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INSIGHTS

When pregnancy tames the wolf

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A state of relative immunosuppression exists in normal pregnancy. In this issue of *JEM*, Hong et al. (https://doi.org/10.1084/jem.20190185) perform blood immunomonitoring in pregnancy, in both healthy women and women with lupus, and observe early and sustained transcriptional modulation of lupus-related pathways in both groups. When signatures of inflammation did not normalize in lupus, risk of pregnancy complications was increased.

Pregnancy is a time of major immunological change for the mother. This is understandable, as the mother has to immunologically tolerate a developing fetus that is genetically derived half from the father and half from herself. It is not fully understood how this amazing process happens, even in normal pregnancies. Lupus is a severe multisystem autoimmune disease, which can result in inflammation in many organ systems, including the joints, blood, and kidneys. The name "lupus" comes from the Latin word for wolf, as the skin rash can be so severe that a thirteenth century physician thought it looked like a wolf bite. Lupus affects women nine times more frequently than men for reasons that are unclear, and lupus often begins during the early reproductive years (Weckerle and Niewold, 2011). This pattern of incidence means that pregnancy in lupus is relatively common. One can imagine that lupus could be either worsened or improved during pregnancy—the exposure to foreign antigens from the fetus could be activating for the immune system, or the natural immunosuppression that allows for carriage of the fetus during pregnancy could improve lupus. It is likely that both of these things occur, and that the balance can differ between different people and at different times in pregnancy. When lupus becomes active or flares up during pregnancy, it is a major clinical problem. Many medications for a lupus flare are either difficult to use or relatively untested in pregnancy, but uncontrolled lupus is also dangerous for both the mother and the baby. For women with lupus, there is an increased rate of preeclampsia and other complications of pregnancy, and it is known that increased disease activity at the time of pregnancy is a risk factor for these complications (Buyon et al., 2015). Further insight into this process is critical, both from the pathogenesis perspective to understand the immunological events that underlie complications of lupus pregnancy, and also whether there are any predictive markers that might be useful in the clinic. Prognostic markers could help physicians potentially intervene earlier in the process in a more proactive way.

In the current study, Hong et al. address these questions by studying whole-blood transcriptional profiles in healthy mothers and mothers with lupus to determine changes that are associated with lupus pregnancy and predictors of adverse outcomes. They studied 135 women (43 healthy and 92 with lupus) at multiple time points in their pregnancy, including <16 wk, 16–23 wk, 24–31 wk, 32–40 wk, and 8–20 wk postpartum. They found that a number of lupus-associated transcriptional patterns are down-regulated during both healthy and lupus pregnancy, including type I interferon, plasmablast signatures, and others. This supports the idea that in some cases, pregnancy can "tame the wolf," reducing the lupus-associated blood signatures. There were also some patients who did not down-regulate their lupus-associated gene signatures. Interestingly, in the subset of lupus patients who had pregnancy complications, these transcriptional signatures did not normalize as frequently as those who did not have pregnancy complications. This suggests that the inability to down-regulate disease-associated transcriptional patterns is a risk factor for adverse pregnancy outcome in lupus.

Insights from Timothy B. Niewold and Shilpi Mehta-Lee.

Hong et al. (2019) also examined whether transcriptional patterns in early pregnancy could predict later adverse pregnancy outcomes. They used machine learning to identify predictors of preeclampsia and found a number of transcripts related to interferon-inducible and plasma cell–related transcripts, as well as transcripts related to platelet aggregation and inflammation. These data would have to be validated, as they are derived from this one study, but interestingly, the pathways overlap significantly with those observed in women who had complications, suggesting that the transcriptional abnormalities might precede the clinical signs of adverse outcomes.

Type I interferon is interesting in the context of both lupus and pregnancy. Type I interferon levels are high in many lupus patients, and have been associated with autoantibody production as well as genetic factors (Weckerle et al., 2011; Kariuki et al., 2015). While type I interferon levels can fluctuate somewhat in lupus, it seems that

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high interferon status is fairly stable over time, designating a particular pathogenic subgroup comprising ∼50% of lupus patients (Petri et al., 2009; Weckerle et al., 2011). It seems likely that overactivity in the type I interferon pathway contributes to the break in tolerance observed in lupus patients (Muskardin and Niewold, 2018). In this study, the type I interferon signature decreased in both healthy and lupus pregnancy. This makes sense, as elevated type I interferon has been implicated in loss of tolerance in a number of other conditions beyond lupus and autoimmune disease, such as solid organ transplantation (Alegre et al., 2009; Matz et al., 2018). This, taken together with the lupus data referenced above and in the Hong et al. (2019) article, furthers the case that type I interferon is an important determinant of immunological tolerance.

The authors investigate whole-blood transcriptional patterns in this study. This method allows ease of blood collection and standardized processing, but results in data from all cell populations mixed together. Differences in cell numbers that contribute to the mixture will result in greater numbers of transcripts related to that cell type. Differences in proportions of white blood cell types are common; for example, lupus patients can have variable lymphopenia, which can fluctuate with disease activity, and steroids, which are frequently used to treat lupus, cause an increase in neutrophils. The authors address this mixed-cell population problem using an innovative method for statistical deconvolution of the transcriptional patterns. This method helps to mitigate the mixed-cell population problem, and findings can be validated in follow-up orthologous studies using flow cytometry or purified cell populations. In this study, the authors use flow cytometry to validate the differences in cell populations that were predicted by the deconvolution strategy.

These results could potentially be applied to the clinic in a prognostic or diagnostic fashion. Blood signatures could be followed prospectively in lupus patients as a predictor of adverse outcome, which could lead to closer follow up and more expectant management in high risk groups. Also, in some cases it can be difficult to distinguish between the renal dysfunction associated with preeclampsia and the renal dysfunction associated with lupus kidney inflammation. This large dataset of lupus patients with and without preeclampsia could suggest potential markers to discriminate these possibilities as well. Thinking further in the future, one could imagine that these pathways could be modulated in high risk pregnancies to prevent or treat pregnancy complications like preeclampsia. It could be that the ways in which pregnancy can "tame the wolf" may provide lessons more generally for the treatment or prevention of pregnancy complications.

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