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Intrauterine infection and preterm labor

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Summary

Preterm labor is defined as labor that begins before 37 completed weeks of pregnancy. More than 12% of infants born in the USA are preterm. At least 40% of preterm births are associated with intrauterine infection. Toll-like receptors (TLRs) are members of a family of cell-surface proteins responsible for recognition of a diverse spectrum of bacterial, viral and fungal pathogens. TLRs initiate the host innate (i.e. non-adaptive) immune response, inducing a proinflammatory cascade involving cytokines, chemokines, prostaglandins, and other effector molecules that result in the characteristic phenomena of labor, such as uterine contractions and rupture of fetal membranes. These cascades may also be activated by mechanisms that are not primarily infectious but are accompanied by inflammatory responses. Now that the molecular mechanisms linking infection and labor have been, to a large extent, elucidated, the challenge is to identify points of overlap with non-infectious causes of labor and to find intervention strategies that can minimize the negative impact of preterm delivery.

Keywords

Chorioamnionitis; Cytokines; Preterm delivery; Preterm rupture of membranes; Toll-like receptor

[A]Introduction

Preterm labor is defined as labor that begins before 37 completed weeks of pregnancy. More than 12% of infants born in the USA are preterm.¹ Preterm birth is the major cause of neonatal morbidity and mortality in developed countries. Sequelae of preterm birth are common in the neonatal period, may persist into adulthood and are inversely related to gestational age.

Preterm birth may result from either spontaneous developments or medically indicated interventions. Known causes of spontaneous preterm labor include infection (intrauterine or extrauterine), multiple gestation, placental abruption, hormonal disruptions and other

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factors,² though a large proportion of preterm births are ‘idiopathic’, or without known cause.

At least 40% of preterm births are associated with intrauterine infection.³ In individual cases it is often difficult to determine whether infection is the cause or consequence of the processes leading to preterm delivery. However, there is abundant evidence that infection and the inflammation generated by infection, whether within the gestational tissues or elsewhere, are a primary cause of a substantial proportion of preterm births. This evidence includes the following: (a) the amniotic fluid of patients with preterm labor has higher rates of microbial colonization and levels of inflammatory cytokines than preterm patients not in labor and term patients in labor;⁴ (b) intrauterine or systemic administration of microbes or microbial products to pregnant animals can result in preterm labor and delivery;^{5–11} (c) extrauterine maternal infections such as pyelonephritis,¹² pneumonia¹³ and periodontal disease¹⁴ have been associated with premature parturition; (d) subclinical intrauterine infections are associated with preterm labor and delivery;¹⁵ (e) patients with intra-amniotic infection¹⁶ or intrauterine inflammation (i.e. elevation of amniotic fluid cytokines¹⁷ and matrix-degrading enzymes¹⁸) identified as early as the mid-trimester are at risk for subsequent preterm delivery.

It is notable that the molecular signals for the onset of parturition, whether normal parturition at term or various forms of abnormal parturition, are not well understood. Nonetheless, the mechanisms by which infection leads to labor have been elucidated, at least in part. There is some evidence that normal spontaneous labor at term has features characteristic of inflammatory processes¹⁹ but the extent to which the mechanisms of normal and abnormal labors overlap to produce uterine contractions is largely unknown. Furthermore, it is not well understood how risk factors for preterm delivery (such as African ancestry, smoking, cervical shortening and others) impact upon molecular events to increase the likelihood of early labor, though several of these factors have been linked to inflammatory processes.

A similar lack of clarity exists for the phenomenon of rupture of membranes (ROM). While ROM is a feature of most spontaneous labors, its occurrence prior to the onset of labor (known as ‘premature’ – or ‘prelabor’ – rupture of membranes, or PROM) is considered, at least in some contexts, abnormal. When PROM occurs prior to 37 weeks of gestation, it is known as ‘preterm PROM’, or PPRM. PPRM complicates 2–4% of all singleton and 7–20% of twin pregnancies and is associated with 18–20% of perinatal deaths.²⁰ The processes leading to ROM in general, and to PROM/PPROM in particular, are incompletely understood. Again, there is evidence of a role for inflammatory processes with a secondary component of protease activity leading to weakening of the membranes,²¹ but how all these events are timed or produced in sequence has not been well defined. For the purposes of this review, unless otherwise stated we include both spontaneous preterm labor with intact membranes and PPRM as part of the same spectrum of phenomena leading to early delivery.

