated lipopeptides, while TLR-2/TLR-6 recognizes zymozan and diacetylated lipopeptides [80, 81]. TLR-4 recognizes LPS from Gram-negative bacteria, an important macrophage activator and initiator of septic shock [82].

Kim et al. [83] showed increased expression of TLR-2 in chorioamniotic membranes with hCAM. Our group provided the first report of increase in TLR-1 and TLR-2 mRNAs in fetal membranes of preterm pregnancies with hCAM, when compared to preterm membranes without hCAM [84]. Kumazaki et al. [32] showed that placental macrophages from preterm pregnancies complicated by CAM had increased immunoreactivity to TLR-4, when compared to those without inflammatory infiltrate or term placentas. Using immunohistochemistry techniques, Rindsjö et al. [85] demonstrated an important reduction in TLR-2 expression in placentas in the setting of hCAM and reasoned that the expression of this receptor is probably affected by inflammatory processes in the membranes. Moreover, Kacerovsky et al. [86, 87] showed that pregnant women with PPRM and microbial invasion of the AC had higher levels of soluble TLR-1, TLR-2, TLR-4, and TLR-6 in amniotic fluid.

The expression of TLR-2 and TLR-4 by amniotic epithelium suggests that the epithelium not only works as a mechanical barrier against microorganisms but also plays an important part in the activation of innate immunity [83]. According to Kim et al. [83], the increased expression of these receptors in term membranes reinforces the association between labor and inflammation, as described by Keelan et al. [88]. This upregulation of TLRs may enhance maternal and fetal protection against microbial invasion of the AC. However, Holmlund et al. [89] did not observe differences in TLR-2 and TLR-4 expression between trophoblastic cells, stimulated with zymozan and LPS, and nonstimulated trophoblasts. A possible explanation is that both receptors may be overexpressed in uterine tissue as a defense mechanism, which can protect the fetus against infection during pregnancy and labor. Gonzalez et al. [90] showed that pregnant and nonpregnant mice present different TLR expression in their uterine tissue and that the expression of TLR-2, -3, -4, and -9 increases throughout pregnancy. This finding is in agreement with those of Beijar et al. [91], who reported lower expression of TLR-4 in first trimester villi, when compared to term villi. The apparent disagreement among studies may reflect differences in response to infection in distinct sites of the placenta and gestational tissues.

While several studies showed that gestational tissues express TLRs and are capable of responding to pathogens who present TLR-specific ligands, few studies have discussed the expression of NLRs at the maternal-fetal interface during normal and complicated pregnancies [92–97]. Gene expression of NOD1 was observed in the placenta of pregnant women at term [92, 93], while first trimester placenta villi expressed NOD1 and NOD2 mRNA, both by syncytiotrophoblast and

cytotrophoblast cells [94]. This differential expression is also observed functionally; the first trimester trophoblast cells trigger an inflammatory response following exposure to the NOD1 and NOD2 protein ligands, while trophoblast cells from term pregnancies only respond to the NOD1 ligand [94]. Interestingly, Wang et al. demonstrated that expression of NOD1 and NOD 2 in placental villi and decidua was higher in epithelium than in tissue stroma, reinforcing the idea that epithelial tissues are strongly involved in the host defense response at the maternal-fetal interface [96].

Regarding chorioamnionitis, Romero et al. [95] observed that the expression of NOD2 and NLRP3 in chorioamniotic membranes was higher during labor at term in the presence of histologic chorioamnionitis (hCAM), than in membranes without hCAM; however, only the NLRP3 protein concentration was increased in chorioamniotic membranes in the presence of hCAM. Additionally, Pontillo et al. [97] observed that LPS from Gram-negative bacteria increases expression of the NLRP3 inflammasome in trophoblast and decidual stromal cells, suggesting that this multiprotein complex could be important in placental immune defense against invading pathogens.

4. Conclusion

Inflammation and oxidative stress are important to the success of normal pregnancy, and their disruption is closely related with pregnancy complications. Regarding inflammatory responses, special receptors of the maternal innate immune system are capable of responding to microbial ligands present in amniotic fluid during intra-amniotic infection, resulting in an exacerbation of inflammatory mediator production, which is associated with the precocious activation of the parturition pathway. Additionally, studies have demonstrated the participation of oxidative stress in the physiopathology of PPRM, highlighting the similarity between PPRM and term pregnancies in relation to degradation and aging of fetal membranes. In this way, PPRM would be a consequence of notable tissue damage resulting from chronic oxidative stress, while PTL would be associated with minimal tissue degradation, resulting from acute exposure associated with a better antioxidant status. This indicates that exacerbation of the maternal inflammatory response and oxidative stress operates in an interdependent way in the pathophysiology of spontaneous preterm birth, including PTL and PPRM.

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Conflict of interest

The authors declare that this research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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