

Fetal-to-maternal signaling to initiate parturition

Erin L. Reinl, Sarah K. England

J Clin Invest. 2015;125(7):2569-2571. <https://doi.org/10.1172/JCI82576>.

Commentary

Multiple processes are capable of activating the onset of parturition; however, the specific contributions of the mother and the fetus to this process are not fully understood. In this issue of the *JCI*, Gao and colleagues present evidence that steroid receptor coactivators 1 and 2 (SRC-1 and SRC-2) regulate surfactant protein-A (SP-A) and platelet-activating factor (PAF) expression, which increases in the developing fetal lung. WT dams crossed with males deficient for both SRC-1 and SRC-2 had suppressed myometrial inflammation, increased serum progesterone, and delayed parturition, which could be reconciled by injection of either SP-A or PAF into the amnion. Together, the results of this study demonstrate that the fetal lungs produce signals to initiate labor in the mouse. This work underscores the importance of the fetus as a contributor to the onset of murine, and potentially human, parturition.

Find the latest version:

<https://jci.me/82576/pdf>



Fetal-to-maternal signaling to initiate parturition

Erin L. Reini and Sarah K. England

Department of Obstetrics and Gynecology — Basic Science Division, Washington University School of Medicine, St. Louis, Missouri, USA.

Multiple processes are capable of activating the onset of parturition; however, the specific contributions of the mother and the fetus to this process are not fully understood. In this issue of the *JCI*, Gao and colleagues present evidence that steroid receptor coactivators 1 and 2 (SRC-1 and SRC-2) regulate surfactant protein-A (SP-A) and platelet-activating factor (PAF) expression, which increases in the developing fetal lung. WT dams crossed with males deficient for both SRC-1 and SRC-2 had suppressed myometrial inflammation, increased serum progesterone, and delayed parturition, which could be reconciled by injection of either SP-A or PAF into the amnion. Together, the results of this study demonstrate that the fetal lungs produce signals to initiate labor in the mouse. This work underscores the importance of the fetus as a contributor to the onset of murine, and potentially human, parturition.

Maternal control of gestational length

Worldwide, 12% of babies are born preterm (<37 completed weeks of gestation), putting them at increased risk of mortality or lifelong disability. In fact, according to the World Health Organization, preterm birth is the leading cause of death in children under five years of age (1). Unfortunately, the ability to intervene to delay parturition (delivery) is limited. For example, tocolytics, which are used to acutely inhibit uterine contractions, are ineffective for long-term pregnancy maintenance. The successful development of effective interventions requires a more complete understanding of the molecular mechanisms that transition the uterus from a quiescent, noncontractile state during gestation to a highly activated, contractile state during parturition.

The transition to activation and parturition is widely accepted as an inflammatory process (reviewed by Shynlova et al., ref. 2). Toward term, myometrial smooth muscle cells (MSMCs) produce chemokines, such as CCL-2, that attract leukocytes into the myometrium (3). These leukocytes then

produce a multitude of cytokines (e.g., IL-8, TNF- α , IL-6, and IL-1 β), thereby activating a feed-forward inflammation pathway (4). Within the MSMCs, cytokines activate the proinflammatory transcription factor NF- κ B, which induces expression of several genes that promote parturition. These include receptors for the contraction inducers (uterotonins) oxytocin (5) and prostaglandin F_{2 α} (PGF_{2 α}) (6) and the prostaglandin synthase enzyme cyclooxygenase-2 (7). Additionally, NF- κ B and mechanical stretch induce expression of the gap junction protein connexin-43 (8) and structural and contractile proteins (9, 10), known collectively as contraction-associated proteins (CAPs). The increased expression of CAPs enhances the sensitivity of the uterus to uterotonins, resulting in forceful and synchronous contractions. Coinciding with the increased NF- κ B signaling at term is the downregulation of the antiinflammatory hormone progesterone, which is key for pregnancy maintenance. By lifting the effects of progesterone, either by a reduction in circulating progesterone via luteolysis (rodents) or by a functional withdrawal (humans), labor con-

tractions can initiate. The importance of both progesterone withdrawal and inflammatory signaling is shown by the guaranteed induction of labor by treatment with the antiprogestin RU486 or by intrauterine injection of the endotoxin LPS.

Does the fetus have a say in gestational length?

In addition to the well-accepted role of the mother's physiology in triggering parturition, a signal from the growing fetus has long been thought to induce the cascade of events required for parturition. Previous work from Carole Mendelson's group (11) demonstrated that surfactant protein-A (SP-A) from the fetal lung induces parturition. In murine models, injection of SP-A into the amnion resulted in preterm delivery. Conversely, injection of an anti-SP-A antibody delayed parturition. The Mendelson group further demonstrated that SP-A promotes parturition by shuttling amniotic fluid macrophages to the myometrium and increasing uterine IL-1 β levels. A subsequent study reported that parturition is delayed by an average of 12 hours in the second pregnancies of SP-A-deficient mice (12). However, as both mother and fetuses lacked SP-A, these experiments did not reveal whether fetal SP-A is indeed a signal for parturition.

