MedicalXpress

Study describes potential clinical test and treatment for preterm birth

March 9 2017

Scientists identified a molecular driver of inflammation that may finally answer a key question about what causes mild systemic prenatal infections to trigger preterm birth.

The finding is an important step to developing a treatment or clinical test for early detection of an entrenched global health problem, according to researchers at Cincinnati Children's Hospital Medical Center, who report their data March 9 in *The Journal of Clinical Investigation Insight (JCI Insight)*.

Researchers implicate a molecular signaling receptor that helps regulate the immune system called type I Interferon receptor (IFNAR). INFAR signaling induces infection-driven preterm birth, the authors report. The problem starts in pregnant mothers that develop systemic viral and bacterial infections that are considered subclinical - or not severe enough to present definite or readily observable symptoms.

The researchers show that during these infections, engagement of INFAR receptors on the surface of blood immune cells by the immune protein type I Interferon (type I IFN) fuels production of pro-inflammatory cytokines during secondary inflammatory challenge. This induces preterm birth.

"Preterm birth is a leading worldwide cause of illness and death in infants," says Senad Divanovic, PhD, lead scientific investigator on the study and a member of Division of Immunobiology. "The biological

processes linked to the ability of pathogens to help cause preterm birth have been unknown. Identifying active type I IFN/IFNAR as an immunological driver provides an actionable biomarker and potential therapeutic target for reducing preterm birth risk in these circumstances."

Although inflammation from microbial infection is a known factor in preterm birth, it isn't known why a subset of microbes causes the problem. The authors note that not all microbes found in the maternal and fetal tissues of pregnant women induce preterm birth - suggesting the difference is in underlying biological triggers.

To find these triggers, authors of the current study tested induced preterm birth in mouse models and analyzed blood and uterine cell samples from Rhesus monkeys, as well as donated human tissues, to look for biological indicators of type I IFN/IFNAR.

Conserved Mammalian Processes

Despite differences among mammals in the biology of pregnancy and birth, animal models have been useful for studying the molecular processes involved in immune regulation of preterm birth. Unlike the action of giving birth, regulation of the immune process is fairly conserved and similar among different species of mammals, according to the research team. In fact, the current study shows that type I Interferon priming of inflammatory cells is highly conserved among murine, non-human primates and human immune cells in a secondary inflammatory challenge, such as pro-inflammatory cytokine production.

In pregnant wild type mice (those not genetically altered) the researchers tested the role of type I IFN/IFNAR in initial subclinical viral (influenza) infection prior to secondary bacterial inflammation. Notably, initial viral infection prompted activation of type I IFN/IFNAR to fuel

an overabundance of systemic pro-inflammatory production of cytokines like Interleukin (IL-6), in the blood and reproductive sites.

PTB Prevention

In tests where researchers genetically deleted type I IFN, IFNAR or IL-6 in mice, or administered neutralizing antibodies to IL-6, the animals were protected from preterm birth, they report.

Divanovic said the research team are now trying to determine exactly where in the body that sensitization of pro-inflammatory pathways and cells initially occurs. They also want to widen the scope of their analyses into different molecular and bacterial processes to determine how broad and persistent regulation of type I IFN is during infections and how such changes modulate increased susceptibility to preterm birth.

Lastly, they want to test whether targeted inhibition of type I IFN/IFNAR prevents preterm birth in non-human primates and whether such approaches would be useful for clinical testing of preterm birth risk.

More information: Monica Cappelletti et al, Type I interferons regulate susceptibility to inflammation-induced preterm birth, *JCI Insight* (2017). DOI: 10.1172/jci.insight.91288

Provided by Cincinnati Children's Hospital Medical Center