Commentary

Intergenerational Effects of Endocrine Disorder on Metabolism

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The percentage prevalence of metabolic disorders, especially diabetes and obesity, has increased by 2–4 folds in the U.S. over the past 4 decades. Although genetic factors play a role in individual susceptibility, such a sharp rise of the disease can only be explained by the environment, including unhealthy diet and lack of physical exercise. In addition to direct effects of the environment on adults, accumulating evidence suggests that lifestyle factors and other environmental exposure have intergenerational or transgenerational effects, which can predispose offspring to metabolic disorders (Barua and Junaid, 2015; Heard and Martienssen, 2014). The ‘fetal origins hypothesis’ suggests that environmental exposure at the fetus stage could impact the health at later stages in life (Barker and Thornburg, 2013). A more general theory of ‘developmental origins of health and disease’ (DOHaD) proposes that a wide range of environmental conditions both before and immediately after birth could determine susceptibility to diseases later in adult life (Silveira et al., 2007).

These theories are supported by several findings from both animal models and human studies, among which are the most well-known Swedish Overkalix study and the Dutch famine study. The Swedish Overkalix study found that one’s mortality can be affected, in a sex-specific manner, by nutritional status of their grandparents (Pembrey et al., 2014). The Dutch famine study found that offspring born during famine are more susceptible to develop glucose intolerance (Lumey et al., 2011). It has also become clear that gestational diabetes predispose offspring to metabolic disorders and diabetes in both human and animal studies (Barua and Junaid, 2015), which has provided compelling rationale to screen and treat gestational diabetes in pregnant women. In addition to maternal glycemic status or famine, maternal exposure to a variety of dietary factors or environmental chemicals have also been found to affect glucose metabolism in offspring (Barua and Junaid, 2015).

Compared to the exposure to the external environment, whether and how the internal endocrine environment can illicit intergenerational effects is less understood. Hyperandrogenism is a common endocrine disorder that happens in 5–10% of reproductive-aged women. Previous animal studies suggest that intrauterine exposure to elevated androgen levels could impair glucose tolerance in offspring (Amalfi et al., 2012; Nohara et al., 2013). Whether this is true in human has not been determined.

In this issue of EBioMedicine, a research team at the International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University addresses this important question (Tian et al., in 2017–this issue). They measured basal blood androgen levels in pre-gestational women and then performed glucose tolerance tests in their children at the age of 5 years. Total of 156 children from 147 women with hyperandrogenism (testosterone >2.4 nmol/L or dehydroepiandrosterone >8.8 μmol/L) were tested, while 1060 children from 969 women served as control. They found that maternal hyperandrogenism significantly increased the chance, by nearly 4-fold, of developing prediabetes in offspring children (fasting glucose 5.6–6.9 mmol/L). In addition, children born to the mothers with pregestational hyperandrogenism have significantly higher glucose and insulin levels during oral glucose tolerance tests, suggesting development of insulin resistance.

To explore the underlying molecular mechanism, the authors checked DNA methylation at imprinted genes previously implicated in pathogenesis of diabetes (Barua and Junaid, 2015; Ding et al., 2012). They found that children born to mothers with pre-gestational hyperandrogenism have lower DNA methylation levels and higher gene expression levels in two imprinted genes Igf2 (Insulin-like growth factor 2) and Grb10 (Growth factor receptor-bound protein 10) in blood lymphocytes. The authors went on to show that the lower DNA methylation levels and higher gene expression levels of Igf2 occurred in both F0 oocytes and F1 pancreatic islets in a rat model of pre-gestational hyperandrogenism, which further supports a gamete-mediated mechanism in this maternal effect. These findings also suggest that pancreatic islets is a major target tissue contributing to the glucose intolerance phenotype in F1 offspring.

The nice study by Tian et al. raised several interesting questions that warrant future investigation. Is the pancreatic defect a bona fide cause of prediabetes in the F1 offspring? A clear defect in glucose-stimulated insulin secretion (GSIS) was observed in the F1 offspring in rat, but not in...
human. In addition, how does hyperandrogenism alter DNA methylation or change DNA methyltransferase expression in oocytes? Can the change in Igf2 and Grb10 gene expression fully explain the pre-diabetes phenotype in the F1 offspring? Would the F1 metabolic phenotype be rescued by correcting the DNA methylation changes in either oocyte or pancreas using epigenome-editing techniques in the animal model?

Disclosure

The authors declared no conflicts of interest.

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