In this issue, the Mendelson group addressed the role of the fetus by using genetic mouse models that are deficient for key transcriptional regulators of SP-A, steroid receptor coactivators 1 and 2 (SRC-1 and SRC-2) (13, 14). Gao et al. report that pups born to WT mothers crossed with males that were deficient for both SRC-1 and SRC-2 had decreased SP-A in their lungs and amniotic fluid (15). Additionally, myometrial inflammation was suppressed, maternal progesterone was increased, and parturition was delayed by an average of approximately 38 hours — a considerable length of time for an animal with a total gestational length of 19.5 days. Moreover, the extent of delay correlated with the proportion of fetuses that were deficient for both SRC-1 and SRC-2.

► Related Article: p. 2808

Conflict of interest: The authors have declared that no conflict of interest exists.

Reference information: *J Clin Invest.* 2015;125(7):2569–2571. doi:10.1172/JCI82576.

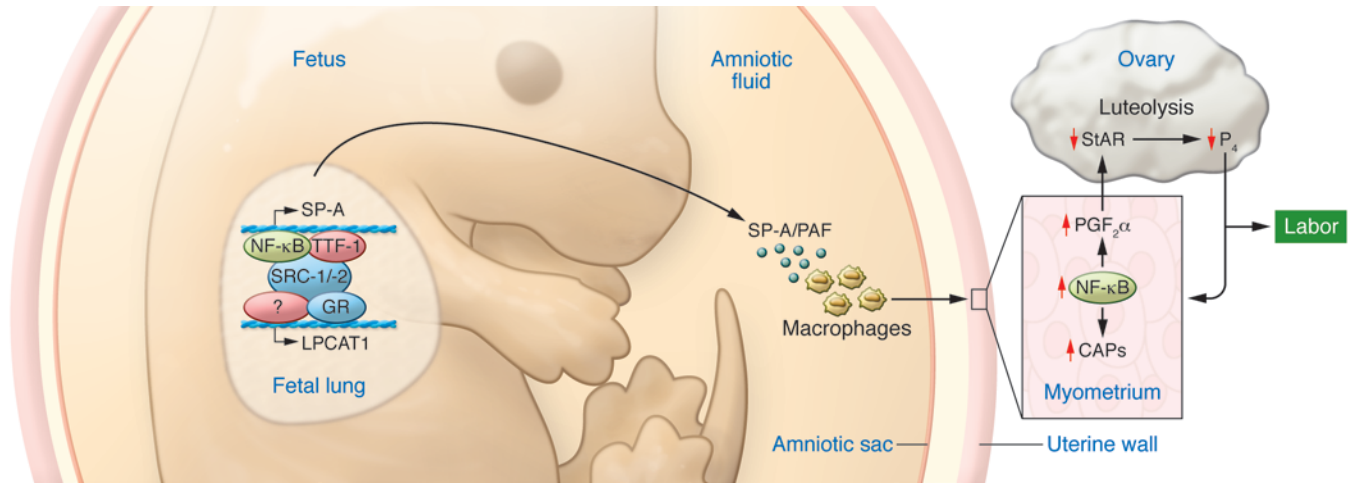


Figure 1. Mechanism of fetal signaling to initiate parturition. Late in fetal lung development, the transcriptional regulators SRC-1 and SRC-2, in coordination with NF-κB, TTF-1, and GR, promote SP-A and LPCAT1 expression. SP-A and PAF are released into the amniotic fluid, where they initiate the shuttling of macrophages to the myometrium, resulting in an increase in myometrial NF-κB, leading to an increase in PGF₂α and CAPs. A rise in circulating levels of PGF₂α promotes luteolysis by decreasing StAR expression, leading to a drop in maternal progesterone (P₄) and the onset of parturition.

Gao et al. went on to uncover the mechanisms by which these effects occurred (15). First, mothers of SRC-1/-2-deficient pups had a decreased inflammatory response and reduced expression of CAPs in the uterus. Additionally, circulating levels of PGF₂α were decreased, preventing luteolysis and the precipitous drop in maternal progesterone levels required for parturition. Next, Gao et al. showed that levels of ovarian steroidogenic acute regulatory protein (StAR), which catalyzes the rate-limiting step of steroidogenesis and thus maintains progesterone levels during pregnancy, remained elevated in the mothers of the SRC-1/-2-deficient pups (15). As with the extent of delivery delay, the proportion of SRC-1/-2-deficient pups in each litter correlated with circulating progesterone levels in the mothers, emphasizing the fine-tuned interaction between fetal genotype and maternal physiology.