Inflammation can be considered a regulated process by which the body responds to injurious stimuli in an attempt to limit the scope of damage and repair affected tissues. One convenient conceptual model for inflammatory responses in pregnancy is that they are part of a maternal self-preservation reaction to threats to the mother, fetus or both. The resultant production of labor is not so much a ‘side-effect’ as a direct and possibly desired consequence: it leads to the evacuation of an infected body cavity that jeopardizes the health and/or the life of the mother, so that reproductive capacity is preserved for the future.

[A]Frequency and clinical significance of intrauterine infection

Intrauterine infections caused by bacteria are considered to be the leading cause of infection-associated preterm labor. The amniotic cavity is normally sterile; <1% of women not in labor at term will have bacteria in the amniotic fluid. Therefore, the isolation of bacteria in the amniotic fluid is a pathologic finding, known as microbial invasion of the amniotic cavity (MIAC). Most such colonization is subclinical and is undetectable without amniotic fluid analysis. The frequency of MIAC depends upon clinical presentation and gestational age. In patients with preterm labor with intact membranes, the rate of positive amniotic fluid cultures is 12.8%.²² However, among those patients who have preterm labor with intact membranes who go on to deliver a preterm neonate, the frequency is nearly double (22%). Among women with PPRM, the rate of positive amniotic fluid cultures at admission is 32.4%; however, by the time labor begins, as many as 75% will have MIAC,²² suggesting that microbial invasion is enhanced by removal of the physical barrier of the membranes after they rupture. The frequency of MIAC among women with cervical insufficiency is as high as 51%.²³ If the cervix is short (sonographic cervical length <25 mm, an independent risk factor for preterm birth) MIAC has been noted in 9% of cases.²⁴ All of the above values are likely to be underestimates, given that recent studies have demonstrated the relative inferiority of traditional culturing methodologies compared to polymerase chain reaction for detection of bacterial and viral pathogens.²⁵

Patients with MIAC are more likely to deliver preterm, have spontaneous ROM, develop clinical chorioamnionitis, and experience adverse perinatal outcomes than patients with preterm labor or PPRM with sterile amniotic fluid. The lower the gestational age at presentation (preterm labor with intact membranes or PPRM), the higher the frequency of positive amniotic fluid cultures.²⁶ Thus, infection is more prevalent in earlier spontaneous preterm birth.

As noted above, it is likely that not only infection per se, but also the inflammation that results from infection and, indeed, inflammatory states not due to infection, which is responsible for the phenomena of preterm labor and PROM. This may account for many cases in which there is neither clinical nor microbiological evidence of intrauterine infection, or in which infection occurs in sites remote from the gestational tissues.

[A]The role of viruses in preterm labor

Data related to viruses and preterm birth are relatively scarce, though evidence suggests that viral entry into trophoblast cells induces apoptosis and the resultant inflammatory events can lead to preterm birth.²⁷ Viral DNA is detected in the amniotic fluid of up to 15% of asymptomatic low-risk pregnancies.²⁸ The most common viral DNA isolates, either in low- or high-risk pregnancies, are adenovirus, cytomegalovirus, and enterovirus. The absence of a global marker for viral genomes (paralleling bacterial 16S ribosomal RNA, common to many different bacterial species) limits current molecular methods to screening for specific, known viruses.

