Minireview: Fetal-Maternal Hormonal Signaling in Pregnancy and Labor

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Mechanisms underlying the initiation of parturition remain unclear. Throughout most of pregnancy, uterine quiescence is maintained by elevated progesterone acting through progesterone receptor (PR). Although in most mammals, parturition is associated with a marked decline in maternal progesterone, in humans, circulating progesterone and uterine PR remain elevated throughout pregnancy, suggesting a critical role for functional PR inactivation in the initiation of labor. Both term and preterm labor in humans and rodents are associated with an inflammatory response. In preterm labor, intraamniotic infection likely provides the stimulus for increased amniotic fluid interleukins and migration of inflammatory cells into the uterus and cervix. However, at term, the stimulus for this inflammatory response is unknown. Increasing evidence suggests that the developing fetus may produce physical and hormonal signals that stimulate macrophage migration to the uterus, with release of cytokines and activation of inflammatory transcription factors, such as nuclear factor κB (NF-κB) and activator protein 1 (AP-1), which also is activated by myometrial stretch. We postulate that the increased inflammatory response and NF-κB activation promote uterine contractility via 1) direct activation of contractile genes (*e.g. COX-2*, *oxytocin receptor*, and *connexin 43*) and 2) impairment of the capacity of PR to mediate uterine quiescence. PR function near term may be compromised by direct interaction with NF-κB, altered expression of PR coregulators, increased metabolism of progesterone within the cervix and myometrium, and increased expression of inhibitory PR isoforms. Alternatively, we propose that uterine quiescence during pregnancy is regulated, in part, by PR antagonism of the inflammatory response. (***Molecular Endocrinology*** **23: 947–954, 2009)**

Preterm labor is the major cause of neonatal morbidity and mortality in developed countries. In the United States, the incidence of preterm birth has increased steadily over the past two decades and now approaches approximately 13% of all live births (www.marchofdimes.com/peristats). Preterm birth is even more prevalent among certain racial and ethnic groups. For example, about 18.0% of Black infants are born prematurely, whereas the prematurity rate in White infants is about 11% (www.marchofdimes.com/peristats). This racial disparity remains, even after adjustments are made for socioeconomic status, geographic location, and access to healthcare. Of the approximately 500,000 babies born prematurely in the United States each year, about 25,000 develop respiratory distress syndrome, which is caused by the immaturity of the neonatal lungs and their inability to produce adequate amounts of pulmonary surfactant, a developmentally regulated, glycerophospholipid-rich lipoprotein that reduces alveolar surface tension and is essential for air breathing (1). The relatively high incidence of preterm birth is due, in part, to our incomplete understanding of the pathways that maintain uterine quiescence throughout pregnancy as well as those that promote increased uterine contractility and cervical ripening leading to labor. There is increasing evidence to suggest that both term and preterm labor are associated with an inflammatory response within the maternal uterus and cervix and that uterine quiescence during most of pregnancy is maintained by the antiinflammatory actions of progesterone acting via its nuclear receptor [progesterone receptor (PR)]. In this mini-review, we will consider the roles of fetal hormones and factors in the induction of the inflammatory response leading to parturition. We also will review findings to support the concept that maintenance of uterine quiescence *vs.* induction of contractility is precisely controlled by the relative impact of the antiinflammatory actions of progesterone/PR *vs.* those of transcription factors, such as nuclear factor-κB (NF-κB)

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Abbreviations: AP-1, Activator protein 1; COX-2, cyclooxygenase-2; DHEA, dehydroepiandrosterone; dpc, days postcoitum; GR, glucocorticoid receptor; GRE/PRE, GR/PR response element; 20αHSD, 20α-hydroxysteroid dehydrogenase; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor κB; PR, progesterone receptor; SP-A, surfactant protein A; SRC, steroid receptor coactivator.

and activating protein-1 (AP-1). These transcription factors serve to up-regulate inflammatory response pathways and impair PR function. Mechanisms that result in the attenuation of PR function leading to labor also will be considered.

