EDITORIAL

Transcriptional Regulation of Human Myometrium and the Onset of Labor

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Significant progress has been made in understanding the mechanisms of parturition in animal species, but identification of the pathways leading to human labor remains obscure. In most animal species progesterone contributes to the maintenance of quiescence during pregnancy, and withdrawal of this progesterone effect, manifest as a decline in maternal circulating progesterone levels, generally precedes the onset of labor at term. However, it is clear that there is no such fall in plasma or tissue progesterone levels in women. A central paradox of human obstetrical research for more than 50 years has therefore been how the processes of uterine activation and stimulation can occur in the absence of systemic progesterone withdrawal. An explanation has come from the suggestion that in women the birth process at term and preterm is affected more by local paracrine/autocrine interactions between effectors within the myometrium and fetal membranes. It is evident that a series of positive feed-forward cascades occur in these tissues, and regulation of key enzymes and protein effectors may be regulated by progesterone, potentially in a tonic-modulated fashion. Furthermore it is clear that there is regionalization in the regulation of the human myometrium. This raises the possibility that systemic progesterone levels remain elevated in women during term labor to induce genes within the lower uterine segment that promote relaxation and promote descent of the fetus, while mechanisms exist in the fundal region to affect local functional withdrawal.

Targeted mutagenesis to create knockout mice has demonstrated the requirement for several genes (including 5α-reductase, platelet-derived growth factor [PDGF] receptor, cytoplasmic phospholipase, and prostaglandin synthase-1) in the labor process. Unfortunately, in the mouse, absence of these genes is associated with maintained progesterone levels, presumably as a failure of luteolysis of the corpus luteum. Because exogenous progesterone blocks myometrial activation and the onset of labor in the mouse, these data are only partially informative. In rodents and many other species there is an increase in the ratio of maternal estrogen to progesterone at term, and this subserves increased expression of so-called contraction-associated proteins (*CAP* genes) in the myometrium. These include Cx-43, the oxytocin receptor, and the PGF receptor (*FP*). Expression of these genes is suppressed by exogenous progesterone, while removal of progesterone or antagonism of its action leads to premature expression of these genes and labor. This action is amplified by the mechanical tension on the myometrium that is generated by the growing fetus.

In this issue of the *Journal*, Long et al[1] examine changes in the expression of transcriptional coactivator proteins in human myometrium from non-pregnant women and from patients at term in the presence or absence of labor. The proteins examined, CREB-binding protein (CBP) and p300, are present in limited amounts in myometrium and regulate activity of transcription factors such as cyclic adenosine monophosphate (cAMP) response element binding protein (CREB)/modulator (CREM), activating transcription factor 2 (ATF-2) and nuclear factor-κB (NF-κB). Differential expression of these transcription factors occurs in myometrium in a spatial and temporal manner during pregnancy. Their expression reflects modulation through pathways such as cAMP/protein kinase A, which facilitates uterine quiescence. Long et al[1] show that the level of CBP is much higher in myometrium from women at term in the absence of labor than in labor and that this protein is regulated differentially from p300. Evidence is presented to show association of CBP with the transcription factors listed earlier, raising the possibility that CBP may play an important role in influencing their function at parturition. Simplistically, diminished effectiveness of a mechanism that helps promote myometrial quiescence during pregnancy would seem an attractive way to enhance the labor process.

Recently, several mechanisms have been proposed to account for functional withdrawal of progesterone and the onset of human labor. There is no evidence for altered expression of 3β-hydroxysteroid dehydrogenase in the human placenta at term or preterm,[2] consistent with lack of progesterone withdrawal. It is possible that the action of progesterone is countered by a metabolite or competition with another steroid such as cortisol for progesterone receptor (PR) or GR binding. Grazzini et al[3] suggested that oxytocin binding and uterine contractility was inhibited by progestogen activity, and others have proposed increased metabolism of progesterone through up-regulation of the enzyme 20α-hydroxysteroid dehydrogenase as a way of inducing local progesterone withdrawal.[4] Progesterone actions are conferred through a nuclear ligand-inducible transcription factor, the PR, for which at least three isoforms have been described. In mammals PR-B functions predominately as an activator of progesterone-responsive genes, while PR-A serves as a modulator or repressor of PR-B function antagonizing progesterone action. Mesiano and colleagues[5] demonstrated an increase in the ratio of PR-A:PR-B inferred from measurements of mRNA levels, possibly mediated by prostaglandins,[6] but these data remain somewhat controversial.