Acute intrauterine viral exposure may result in preterm labor and delivery. Pregnant women are at higher risk of spontaneous preterm birth if they have circulating hepatitis B virus antigens.²⁹

Experimental models also suggest the possible induction of labor by viral infection. Polyinosinic:cytidylic acid [poly(I:C)] is a toll-like receptor (TLR)3 ligand and a synthetic analog of double-stranded RNA (a replication intermediate in the life cycle of most viruses). Poly(I:C) induces preterm delivery in mice when injected into the uterus in mid-late gestation³⁰ or systemically in late gestation.³¹

[A]Molecular mechanisms linking infection and labor

Micro-organisms are recognized by TLRs and other pattern recognition receptors and activate the innate immune system, inducing a proinflammatory cascade orchestrated by, among other elements, the transcription factor NF- κ B.³² This cascade results in the elaboration of effector molecules such as cytokines [e.g. interleukin (IL)-1 and tumor necrosis factor (TNF- α)], chemokines (e.g. IL-8),²² prostaglandins,³³ proteases and other enzymes,³⁴ to produce a coordinated response featuring uterine contractions, placental detachment, infiltration of inflammatory cells into gestational tissues, a series of biochemical and structural changes in the cervix known as ‘ripening’ and weakening of the fetal membranes (Fig. 1). These cascades may also be activated by mechanisms that are not primarily infectious but are accompanied by inflammatory responses, including activation of complement^{35,36} and generation of thrombin.³⁴

The evidence that the above mechanisms are in play is abundant, and includes both data from humans (associating inflammatory mediators with preterm labor and infection) and experiments performed in animal models (mice,^{10,11,30} rats,⁵ rabbit,⁹ sheep,^{7,37} non-human primates,⁸ and other species) in which bacteria,⁹ bacterial products^{6,10,37–39} or inflammatory cytokines^{8,11} induce labor accompanied by the stereotypical expression of inflammatory markers. The clinical use of prostaglandins to induce labor and, conversely, of prostaglandin synthase inhibitors to suppress uterine contractions is well known. The anti-inflammatory cytokine IL-10 has been shown to prevent delivery in a monkey model of bacterially induced preterm labor⁸ and LPS-induced preterm birth in mice⁴⁰ and rats.⁴¹

Genetic evidence also supports the involvement of TLRs, inflammatory cytokines and proteases in infection/inflammation-associated preterm birth. Genetic polymorphisms for TLR4, TNF- α , IL-1 β , interferon (IFN)- γ , IL-6, matrix metalloproteinase (MMP)-1 and MMP-9 have been associated with differential risk of spontaneous preterm birth.^{42–46} Some of these genetic risks appear to be specific for racial groupings or environmental exposures, emphasizing the multifactorial nature of genetic risk and the importance of gene–environment interaction in determining phenotype.^{45,46}

The evidence suggests that molecular cascades leading to preterm delivery may be activated well before preterm labor becomes clinically apparent and may account for the observation that antibiotic therapy is ineffective for treating preterm labor even in cases of overt infection. The search for pre-existing infection and inflammation has extended as far back as the interval prior to conception, though antibiotic treatment trials conducted in the preconception period⁴⁷ and first-trimester⁴⁸ have not been effective in impacting the risk of subsequent preterm delivery.

The recent clinical re-discovery of progesterone as an effective agent to prevent preterm birth is also relevant.^{49–51} Data have supported the concept that progesterone’s mechanism of action involves suppression of inflammation⁵² (see below).

[A]Molecular intermediates of infection- and inflammation-associated preterm labor

[B]Toll-like receptors (TLRs)

Activation of the innate immune system by ‘pathogen-associated molecular patterns’, or PAMPs, is the first step by which micro-organisms are thought to initiate an inflammatory response. TLRs are members of a family of cell-surface proteins responsible for recognition of a diverse spectrum of pathogens and for generating downstream signals coordinating the host immediate (i.e. non-adaptive) response against non-self. TLRs typically dimerize or

hetero-dimerize and link to additional proteins (e.g. binding proteins, adaptor proteins, etc.) to exert their effects.

Recognition of PAMPs by TLRs on leukocytes (e.g. monocytes, neutrophils, macrophages)⁵³ and other cells and tissues (such as dendritic cells, epithelial cells and trophoblast⁵⁴) induces an intracellular signal transduction cascade that leads to the transcription of genes such as inflammatory cytokines, chemokines, interferons, and other effectors (Fig. 1).