Inflammatory Pathways and the Initiation of Labor

As mentioned above, both term and preterm labor are associated with an inflammatory response. This is exemplified by increased concentrations of proinflammatory cytokines (*i.e.* IL-1β) in amniotic fluid (2) and infiltration of the myometrium, cervix, and fetal membranes by neutrophils and macrophages (3–5). The invading immune cells secrete cytokines and chemokines (6), resulting in activation of NF-κB and other proinflammatory transcription factors in the myometrium (4, 7) and in cervical epithelial and amnion cells (8–10). Activated NF-κB, in turn, increases expression of genes promoting myometrial contractility, including the *prostaglandin $F_2\alpha$ receptor* (11), the gap junction protein *connexin 43* (12), the *oxytocin receptor* (13), and *cyclooxygenase-2* (*COX-2*) (14). In preterm labor, intraamniotic infection associated with chorioamnionitis may provide the stimulus for increased amniotic fluid interleukins and inflammatory cell migration (15). At term, mechanical stretch (16, 17) caused by the growing fetus, as well as hormonal signals produced by the developing fetus near term (4, 18–20), promote production of chemokines leading to macrophage migration and up-regulation of inflammatory response pathways.

Fetal Signals and the Initiation of Labor

Whereas infection with associated chorioamnionitis has been suggested to serve as a stimulus for enhanced leukocyte activation and proinflammatory cytokine production leading to preterm labor (6), the signals for the increased inflammatory response associated with labor at term has remained less clear. There is increasing evidence to suggest that the fetus may generate signals that contribute to the initiation of labor. Described below are the fetal tissues and signaling molecules that have been proposed to serve a role in the initiation of parturition at term in different animal models.

Fetal adrenal gland: cortisol

In sheep, maturation of the hypothalamic-pituitary-adrenal axis during the last 2–3 wk of gestation with increased cortisol production by the fetal adrenal gland has been suggested to serve a role in the initiation of labor (21). The elevated fetal cortisol production has been proposed to enhance *COX-2* expression in the placenta, leading to increased production of prostaglandins, which stimulate expression of 17α-hydroxylase/17,20-lyase (product of the *CYP17* gene). This, in turn, is proposed to enhance placental production of C_{19}-steroids, which are metabolized to estrogens by placental aromatase P450 (product of the *CYP19* gene). The increased estrogens are suggested to augment uterine contractility by antagonizing PR function (19). Importantly, the surge of fetal cortisol also increases maturation of the fetal lung and its capacity to synthesize surfactant (22), which as discussed below, may also serve as a fetal signal for initiation of labor.

Placenta: CRH

The primate placenta is unique in its ability to produce CRH (23), whereas it lacks the capacity to express *CYP17*. Thus, the human placenta cannot synthesize C_{19}-steroids, which instead are produced in large quantities by the fetal adrenal glands (24). In the human, it has been suggested that CRH, which is secreted in increasing amounts by the placenta near term, provides a fetal signal for the initiation of labor (25, 26). The increased fetal CRH is proposed to up-regulate secretion by the fetal pituitary of ACTH, which enhances production of cortisol and dehydroepiandrosterone (DHEA) sulfate by the fetal adrenal. DHEA sulfate subsequently is metabolized to DHEA and aromatized within the placental syncytiotrophoblast to estrogens, which as mentioned above, have been proposed to oppose the action of progesterone/PR to maintain uterine quiescence. Interestingly, progesterone has a pronounced inhibitory effect on CRH expression by cultured human trophoblast cells (27, 28). CRH mRNA also is developmentally induced to relatively high levels in bronchiolar epithelium of fetal mouse lung between 13.5 and 17.5 d postcoitum (dpc) and is then extinguished at 18.5 dpc (29). This rise in CRH expression precedes the developmental induction of synthesis of the major surfactant protein, surfactant protein A (SP-A), by the fetal lung. Developmental induction of *SP-A* expression was found to be delayed together with lung maturation in *CRH*-null mouse fetuses of *CRH*-deficient mothers (30). Therefore, CRH may contribute to the initiation of labor by acting indirectly to enhance fetal ACTH and adrenal cortisol production and/or directly to stimulate fetal lung maturation and the production of surfactant components. In this regard, we and others have suggested that augmented surfactant production by the maturing fetal lung may serve as a fetal signal for the initiation of labor.