Recently, Condon et al[7] reported decreased levels of coactivator SRC-1 and SRC-3 in human fundal myometrium at labor that might diminish the function of PR. Our own studies

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(unpublished results) have suggested that these coactivators are increased in the lower uterine segment, providing additional evidence for progesterone signaling. In addition, we[8] have identified a novel corepressor of PR that provides an additional mechanism to account for the functional withdrawal of progesterone. This repressor, polypyrimidine tract binding protein-associated splicing factor (PSF), blocks PR signaling through two distinct mechanisms. First, PSF binds to the DNA binding domain of PR, inhibiting interaction of the receptor with its response element in target genes. Second, PSF also targets PR for degradation through the proteosomal pathway. Expression of PSF increases in rat myometrium at the time of labor in association with a reduction in the level of PR protein. Further, cytokines such as tumor necrosis factor-α (TNFα) can increase expression of PSF in mammalian cells, consistent with infection-associated preterm birth also resulting in changes in functional progesterone withdrawal.

These different studies point to the complexity of the mechanisms appearing to underlie the birth process. Elucidation of the respective roles of these different coactivator, corepressor pathways will help enhance understanding of the transcription regulation of key genes involved in labor. The study from Long et al[1] suggests a further important example of this type of interaction. The hope of these studies clearly is that they will lead to specific novel markers of preterm labor that might indicate cause as well as diagnosis, and will then lead to the development of new therapeutic modalities that respond to the underlying pathophysiology of this condition.

REFERENCES

1. Long AA, Innes B, Europe-Finner GN, Robson SC. Expression and interaction of the transcriptional co-regulators, CBP/p300, in the human myometrium during pregnancy and labor. J Soc Gynecol Investig 2005;12:92–7.
2. Riley SC, Bassett NS, Berdusco ET, et al. Changes in the abundance of mRNA for type-I 3β-hydroxysteroid dehydrogenase/Δ5→Δ4 isomerase in the human placenta and fetal membranes during pregnancy and labour. Gynecol Obstet Invest 1993;35:199–203.
3. Grazzini E, Guillon G, Mouillac B, Zingg HH. Inhibition of oxytocin receptor function by direct binding of progesterone. Nature 1998;392:509–12.
4. Condon JC, Mendelson CR. Increased migration of fetal amniotic fluid macrophages containing elevated 20 alpha-hydroxysteroid dehydrogenase (20 alpha-HSD) activity to the pregnant uterus near term results in local progesterone withdrawal and the onset of labor (abstract). Endocrine Society's 86th Annual Meeting, New Orleans, LA, June 2004: 148A.
5. Mesiano S, Chan EC, Fitter JT, et al. Progesterone withdrawal and estrogen activation in human parturition and coordinated by progesterone receptor A expression in the myometrium. J Clin Endocrinol Metab 2002;87:2924–30.
6. Mesiano S. Myometrial progesterone responsiveness and the control of human parturition. J Soc Gynecol Investig 2004;11:193–202.
7. Condon JC, Jeyasuria P, Faust JM, Wilson JW, Mendelson CR. A decline in the levels of progesterone receptor coactivators in the pregnant uterus at term may antagonize progesterone receptor function and contribute to the initiation of parturition. Proc Natl Acad Sci U S A 2003;100:9518–23.
8. Dong X, Challis JRG, Lye SJ. Mechanisms underlying the actions of a novel co-repressor of progesterone receptor, PSF that may contribute to a functional withdrawal of progesterone during labour (abstract). Endocrine Society's 86th Annual Meeting, New Orleans, LA, June 2004.