Among the presently known 13 TLRs, only TLR1–10 have been found in humans.⁵⁵ The expression of all 10 TLRs has been described in the human placenta, and the dominant cell type expressing these TLRs is the trophoblast.⁵⁶ TLRs are differentially expressed by trophoblast according to the gestational age and stage of differentiation. The lack of TLR expression by the outer trophoblast layer suggests that the first- and second-trimester placenta will only respond to a microbe that has broken through this outer layer,⁵⁷ a possible mechanism for minimizing over-reactions to exposures that do not represent a real threat to the pregnancy. Expression of TLRs across gestation has been demonstrated in the uterus, cervix, and placenta of mice.⁵⁸

[C]TLR2—TLR2 plays a major role in Gram-positive bacterial recognition.⁵⁵ TLR2 hetero-dimerizes with either TLR1 or TLR6. These dimers recognize constituents of Gram-positive bacteria such as peptidoglycan (PGN), lipoteichoic acid (LTA), meningococcal porins and molecular patterns associated with fungi, parasites and viruses. Studies in pregnant mice demonstrate that group B streptococcus⁵⁹ and PGN (extracted from Gram-positive cell walls)⁶ can induce preterm delivery in a dose-dependent manner.

Women with chorioamnionitis who deliver preterm show significant upregulation of the TLR2 receptor in the fetal membranes, implicating a role for the receptor in preterm birth and infection.⁶⁰ Systemic administration of PGN induces activation of the NF- κ B transcription factor, and first trimester trophoblast cells produce significant amounts of IL-8 and IL-6, ultimately leading to apoptosis after engagement of TLR2.⁶¹

[C]TLR3—As noted above, TLR3 is involved in the response to viral infection by recognizing double-stranded RNA.⁵⁵ Activation of TLR3 via administration of the synthetic analog poly(I:C) induces preterm delivery in the mouse along with the enhanced production of the transcription factor NF- κ B, IFN- β and the chemokine (C-C motif) ligand 5 (CCL5) in gestational tissues.^{6,31}

[C]TLR4—TLR4 recognizes lipopolysaccharide (LPS) motifs found in the majority of Gram-negative bacteria. Using TLR4-deficient animals, it has been demonstrated that TLR4 is necessary for normal susceptibility to preterm delivery induced by LPS¹⁰ or *E. coli*.⁶² TLR4-neutralizing monoclonal antibody significantly reduces the incidence of inflammation-induced preterm delivery and fetal death in mice.⁶³ Pretreatment with TLR4 receptor antagonists inhibits LPS-induced preterm uterine contractility, cytokines and prostaglandins in rhesus monkeys.⁶⁴ Elevated leukocyte TLR4 levels may be a useful biomarker associated with preterm labor.⁶⁵

[C]TLR9—TLR9 recognizes unmethylated CpG DNA motifs. Such motifs are present in double-stranded DNA viruses, fetal DNA, and in >80% of bacterial genomes.⁵⁵ In a study using CpG to activate TLR9 in pregnant mice, IL-10 KO mice were highly susceptible to CpG-mediated inflammatory responses comprised of macrophage and neutrophil migration to the placenta coupled with a marked increase in serum TNF- α and preterm birth.⁶⁶

[B]Synergy among TLR signaling pathways

TLR2 and TLR4 signaling pathways act in a synergistic fashion with TLR3 pathways.^{6,67,68} Combined stimulation with TLR2 and TLR3 agonists leads to the induction of preterm delivery and to synergistic expression of both TLR2- and TLR3-dependent proinflammatory mediators both in vivo and in vitro (Fig. 2). This synergy is mediated in part via induction of TLR2 by both TLR2 and TLR3 ligand.⁶ In a second example of synergy, TLR4 activation by LPS treatment of mice infected with murine gammaherpesvirus-68 induces preterm delivery in 100% of animals in <24 h, but in only 29% of mice without prior viral infection. This synergy leads to upregulation of proinflammatory cytokines and chemokines in placenta and decidua in vivo.^{67,68}