Fetal lung: surfactant lipids and proteins

The synthesis and secretion of pulmonary surfactant by the fetal lung is initiated during the third trimester of gestation. Surfactant, a glycerophospholipid-rich lipoprotein, is produced by alveolar type II pneumocytes and is secreted into amniotic fluid with fetal breathing movements. Surfactant contains four essentially lung-specific proteins, SP-A, SP-B, SP-C, and SP-D (31, 32). Whereas SP-B and SP-C are lipophilic proteins that work together with surfactant lipids to reduce alveolar surface tension (31, 33), SP-A and SP-D are C-type lectins that function as part of the innate immune system. As such, they bind to a variety of microbial pathogens and enhance their phagocytosis by immune cells (*e.g.* macrophages) within the lung alveolus (32, 34, 35).

Lopez-Bernal *et al.* (36) observed that pulmonary surfactant isolated from human amniotic fluid stimulated the synthesis of prostaglandin E in discs of human amnion. They postulated that surfactant phospholipids secreted by the fetal lung into amniotic fluid provide a source of arachidonic acid as precursor for prostaglandin synthesis by the amnion. Mitchell and colleagues (20) reported that a substance in amniotic fluid caused a marked increase

in prostaglandin E_2 production by cultured human amnion cells. Although they postulated that this might arise from the fetal kidney, the nature and source of this substance were never identified. Johnston and colleagues (37) proposed that platelet-activating factor, a highly bioactive phospholipid component of fetal lung surfactant that is secreted into amniotic fluid near term, may play an important role in the activation of myometrial contractility.

Our findings suggest that SP-A, secreted by the fetal lung into amniotic fluid in large amounts near term, may provide an important signal for the initiation of labor (4). Postnatally, SP-A enhances immune function within the lung alveolus by activating alveolar macrophages, increasing cytokine production, and activating NF-κB (34, 35, 38, 39). SP-A synthesis by the fetal lung is initiated only after about 80% of gestation is complete, in concert with augmented synthesis of surfactant glycerophospholipids, and reaches maximal levels before term (40). In studies using human fetal lung type II cells in culture, we observed that *SP-A* gene expression is itself increased by proinflammatory stimuli; *SP-A* expression is up-regulated by IL-1 via activation of NF-κB (41) and by hormones and factors that increase cAMP (41, 42). Furthermore, others have demonstrated that intraamniotic administration of IL-1 in pregnant rabbits increased SP-A expression in fetal lung (43) and caused preterm birth (44). By contrast, cAMP and IL-1 induction of *SP-A* expression in human fetal lung type II cells is blocked by glucocorticoids, which exert antiinflammatory actions through glucocorticoid receptor (GR) antagonism of NF-κB activation and binding to the *hSP-A* promoter (45, 46). Glucocorticoids also cause histone modifications indicative of repressed chromatin (45).

In the mouse, SP-A mRNA, which is barely detectable in fetal lung at 16 dpc, is up-regulated at 17 dpc and increases markedly toward term (19 dpc) (47, 48). SP-A protein, which is absent in amniotic fluid at 16 dpc, is readily detectable at 17 dpc and increases to extremely high levels at 19 dpc (4). This gestational increase in SP-A secretion by the fetal lung was associated with a parallel increase in IL-1β protein expression in macrophages isolated from amniotic fluid, migration of activated macrophages to the pregnant uterus, and activation of uterine NF-κB (4). Accordingly, SP-A treatment of mouse amniotic fluid macrophages at 15, 17, and 19 dpc enhanced IL-1β expression. Using a transgenic mouse model in which fetal macrophages stained positively for β-galactosidase, we obtained evidence that a proportion of the macrophages present within the maternal uterus near term are derived from the fetus (4).

