Prevention of preterm birth: Novel targets of inflammation in the myometrium

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Preterm birth is one of the most significant health care issues globally. Fifteen million babies are born prematurely each year, with rates as high as 18% in some countries. It is the leading direct cause of early neonatal death, while survivors have greatly increased rates of long term disabilities including cerebral palsy and intellectual handicap and chronic lung disease. The majority of preterm births are the result of spontaneous preterm labour (*i.e.* early activation of the normal labour process). Treatments to stop preterm labour do not exist and their development is hampered by the fact the process of human parturition remains incompletely understood. What we do know is that inflammation is commonly implicated in spontaneous preterm birth and thought to have a driving role in initiating, and maintaining uterine contractions.

Inflammation, which can be triggered by infection or by sterile pro-inflammatory insults, leads to activation of the maternal immune system which produces pro-inflammatory cytokines (*e.g.* TNF-α, IL-1β, IL-6) and chemokines (IL-8, MCP-1, GRO-α). Chemokines activate maternal peripheral leukocytes (a rich source of cytokines) and induce their infiltration into uterine tissue. In turn, cytokines induce uterine activation of contraction-associated proteins, such as oxytocin receptor, connexin 43, cyclooxygenase-2 (COX-2) and prostaglandin receptors, in myometrium and production of uterotonic factors such as prostaglandins, culminating in the onset of preterm labour and birth. The biochemical pathways involved in the formation of these mediators thus represent potential sites for intervention that may translate to therapeutic interventions to delay or prevent preterm labour and delivery. Indeed, data generated over the past decade strongly implicate the nuclear factor-κB (NF-κB) family as candidate upstream regulators of the multiple labour-associated processes.

More recently, however, we have identified a number of immune regulatory proteins important in human labour including the immunoproteasome subunit LMP7. Using our unique biobank of human clinical samples as well as mouse models of preterm birth, we have characterized the role of LMP7 in the processes of labour. In vitro, the LMP7 inhibitor ONX-0914 and siRNA knockdown of LMP7 in human myometrium showed that LMP7 exerted pro-labour effects *via* NF-κB in response to various inflammatory or infection stimuli. Quite promisingly, our *in vivo* studies show inhibition of LMP7 can significantly decreases the genesis of pro-inflammatory and pro-labour mediators in myometrium of pregnant mice, while our *ex situ* studies demonstrates the potential role of the LMP7 inhibitor ONX-0914 as a tocolytic agent to suppress human uterine smooth muscle contractility.