A study of mice and human cells provides insight into how genes and environment can interact to induce preterm birth. The findings hint at new ways to treat women at risk for this condition.

Very little is known about why some babies—about one in ten worldwide—are born prematurely. Many factors can contribute, including genetic predisposition, increased maternal age, infection and inflammation, and oxidative stress. The relative contributions of the various factors and their interactions are a black box.

To begin to study such questions, Yasushi Hirota and his colleagues had previously developed a mouse model of preterm birth. These mice have a uterine deletion of Trp53, which encodes the tumor suppressor protein p53.

About half of these mice undergo spontaneous preterm birth, a phenotype that has been traced to premature senescence of the decidua, the endometrial stromal tissue that is modified during gestation. Drugs that counteract decidual senescence, such as rapamycin, which targets the senescence-associated signaling molecule mTORC1, are effective in this mouse model.

In the new study, Jiyeon Cha et al. exposed these mice to a mild inflammatory insult with lipopolysaccharide (LPS), which provoked preterm birth in 100 percent of the animals. The combination of genetic and environmental insult affected the decidua and increased inflammation, as indicated by prostaglandin synthesis, and it also quelled production of progesterone by the ovary. Even a small amount of LPS trigged a drop in serum levels of progesterone, an effect only observed at high doses of LPS in wild-type animals. The researchers could prevent preterm birth in the mice without inducing adverse effects in the mothers or their offspring by treatment with both rapamycin and progesterone.

Progesterone is sometimes used clinically to fend off preterm birth, though its effectiveness is limited and only some women benefit. The therapeutic potential of combinations of progesterone with other agents, such as rapamycin, may be a fruitful avenue of investigation. The researchers’ observations in human cells support this approach; for instance, they observed higher mTORC1 signaling in decidua of mothers who had given birth prematurely. Moreover, adding progesterone or rapamycin or both to cultured human decidual cells quelled the inflammatory response to LPS.

Exactly how p53 deletion and LPS signaling interact to yield effects on the decidua and ovarian secretion of progesterone is, as yet, unclear. But the researchers suggest that a healthy decidua is key to proper birth timing, particularly since the decidua may in turn signal the ovary.


The composition of the bacteria in the gut may help explain why females are more susceptible to autoimmune diseases than males, a study in mice suggests. The findings highlight the complex ways that sex hormones interact with the immune system, an increasingly recognized area of biological research that was highlighted this July at the Annual Meeting of the Society for the Study of Reproduction (SSR 2013) in Montréal.

In the new study, Alexander Chervonsky and colleagues took a close look at non-obese diabetic (NOD) mice, which model type 1 diabetes, an autoimmune disorder. Previous studies had shown that female NOD mice are more susceptible to disease than male NOD mice. Curiously, NOD mice raised in germ-free facilities, lacking gut bacteria, are at much greater risk for disease, with the males almost as susceptible as the females. The researchers sought to tease out the relationships between hormonal and microbial influences on disease.

Chervonsky et al. now report that the gut microbiota differ between male and female NOD mice, and that castrating the males results in the microbiota taking on the female composition [1]. The researchers also found that some defined microbial communities, inoculated into germ-free NOD mice, could protect males—but not females—against diabetes. The protective effect required testosterone to be present, but the level of protection did not correlate with the level of testosterone in the blood.

The findings suggest that a threshold level of testosterone is needed for microbes to exert their protective effect, and that hormones and microbes work together to trigger protective pathways. Although the mechanisms are likely to be complex, the findings also hint that the cytokine interferon-gamma may help mediate protection in males. This study may provide insight into why autoimmune diseases are about 80 percent more common in women than men.

Not only are women more susceptible to autoimmune diseases, but their response to infection also differs from that of men. This is an area studied by Sabra Klein, who spoke at SSR 2013. She notes that women have more pronounced responses to vaccines than men and are known to report worse symptoms when they are infected with an influenza virus. Such observations jibe with numerous studies suggesting sex-specific differences in immune responses—perhaps not surprising, given that immune cells have receptors for estrogen and other hormones.

At the meeting, Klein highlighted her work showing that influenza infection in female mice prompts a heightened pro-inflammatory response, compared to male mice [2]. The inflammatory response can be protective, shielding against infection, but when it is over-amplified, disease can worsen. In her studies, some previously published [3], Klein found that treating flu-infected mice treated with estradiol or agonists of the estrogen receptor eases the inflammatory response and illness from flu. As with autoimmune diseases, continuous (as opposed to cyclical) low levels of estrogen seem to dampen the inflammatory responses and protect against tissue damage and even death.