To directly assess the capacity of SP-A to initiate labor *in vivo*, parallel groups of mice were injected with purified SP-A or with a control, SP-A-depleted preparation (4). The majority of mice injected with SP-A on 15 dpc delivered prematurely on d 16–17 of gestation. Fetuses in the uninjected horn were not delivered and were ultimately resorbed. Importantly, fetal macrophage migration and NF-κB activation were detected within the SP-A-injected uterine horn by 4.5 h but not in the uninjected horn, suggesting a local inflammatory response. To further evaluate the role of endogenous SP-A in the initiation of labor, another series of 15-dpc pregnant mice were intraamniotically injected with an antibody raised against SP-A to deplete endogenous levels of the surfactant protein in amniotic fluid. Interestingly, all of the mice in this group delivered viable pups 24 h late (20 dpc) (4).

Based on these collective findings, we suggest that augmented production of SP-A by the maturing fetal lung near term provides a hormonal stimulus for activation of a cascade of inflammatory signals within the maternal uterus that culminate in the enhanced myometrial contractility leading to parturition (49). This hormonal signal, which is transmitted to the uterus by fetal macrophages, reveals that the fetal lungs are sufficiently developed to withstand the critical transition from an aqueous to an aerobic environment. Our findings further suggest that NF-κB serves as a key transcriptional mediator of the uterine inflammatory response leading to labor. We propose that activated NF-κB promotes increased uterine contractility by direct and indirect mechanisms. For example, NF-κB can bind directly to the promoters of genes that mediate increased uterine contractility, including the *prostaglandin $F_2\alpha$ receptor* (11), the gap junction protein *connexin 43* (12), the *oxytocin receptor* (13), and *COX-2* (14). Alternatively, NF-κB can block the capacity of the PR to activate genes that control uterine quiescence.

Progesterone/PR Maintains Uterine Quiescence via Antiinflammatory Actions

Uterine quiescence is maintained throughout most of pregnancy by elevated levels of circulating progesterone acting through PR. However, to date, the PR target genes that prevent uterine contractility remain to be identified. Recent findings suggest that progesterone/PR action to maintain uterine quiescence may be indirect; by inhibiting activation of inflammatory response pathways and expression of contractile genes within the uterus and cervix and blocking the production of chemokines that promote chemotaxis of immune cells. Interestingly, even during the estrous cycle in rodents, migration of macrophages and neutrophils to the uterus is stimulated by estrogen and inhibited by progesterone (50–52). This antagonistic effect of progesterone on estrogen-induced macrophage/neutrophil migration fails to occur in mice with a deletion of the *PR* gene (*PRKO* mice) and is, therefore, PR dependent (52). Furthermore, *PRKO* mice manifest a massive uterine inflammatory response upon estrogen (52) or estrogen plus progesterone treatment (53).

Expression of the β-chemokine, monocyte chemoattractant protein-1 (MCP-1/CCL-2), which attracts and activates macrophages, was found to be stimulated by NF-κB and inhibited by progesterone/PR in choriodecidual and breast cancer cells (54). Notably, MCP-1 was reported to be up-regulated in myometrium of women in labor, as compared with myometrium from term pregnant women not in labor (55) and of pregnant rats before and during parturition (16). Furthermore, MCP-1 expression and macrophage infiltration were greatly increased in the pregnant rat uterus after PR blockade by RU486 treatment, which caused preterm parturition, and were inhibited by progestin treatment, which delayed parturition (16). In unilaterally pregnant rats, increased MCP-1 mRNA was evident only in the gravid horn, implying a possible role of fetal-derived factors and/or of uterine stretch (16).

Using telomerase-immortalized human myometrial cells, we observed that progesterone/PR plays a major antiinflammatory role via antagonism of both NF-κB activation and induction of COX-2 (56, 57). A similar phenomenon was noted in studies using human fetal lung type II cells (58), amnion epithelial cells, lower uterine segment fibroblasts (59), and human breast cancer cells (60). By use of chromatin immunoprecipitation analysis, we found that progesterone treatment of the human myometrial cells blocked IL-1 induction of *in vivo* binding of NF-κB p65 to both proximal and distal NF-κB response elements in the *COX-2* promoter (61). The progesterone-mediated decrease in p65 binding to the *COX-2* promoter might be caused, in part, by a direct physical interaction of PR with p65 as was previously observed *in vitro* (62), resulting in a repression of NF-κB DNA-binding and transcriptional activity. On the other hand, the antiinflammatory effect of progesterone within the myometrium also may be mediated by increased expression of IκBα, a crucial inhibitor of NF-κB transactivation. Progesterone caused a rapid induction of IκBα mRNA and protein expression in the immortalized myometrial cells, which preceded its effect to inhibit IL-1β-induced COX-2 expression (61). Moreover, coincubation with IL-1β and progesterone prevented the IL-1β-induced decline in IκBα protein levels, suggesting an effect of progesterone/PR to block IκBα degradation via the proteasome pathway (63). As a consequence of the increased IκBα expression, more NF-κB is likely sequestered in an inactive state in the cytoplasm. Progesterone inhibition of NF-κB activation by induction of IκBα has also been observed in macrophage cell lines (64) and in T47D cells (60, 65). The identification of *IκBα* as a progesterone target gene that mediates myometrial quiescence is of great interest considering that relatively few PR target genes have been identified.