Importantly, fetal SRC-1/-2 deficiency led to longer delays in parturition than loss of SP-A alone, indicating that SRC-1 and SRC-2 have other targets that regulate the onset of parturition (12). Because mice completely lacking SRC-1 or SRC-2 die at birth due to respiratory distress and alveolar collapse, Gao and colleagues examined expression of enzymes that catalyze metabolic reactions required for lung development and found that expression of lysophosphatidylcholine acyl transferase 1 (LPCAT1), an enzyme that is responsible for synthesis of surfactant phospho-

lipid and is known to increase with lung development (16), was decreased in the fetal lungs of SRC-1/-2-deficient mice (15). As a result, levels of platelet-activating factor (PAF), an inflammatory phospholipid of amniotic fluid long thought to be important for parturition (17, 18), were also decreased in both the fetal lungs and amniotic fluid. The results of this study corroborate earlier reports that injection of either SP-A (19) or PAF (18) into the amniotic fluid rescues delayed parturition phenotypes. Finally, Gao et al. showed that many of the phenotypes of SRC-1/-2-deficient mice, including delayed birth and reduced expression of NF-κB, CAPs, and PGF₂α, were all ameliorated by injection of either SP-A or PAF into the amnion, providing firm support that these proteins play an important role in the fetal signal that induces parturition (15).

Remaining questions and future directions

The work by Gao et al. convincingly demonstrates that fetal SRC-1 and SRC-2 participate in determining the length of murine pregnancy (Figure 1). However, important questions remain to be addressed. First, what are the additional transcriptional targets of SRC-1 and SRC-2 that contribute to the parturition phenotype reported? To eliminate the complication of studying transcription factors with multiple targets, the individual contributions of fetal SP-A and PAF to the onset of parturition could

be addressed by transferring embryos lacking either SP-A or LPCAT1 expression into WT female mice. Second, what is the extent to which SP-A and PAF contribute to the onset of human parturition? Along these lines, reports in the literature disagree on the level of SP-A in human amniotic fluid at term and in labor (20), whether fetal macrophages can migrate to the human uterine wall (20), and what the direct effect of SP-A is on macrophages and uterine MSMCs (21). Additionally, luteolysis does not play a role in human parturition (22); therefore, the importance of SP-A and PAF as proinflammatory constituents of the amnion (23) and their role in the functional withdrawal of progesterone in humans remains to be determined.

Finally, this study by Gao and colleagues must be put into context with the knowledge that placental corticotropin-releasing hormone (CRH) is an important fetal determinant of gestational length in humans (reviewed by Smith, ref. 24). Placental CRH production increases exponentially near term, and increased maternal serum CRH levels are predictive of preterm labor (25). CRH has been shown to activate NF-κB signaling and increase cytokine production by MSMCs in vitro (26). Of relevance to the work by Gao et al., CRH (placentally or maternally derived) drives fetal production of cortisol, leading to fetal lung maturation and an increased concentration of lung surfactant in the amnion (24). Thus, future studies should

be aimed at determining whether and how the interplay between placental CRH and fetal SP-A drives parturition in humans.

Acknowledgments

This work was supported by NIH grants F31HD079148 (to E.L. Reinl) and 1R21HD076677-01 and 1R01HD037831 (to S.K. England) as well as March of Dimes grants 21-FY12-133 and 21-FY15-147 (to S.K. England).

Address correspondence to: Sarah K. England, Department of Obstetrics and Gynecology, Division of Basic Science Research, 425 S. Euclid, Box 8064, St. Louis, Missouri 63110, USA. Phone: 314.286.1798; E-mail: englands@wustl.edu.

