



MOLECULAR MODELS OF BIRTH

Pregnancy occurs in many animal species and in nearly all mammals. But the processes of gestating and birthing offspring vary widely across the animal kingdom. Especially stark is the line that divides human reproduction from that of nonhumans. Science is just now beginning to grasp the molecular intricacies of human reproduction and birth (parturition). Because these processes are so complicated, many efforts to test hypotheses are generating interesting data, with more on the way. Here are some of the proposed pathways that are garnering strong support in models of human pregnancy and parturition.

MAINTAINING PREGNANCY

Progesterone interacts with progesterone receptors (PRs) in the cytoplasm of myometrial cells, causing the complex to translocate to the nucleus **A**. There, the activated receptor binds to the promoter of the ZEB1 gene, which leads to upregulation of the transcription factors and subsequent inhibition of genes that code for contraction-associated proteins (CAPs) **B**. PRs in the nucleus also upregulate caspase 3, an enzyme that degrades the contractile architecture of the cell **C**. All of this results in a quiescent uterus that is allowed to stretch and grow as the fetus develops.

INITIATING LABOR

Mechanical stretch forces in the uterus cause a drop in polypyrimidine tract binding protein-associated splicing factor (PSF), a coregulator of the progesterone receptor. This leads to the increased expression of proteins involved in contraction **D**. As the fetal lung matures, it produces an abundance of surfactant protein A (SP-A), which activates macrophages in the amniotic fluid, promoting their migration to the uterus where they release proinflammatory cytokines. Increased cytokine production activates NF- κ B, which translocates to the nucleus of the myometrial cell, where it binds to CAP gene promoters, activating CAP expression. It also binds to PRs, blocking their binding with DNA. This decreases ZEB1 expression, therefore increasing expression of CAPs and decreasing caspase 3 levels **E**. Signals from uterine stretch forces and intraamniotic infection can also increase proinflammatory cytokines and chemokines, which can result in increased CAP expression and the start of labor **F**. Other hormones, such as prostaglandins, contact their receptors in the membranes of myometrial cells, causing an influx of Ca^{2+} and uterine muscle contractions.