The molecular mechanisms that mediate progesterone induction of *IκBα* gene expression have not been defined. Glucocorticoids acting through the GR are known to induce *IκBα* expression in a cell type- and promoter-specific manner (66, 67). It is conceivable that glucocorticoids and progestins may induce IκBα expression through similar mechanisms, because the GR and PR are structurally homologous and bind to a common response element in DNA [GR/PR response element (GRE/PRE)]. Although no consensus GRE/PRE has been identified in the 5′-flanking region of the *IκBα* gene (68), a reporter construct containing 623 bp of *IκBα* 5′-flanking sequence was sufficient for glucocorticoid induction of *IκBα* promoter activity in transfected cells (69). This region contains a GRE half-site that was suggested to mediate glucocorticoid/GR effects to enhance binding of other activating transcription factors, including NF-κB, Ets-1, and Sp1 (68).

Importantly, it appears that PR also inhibits NF-κB activation and *COX-2* induction via ligand-independent mechanisms. In studies using human breast cancer cells in which PR-A and PR-B protein levels were completely suppressed using small interfering RNA-mediated knockdown, COX-2 expression was up-regulated more than 30-fold (61). This phenomenon was observed in the absence of progesterone treatment. Conversely, up-regulation of PR protein expression in breast cancer cells transfected with an RNA duplex complementary to a *PR* promoter sequence, markedly inhibited IL-1β induction of COX-2 expression in a progesterone-independent manner (70).

Decline in PR Function at Term Is Multifactorial and Induced by the Inflammatory Response

As discussed above, it has long been appreciated that progesterone acting through PR plays a critical role in maintaining uterine quiescence throughout most of pregnancy. The finding in rodents that circulating maternal progesterone levels decline precipitously near term (71) has led to the concept that labor is associated with progesterone withdrawal. Although in humans and guinea pigs, circulating progesterone levels remain elevated throughout pregnancy and into labor, as do myometrial levels of PR (19), treatment with PR antagonists mifepristone (RU486) or onapristone can cause increased cervical ripening and spontaneous labor or increased sensitivity to labor induction by oxytocin or prostaglandins (72–75). It should be noted that even in mice, maternal progesterone levels at term remain well above the K_d for binding to PR. These collective findings have led to the concept that parturition in all species is initiated by a complex and concerted series of biochemical events that antagonize the ability of the PR to regulate target genes in the uterus that maintain myometrial quiescence. Recent studies have elucidated potential mechanisms involved in the reduction in PR function in target tissues associated with the onset of labor. These include 1) increased expression of progesterone-metabolizing enzymes, 2) direct interaction of PR with NF-κB, 3) increased expression of inhibitory PR isoforms, and 4) altered expression of PR coactivators and corepressors.

Increased expression of progesterone-metabolizing enzymes

The initiation of labor in mice is accompanied by an increase in expression of the progesterone-metabolizing enzymes 20α-hydroxysteroid dehydrogenase (20α-HSD) and 5α-reductase type I in the uterus (76) and cervix (77, 78), respectively. Consequently, mice with a targeted deletion in the gene encoding 5α-reductase type I, which metabolizes progesterone to inactive products, fail to deliver due to defects in cervical ripening (77, 78). This occurred despite the precipitous fall in maternal circulating progesterone levels near term, suggesting that local metabolism of progesterone within the cervix also is required for progesterone withdrawal and the initiation of spontaneous labor in the mouse. *20α-HSD*$^{-/-}$ mice manifest delayed parturition and increased fetal demise at birth (79, 80). Whereas in one study, progesterone levels were found to remain elevated in *20α-HSD*$^{-/-}$ mice at term (80), in the other, progesterone levels declined significantly (79), suggesting that its local metabolism in PR target tissues, such as the uterus, may be critical.