- Howson C, Kinney M, Lawn J. *Born Too Soon: The Global Action Report On Preterm Birth*. Geneva, Switzerland, USA: World Health Organization; 2012.
- Shynlova O, Lee YH, Srikhajon K, Lye SJ. Physiologic uterine inflammation and labor onset: integration of endocrine and mechanical signals. *Reprod Sci*. 2013;20(2):154-167.
- Shynlova O, Tsui P, Dorogin A, Lye SJ. Monocyte chemoattractant protein-1 (CCL-2) integrates mechanical and endocrine signals that mediate term and preterm labor. *J Immunol*. 2008;181(2):1470-1479.
- Osman I, Young A, Jordan F, Greer IA, Norman JE. Leukocyte density and proinflammatory mediator expression in regional human fetal membranes and decidua before and during labor at term. *J Soc Gynecol Investig*. 2006;13(2):97-103.
- Fuchs AR, Fuchs F, Husslein P, Soloff MS. Oxytocin receptors in the human uterus during pregnancy and parturition. *Am J Obstet Gynecol*. 1984;150(6):734-741.
- Olson DM. The role of prostaglandins in the initiation of parturition. *Best Pract Res Clin Obstet Gynaecol*. 2003;17(5):717-730.
- Soloff MS, Cook DL Jr, Jeng YJ, Anderson GD. In situ analysis of interleukin-1-induced transcription of cox-2 and il-8 in cultured human myometrial cells. *Endocrinology*. 2004;145(3):1248-1254.
- Chow L, Lye SJ. Expression of the gap junction protein connexin-43 is increased in the human myometrium toward term and with the onset of labor. *Am J Obstet Gynecol*. 1994;170(3):788-795.
- Shynlova O, Tsui P, Dorogin A, Chow M, Lye SJ. Expression and localization of alpha-smooth muscle and gamma-actins in the pregnant rat myometrium. *Biol Reprod*. 2005;73(4):773-780.
- Shynlova O, Williams SJ, Draper H, White BG, MacPhee DJ, Lye SJ. Uterine stretch regulates temporal and spatial expression of fibronectin protein and its alpha 5 integrin receptor in myometrium of unilaterally pregnant rats. *Biol Reprod*. 2007;77(5):880-888.
- Condon JC, Jeyasuria P, Faust JM, Mendelson CR. Surfactant protein secreted by the maturing mouse fetal lung acts as a hormone that signals the initiation of parturition. *Proc Natl Acad Sci U S A*. 2004;101(14):4978-4983.
- Montalbano AP, Hawgood S, Mendelson CR. Mice deficient in surfactant protein A (SP-A) and SP-D or in TLR2 manifest delayed parturition and decreased expression of inflammatory and contractile genes. *Endocrinology*. 2013;154(1):483-498.
- Liu D, Benlhabib H, Mendelson CR. cAMP enhances estrogen-related receptor alpha (ERR α) transcriptional activity at the SP-A promoter by increasing its interaction with protein kinase A and steroid receptor coactivator 2 (SRC-2). *Mol Endocrinol*. 2009;23(6):772-783.
- Yi M, Tong GX, Murry B, Mendelson CR. Role of CBP/p300 and SRC-1 in transcriptional regulation of the pulmonary surfactant protein-A (SP-A) gene by thyroid transcription factor-1 (TTF-1). *J Biol Chem*. 2002;277(4):2997-3005.
- Gao L, et al. Steroid receptor coactivators 1 and 2 mediate fetal-to-maternal signaling that initiates parturition. *J Clin Invest*. 2015;215(7):2808-2824.
- Chen X, Hyatt BA, Mucenski ML, Mason RJ, Shannon JM. Identification and characterization of a lysophosphatidylcholine acyltransferase in alveolar type II cells. *Proc Natl Acad Sci U S A*. 2006;103(31):11724-11729.
- Silver RK, Caplan MS, Kelly AM. Amniotic fluid platelet-activating factor (PAF) is elevated in patients with tocolytic failure and preterm delivery. *Prostaglandins*. 1992;43(2):181-187.
- Zhu YP, Hoffman DR, Hwang SB, Miyaura S, Johnston JM. Prolongation of parturition in the pregnant rat following treatment with a platelet activating factor receptor antagonist. *Biol Reprod*. 1991;44(1):39-42.
- Condon JC, Hardy DB, Kovarik K, Mendelson CR. Up-regulation of the progesterone receptor (PR)-C isoform in laboring myometrium by activation of nuclear factor-kappaB may contribute to the onset of labor through inhibition of PR function. *Mol Endocrinol*. 2006;20(4):764-775.
- Chaiworapongsa T, et al. The concentration of surfactant protein-A in amniotic fluid decreases in spontaneous human parturition at term. *J Matern Fetal Neonatal Med*. 2008;21(9):652-659.
- Agrawal V, Smart K, Jilling T, Hirsch E. Surfactant protein (SP)-A suppresses preterm delivery and inflammation via TLR2. *PLoS One*. 2013;8(5):e63990.
- Mitchell BF, Taggart MJ. Are animal models relevant to key aspects of human parturition? *Am J Physiol Regul Integr Comp Physiol*. 2009;297(3):R525-R545.
- Lee DC, et al. Surfactant protein-A as an anti-inflammatory component in the amnion: implications for human pregnancy. *J Immunol*. 2010;184(11):6479-6491.
- Smith R. Parturition. *N Engl J Med*. 2007;356(3):271-283.
- McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling the length of human pregnancy. *Nat Med*. 1995;1(5):460-463.
- You X, et al. Corticotropin-releasing hormone (CRH) promotes inflammation in human pregnant myometrium: the evidence of CRH initiating parturition? *J Clin Endocrinol Metab*. 2014;99(2):E199-E208.