[B]Cytokines and chemokines

Changes in levels of proinflammatory cytokines and chemokines such as IL-1, IL-6, IL-8, and TNF have all been implicated in the onset and progression of preterm labor in humans.^{69,70} The association of preterm labor with elevations in the expression of inflammatory cytokines within the amniotic cavity has been cited above. Women with preterm labor and intact membranes who delivered within 7 days of amniocentesis had higher amniotic fluid concentrations of proinflammatory cytokines than those who delivered more than 7 days after amniocentesis regardless of the amniotic fluid culture results.⁷¹ Various studies have shown that these and other proinflammatory factors are detectable in cervicovaginal fluid during the course of pregnancy in women with bacterial vaginosis or in those who had preterm delivery with associated intra-amniotic infection.^{72,73} Moreover, a significant increase in inflammatory cytokines, such as IL-1 β , IL-6, IL-8 and TNF- α in cervicovaginal fluid has been shown to be a risk factor for preterm labor and birth.^{74,75} These studies suggest that these factors may constitute useful predictors of preterm labor.

In experimental animals (mice and non-human primates) administration of IL-1 or TNF- α into the gestational compartment or the peritoneal cavity was sufficient to induce labor and delivery.^{11,76} The redundancy of cytokine signaling networks has been well established and has led to the conclusion that although sufficient, individual cytokines may not be necessary for preterm labor. Thus, a study using mice lacking receptors for IL-1 and TNF demonstrated that although IL-1 signaling was not required for a normal response to bacterially induced labor, the combination of IL-1 and TNF signaling is necessary.⁷⁷

[B]Prostaglandins

Primary prostaglandins are formed from arachidonic acid through activity of the cyclooxygenase (COX) enzyme complex, with COX-1 considered a constitutive isoform (though this characterization has not proven accurate) and COX-2 an inducible isoform of the enzyme. Prostaglandins stimulate uterine contractions and cervical ripening during labor. Prostaglandin E₂ (PGE₂) and prostaglandin F_{2 α} (PGF_{2 α}) are produced by maternal and fetal tissues during parturition, and the concentrations of both increase in the amniotic fluid during labor.³³ Administration of prostaglandin synthase inhibitors suppresses uterine activity, while exogenous prostaglandin products are commonly used to induce labor. In one report, both COX-1 and COX-2 expression within the uterus was significantly altered within 2 h of LPS administration, with COX-2 increasing and COX-1 decreasing.⁷⁸

The NAD1-dependent 15-hydroxy prostaglandin dehydrogenase (PGDH) is responsible for the initial inactivation of prostaglandins, catalyzing the conversion of primary prostaglandins to their biologically inactive 15-keto derivatives. Expression and activity of PGDH have been demonstrated in feto-maternal tissues of different species. Reduced PGDH expression and activity in myometrium and chorion may be important in term and preterm birth in humans.³³ In the mouse, PGDH mRNA increased in placentas and fetal

membranes.⁷⁹ during late gestation. *PGDH* gene is downregulated during bacterially induced preterm labor.⁶² Thus, the synthesis and degradation of prostaglandins appear to be regulated both in spontaneous and infection-induced labors.

[B]Progesterone

Progesterone has an essential role in maintaining pregnancy primarily by promoting uterine quiescence. In many species the withdrawal of progesterone (e.g. via ovariectomy in rodents or the administration of antiprogestational agents in rodents and humans) leads to labor.

However, the importance of progesterone for maintenance of human pregnancy was for many years obscured by the observation that humans do not experience a drop in circulating progesterone prior to the onset of parturition (unlike some species, such as rodents). Progesterone therapy is an effective intervention for preventing preterm birth in humans with specific risk factors;^{49–51} however, it results in seemingly insignificant alterations of circulating progesterone. This finding and other recent observations have led to the conclusion that a functional, rather than absolute withdrawal of progesterone occurs, possibly within the critical tissues of the cervix or the fetal membranes.^{50,80} One mechanism for such a functional withdrawal might occur via regulation of the relative expression of agonist and antagonist receptors.⁸¹