Antagonistic interaction of PR and NF-κB

A mutual antagonism between the PR and the p65 subunit of NF-κB has been reported in COS-1 and HeLa cells; activation of NF-κB by TNF-α inhibited PR transcriptional activity, whereas PR also repressed p65-mediated transcription (62). Also, in amnion epithelial cells, PR overexpression repressed NF-κB transcriptional activity, whereas IL-1β activated NF-κB and inhibited PR transcriptional activity (8). Based on findings that PR and p65 interact *in vitro* (62), it was suggested that mutual

repression resulted from the formation of an inactive complex of these proteins on the DNA that was incapable of interacting with essential coregulators.

Altered expression of PR isoforms

Human PR exists as two major isoforms, hPR-A (94 kDa), hPR-B (114 kDa). These arise by alternative transcription initiation from different promoters (81) and by alternative translation initiation from different AUG sites (82). Both PR-A and PR-B isoforms bind to PREs in DNA; however, hPR-A lacks one of three transcriptional activation domains that are present in hPR-B and has been reported to repress PR-B transcriptional activity in certain cell and gene contexts (83, 84). The ratio of PR-A to PR-B mRNA was reported to be increased about 10-fold in lower uterine segment myometrium from women in labor, as compared with tissues from women not in labor at term (85). PR-A also was found to inhibit PR-B transcriptional activity in cultured human myometrial cells (86), suggesting a potential antagonistic role of PR-A on PR-B function in the uterus. In this regard, mice deficient in Krüppel-like factor 9 (KLF9) manifested delayed parturition in association with aberrant uterine PR-A expression, as compared with wild type. However, the KLF9-deficient mice also exhibited altered expression of NF-κB p65 (87). The finding that mice with a selective knockout of PR-B are fertile and deliver normally (88) suggests that PR-A can mediate actions of progesterone to maintain myometrial quiescence.

A third N-terminally truncated PR isoform, PR-C, has been characterized (89). PR-C lacks part of the DNA-binding domain and is restricted primarily to the cytoplasm (90). Because PR-C cannot bind DNA but can bind progesterone (91), it may inhibit PR function by sequestering available hormone away from PR-B. PR-C also can bind to PR-B and reduce its capacity to bind to DNA (89). In term fundal myometrium from women before and after the initiation of labor, we observed a marked labor-associated increase in protein and mRNA expression of a truncated (~60 kDa) PR isoform; this was spatially and temporally associated with increased activation of NF-κB (7). A temporal increase in expression of a truncated PR isoform also was observed in mouse uterus during late gestation. It should be noted that the identity of truncated PR isoforms (92, 93) has recently been queried, requiring additional studies in this area.

Membrane G protein-coupled PR isoforms (mPRα and mPRβ) linked to $G_i\alpha$, adenylyl cyclase inhibition, p38 MAPK activation, and increased myosin light-chain phosphorylation also have been characterized in human myometrial cells (94). Increased expression of mPR in myometrium from women in

