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Commentary

Epigenetics of recurrent pregnancy loss

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Pathological epigenetic alterations are particularly important in feto-materal medicine. Maternal pregnancy related diseases such as gestational diabetes and pregnancy induced hypertension are associated with global or gene specific alterations of DNA methylation in the placenta [1,2]. Likewise, offspring's diseases in early and later life have been associated with placental alterations in DNA methylation [3,4]. The reason why epigenetic alterations of the placenta play such an important role in feto-maternal medicine is due to two factors:

a) The placenta is a complex organ that serves as an interphase between mother and child and thus controls fetal exposure to any external environmental factors (supply with micro- and macronutrients, exposure to environmental toxins, oxygen supply etc.) that may impact on fetal development.
b) The placenta is likewise an endocrine organ secreting hormones to the fetus and the mother. These placental hormones are controlling maternal and offspring's phenotype and thus may contribute to maternal and offspring's diseases. Epigenetic mechanisms are in particular important in the placenta, since the placenta is an organ of fast differentiation into highly specialized cell types and this process is controlled by epigenetic mechanisms. If anything goes wrong in the epigenetic control of this differentiation processes this may cause both maternal and/or offspring disease.

Recurrent pregnancy loss (RPL) is one of the most frustrating and difficult areas in feto-maternal medicine. Known risk factors or mechanisms linked to recurrent pregnancy loss include general factors such as advancing maternal age and increasing parity and more specific factors such as genetic factors (abnormalities of chromosome number or structure are the most common cause of sporadic early pregnancy loss), uterine anomalies (septate uterus, leiomyoma and intrauterine adhesions or synechiae) as well as immunologic factors such as antiphospholipid syndrome. Endocrine factors (poorly controlled diabetes mellitus, polycystic ovary syndrome, thyroid antibodies and hypo- or hyper-thyroidism, hyperprolactinemia) are likewise associated with pregnancy loss. However, in a still huge proportion of cases the underlying mechanism is unknown. As with other feto-maternal diseases, there is evidence that epigenetic mechanism might play key role in the pathogenesis of recurrent pregnancy loss. In the current issue of EBioMedicine Mingming Yu et al. [5] identified *CREB5* as a novel risk gene contributing to recurrent pregnancy loss by performing genome-wide DNA methylation analysis combined with RNA-seq analysis in decidua tissue. They showed that hypomethylation of *CREB5* upregulated its expression and caused dysfunction of trophoblast cells, which might contribute to Recurrent pregnancy loss.

Epigenetic mechanisms are well known in feto-maternal pathophysiology. Environmental factors such as micro- and macronutrients even of the father [6] but also psychological factors such as stress during pregnancy [7,8] induce these epigenetic alterations. In other words, changeable environmental factors play a key role in inducing these disease-related epigenetic alterations in the placenta and elsewhere in the offspring's body. The deep understanding of these changeable factors is important, since this might offer new strategies of recurrent pregnancy loss prevention and treatment. This makes this area of research so important given the often frustrating lack of promising therapeutic options if for example pure genetic reasons cause recurrent pregnancy loss. Even in the case that the yet unknown potential environmental causes leading to placental CREB5 hypomethylation are difficult to manipulate, treatment of mothers with methyl group donors such as folate [6] might be a treatment option. This needs to be addressed in further studies.

In conclusion, the study by Mingming Yu et al. [5] provides clear data suggesting a new epigenetic pathway potentially causing recurrent pregnancy loss. However, an independent confirmation study would further strengthen the findings. We also need to understand better how often CREB5 hypomethylation causes recurrent pregnancy loss in different ethnic populations. In particular, environmental factors causing hypomethylation of CREB5 should be a focus of further studies, because this might offer approaches of causal interventions to prevent recurrent pregnancy loss.

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