The mechanism of action of progesterone to prevent delivery may involve its anti-inflammatory properties. Pretreatment with progesterone or medroxyprogesterone acetate in mice injected with intrauterine LPS was associated with suppression of activation of contraction-associated genes and inflammatory mediators, prevention of cervical ripening, reduced expression of TLR2 receptors and a reduction in preterm labor in the mouse.⁵² Similarly, progesterone pretreatment of placental chorionic plate arteries from term pregnancies was associated with reduced production of IL-6 after LPS exposure.⁸² Progesterone exerts a negative effect on prostaglandin production.⁸³

[B]Nitric oxide (NO)

Nitric oxide (NO) is a major paracrine mediator and important regulatory agent in various female reproductive processes, including labor and delivery. Throughout gestation, production of NO remains upregulated in myometrium and contributes to uterine quiescence.⁸⁴ Close to term, NO production decreases. Progesterone is reported to upregulate NO synthase (NOS) II expression and NO production in the uterus.⁸⁵ A decrease in serum progesterone or administration of low-dose antiprogestins enhances the effectiveness of NO inhibitors, causing preterm labor in the mouse.⁸⁶

[B]Reactive oxygen species

Reactive oxygen species (ROS) are generated by the body's response to diverse insults such as infection. Free radicals may activate collagenolytic enzymes and impair fetal membrane integrity.⁸⁷ Human studies have consistently demonstrated that increased ROS production occurs in preterm infants and is associated with a relative lack of antioxidant enzyme concentration and activity. Urinary 8-hydroxy-20-deoxyguanosine (a sensitive marker of oxidative stress) is significantly higher in preterm compared with term infants.⁸⁸

[B]Complement

The complement system is activated in response to infection and leads to the release of several biological components, which can induce smooth muscle contraction, enhance vascular permeability and attract white blood cells. Studies using animal models show that excessive complement activation at the feto-maternal interface places the fetus at risk for growth restriction or death and pregnancy loss.³⁵ Complement activation in early pregnancy

is associated with preterm delivery.³⁶ Clinical studies report that preterm labor in the context of infection is associated with activation of the complement system.³⁶

[B]Platelet-activating factor (PAF)

Platelet-activating factor (1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) is a potent phospholipid inflammatory mediator produced by most cells. Local and systemic release of PAF is tightly regulated by the enzyme phospholipase A₂; the enzyme PAF-acetylhydrolase (PAF-AH) mediates its degradation. Mediators of inflammation decrease levels and transcription of PAF-AH. PAF elicits its diverse effects through activation of a G-protein-coupled receptor, PAF receptor.

Cytokines and endotoxin can decrease the release of PAF-AH from uterine decidual cells.⁸⁹ Systemic levels of PAF-AH decrease, while levels of PAF increase in rats as parturition nears.⁹⁰ PAF is elevated in the amniotic fluid of patients with preterm labor who ultimately deliver preterm.⁹¹ Intrauterine administration of a stable PAF analog (mcPAF) in mice on day 15 of gestation causes preterm delivery.¹⁰

[B]The ‘two-hit hypothesis’ and endogenous toll-like receptor ligands in preterm labor

The discovery of synergy during combined stimulation of TLR2 or TLR4 (receptors for Gram-positive and -negative bacteria, respectively) and TLR3 (viral receptor)^{6,67,68} has led to the development of a ‘two-hit hypothesis’ to explain the pathophysiology of infection-associated preterm labor. As noted above, preterm labor may be viewed as a self-preservation response by the mother, whose health has been jeopardized by an infected bodily compartment. Preterm delivery is an event with dire consequences for the fetus in nature and therefore must have a well-regulated trigger mechanism. A ‘two hit’ trigger and the existence of synergism would tend to blunt the maternal response to mild insults (such as subclinical infection), while providing for rapid and efficient amplification of the labor response in cases of a superimposed more severe infection.

This two-hit postulate might also explain the phenomenon of ‘idiopathic’ preterm labor, or preterm labor for which there is no apparent cause. Several ‘endogenous TLR ligands’ produced by the host have been described. One or more of these endogenous ligands, if expressed at inappropriate levels, times or sites, might constitute the first ‘hit’, with a second hit (normally insufficient to have a deleterious effect) providing a sufficient stimulus to induce labor.