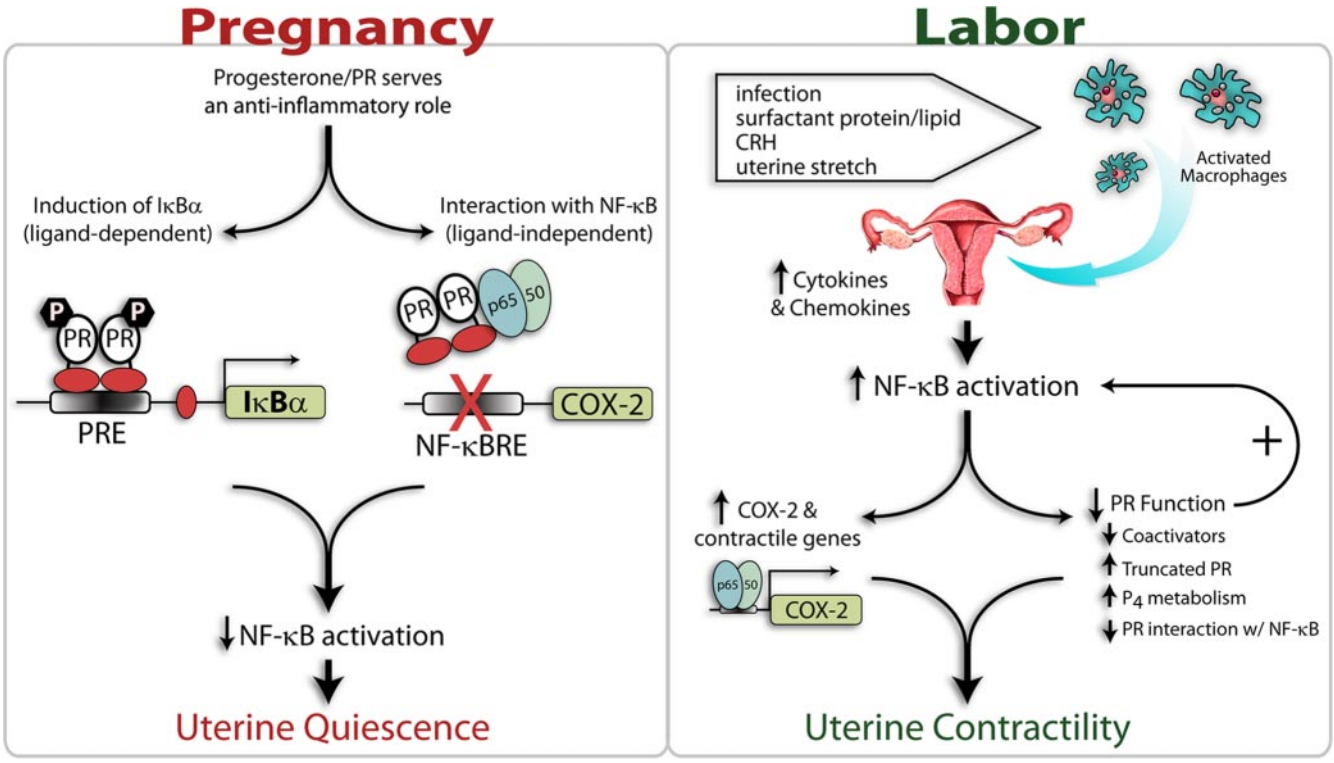

FIG. 1. Mechanisms for progesterone/PR regulation of uterine quiescence during pregnancy and induction of uterine contractility in preterm and term labor. During most of pregnancy, the uterus is maintained in a quiescent state by the PR, which acts in a ligand-dependent and -independent manner to block activation of the inflammatory transcription factors (*e.g.* NF-κB). PR acts in a ligand-dependent manner to up-regulate expression of the NF-κB inhibitor IκBα in myometrial cells. Alternatively, PR acts in a dominant ligand-independent manner (likely via direct protein-protein interaction) to block NF-κB activation, DNA binding, and transactivation of contractile genes within the uterus. Labor can be initiated preterm as a result of bacterial infection, resulting in enhanced migration of macrophages to the maternal uterus with release of cytokines/chemokines and activation of NF-κB. However, at term, enhanced macrophage activation and migration and increased uterine NF-κB activity are likely induced by signals produced by the maturing fetus. These include increased secretion of surfactant proteins and lipids by the fetal lung into amniotic fluid, augmented production of CRH by the placenta, and enhanced uterine stretch caused by the growing conceptus. Within the uterus, the activated NF-κB directly acts to increase expression of contractile genes and causes an impairment of PR function by effecting 1) down-regulation of PR coactivators, 2) increased expression of inhibitory PR isoforms, 3) increased metabolism of progesterone to inactive products, and possibly 4) direct inhibitory interaction with PR. These concerted events culminate in a further increase in NF-κB activation and expression of contractile genes, leading to labor.

labor, as compared with not in labor was suggested to contribute to increased myometrial contractility (94). Collectively, these findings suggest that increased expression of alternative PR binding proteins and isoforms may contribute to a decline in PR function near term.

Altered expression of PR coregulators

Previously, we observed that expression of cAMP response element-binding protein (CREB)-binding protein (CBP), steroid receptor coactivator (SRC)-2 and SRC-3 were decreased in fundal myometrial tissues of women in labor, as compared with those from women not in labor. We also found marked decreases in SRC and CBP coactivator levels in uterine tissues of pregnant mice at term (95). This decline in coactivators in uterine tissues of women in labor and mice at term was associated with decreased levels of acetylated histone H3. Interestingly, administration of trichostatin A (TSA), a potent histone deacetylase inhibitor, to pregnant mice late in gestation increased histone acetylation and delayed parturition by 24–48 h (95). This suggests that the decline in PR coactivator expression and in histone acetylation in the uterus near term may impair PR regulation of genes that maintain uterine quiescence and increase sensitivity of the uterus to contractile stimuli. In cultured human myometrial cells, TNFα antagonism of progesterone/PR-mediated transcription was associated with decreased expression of SRC-1 and SRC-2 (96). This suggests that the decline in coactivator expression in the myometrium near term may be induced by an increased inflammatory response. Moreover, a putative corepressor, termed polypyrimidine tract-binding protein-associated splicing factor (PSF), which promotes PR degradation via the proteasome pathway, inhibits its binding to the PRE and its transcriptional activity, was reported to increase in pregnant rat myometrium at term (97). Thus, PR transcriptional activity near term may be compromised via altered expression of coregulators in response to enhanced inflammatory signals.

Conclusions

The findings presented herein suggest that the suppression of uterine contractility during pregnancy and its increase near term leading to labor are regulated by a complex interplay of signals between fetus and mother. Maintenance of the uterus in a state of near quiescence throughout most of gestation is regulated, in part, by the actions of the PR to block activation of the inflammatory transcription factor NF-κB (Fig. 1). These actions of PR are mediated by ligand-dependent and -independent mechanisms. On the one hand, PR acts in a ligand-dependent manner to markedly up-regulate expression of the NF-κB inhibitor IκBα in myometrial cells. Increased cellular levels of IκBα serve to sequester NF-κB proteins p50 and p65 as an inactive complex in the cytoplasm. PR also acts (possibly via direct protein-protein interaction) in a dominant ligand-independent manner to block NF-κB activation and DNA binding to and transactivation of contractile genes (*e.g. COX-2*). Although it has been suggested that progesterone/PR action within the pregnant myometrium involves activation of genes that maintain quiescence/block contractility, a direct PR target gene within the myometrium that mediates these effects has not been identified. We suggest that *IκBα*, which is markedly up-regulated by progesterone/PR in myometrial cells and serves to block NF-κB transcriptional activation by cytokines, bacterial lipopolysaccharide, and other stimulatory factors, may serve as a key progesterone/PR target gene in the maintenance of the quiescent state.

On the other hand, the initiation of term and preterm labor by signals from the fetus (fetal growth and enhanced uterine stretch, increased SP-A secretion by the fetal lung, and/or increased CRH secretion by the placenta) or infection, respectively, leads to macrophage activation and migration to the pregnant uterus with the release of proinflammatory cytokines and activation of NF-κB and other inflammatory transcription factors (Fig. 1). The activated NF-κB, in turn, binds to enhancers in the regulatory regions of contractile genes, such as *COX-2*, resulting in transcriptional activation and the production of prostaglandins that promote uterine contractility. The inflammatory response also causes an impairment of PR function by inhibiting the expression of critical PR coactivators (95, 96), enhancing expression of inhibitory PR isoforms and increasing local metabolism of progesterone within the uterus (76) and cervix (77, 78). This, in turn, may result in the decreased capacity of progesterone/PR to activate *IκBα* expression and of PR to inhibit NF-κB activation by direct protein-protein interaction. This down-regulation of PR function causes the further activation of contractile genes, which culminates in the initiation of labor.

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