In the context of pregnancy there are several candidates for such a dysregulated endogenous TLR ligand. One of these is surfactant protein (SP)-A, the major lung surfactant protein and a ligand for TLR2 and TLR4. Human myometrial cells express SP-A binding sites and respond to SP-A to initiate signaling events related to human parturition.⁹² Condon *et al.* reported that SP-A secreted by the fetal lung serves as an inflammatory signal for parturition,⁹³ causing activation and migration of fetal macrophages to the maternal uterus leading to premature delivery.

A second candidate, endogenous TLR ligand, is a low molecular weight hyaluronic acid (HA).⁹⁴ HA is a disaccharide glycosaminoglycan polymer (composed of as many as tens of thousands of disaccharide repeats). HA plays an important role in cervical ripening and is involved in the regulation of cervical tissue water content, collagenolytic enzymes and cytokines.⁹⁵ Low molecular weight degradation products of HA polymers are produced during inflammation and are ligands for TLR2 and TLR4.⁹⁴

[A]Conclusions

The link between infection and preterm labor has long been recognized. In recent years the mechanisms underlying this phenomenon have become clearer. It may well be that we are nearing a complete picture of the molecular pathways by which infection leads to labor. Important questions remain, however: where is the mechanistic overlap between infectious and non-infectious causes of labor to produce the same end product of uterine contractions and rupture of membranes? Are idiopathic preterm labors the consequence of inappropriate activation of endogenous inflammatory pathways and, if so, can this be corrected? Can diagnostic and predictive methods be improved in order to identify patients at risk before preterm labor becomes clinically apparent, by which time it is in general too late for existing treatments to be effective? The answers to these and other questions may lead to clinical tools to further reduce the incidence, morbidity and mortality of preterm birth, which, despite decades of research, remains a major source of human suffering.

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Research directions

- Enhance diagnostic and predictive tools in order to improve the identification of patients at risk before preterm labor becomes clinically apparent, by which time it is in general too late for existing treatments to be effective. Such tools might include a molecular signature in serum, cervico-vaginal secretions or amniotic fluid.
- Improve understanding of the role of genetics, epigenetics and gene–environment interactions in the pathophysiology of preterm labor.
- Improve therapeutic interventions to treat preterm labor.
- Elucidate the role of fetus in initiation and perpetuation of preterm labor and delivery.
- Understand the role of endogenously produced factors in the genesis of abnormal labor.

Figure 1.

Overview of proposed pathways of infectious and non-infectious labor. AP-1, activator protein 1; CCL5, chemokine (C-C motif) ligand 5; dsRNA, double-stranded RNA; IL, interleukin; LMW-HA, low molecular weight hyaluronan; LPS, lipopolysaccharide; LTA, lipoteichoic acid; NFκB, nuclear factor κB; PAF, platelet-activating factor; PGN, peptidoglycan; STAT, signal transducers and activators of transcription; TNF, tumor necrosis factor.

Figure 2.

Synergy between toll-like receptor (TLR)-2 and TLR3 activation. (a) In vivo: preterm delivery rates in day-14.5 pregnant CD-1 mice following intrauterine administration of peptidoglycan (PGN) (TLR2 agonist) and/or polyinosinic:cytidylic acid [poly(I:C)] (TLR3 agonist). Preterm delivery was defined as delivery of at least one pup within 48 h (all deliveries occurred in <36 h). *P*-Values are by Fisher's exact test. (b) In vitro: RAW 264.7 cells were stimulated with either phosphate-buffered saline, PGN (1 g/mL), poly(I:C) (10 g/mL) or both PGN and poly(I:C) for 5 h. Real-time polymerase chain reaction was performed for interleukin (IL)-1 β and normalized to the housekeeping gene glyceraldehyde 3-phosphate dehydrogenase (GAPDH). *P*-Value was calculated for all four treatments simultaneously by analysis of variance. *n* = 3 replicates per condition. Depicted is a representative example from among three repeat experiments. Similar results were obtained for tumor necrosis factor- α , nitric oxid synthase 2 and chemokine (C-C motif) ligand 5 (CCL5) (not shown).⁶ Modified from Ilievski and Hirsch.⁶