Commentary

MOLECULAR METABOLISM

Linking maternal obesity to early insulin resistance*

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The current epidemics of obesity and type 2 diabetes are major concerns to our health and health care systems and project major public health problems in future generations. In addition to genetics, lifestyle and nutrition, increasing attention is focused on the non-genetic, trans-generational effects of maternal obesity on the offspring, as risk factors for obesity [1]. While the principle associations between maternal obesity and increased risk of obesity and its metabolic consequences in the offspring are well established in rodents and humans, the underlying molecular mechanisms are under active investigation [2].

In this issue of Molecular Metabolism, Fernandez-Twinn and colleagues demonstrate that maternal obesity during pregnancy and lactation results in hyperinsulinemia, characteristic for insulin resistance, in the male offspring prior to the development of obesity [3]. Thus, the authors show that insulin resistance in the offspring is not a consequence of obesity, which has been previously observed as a result of maternal adiposity [4], but presents either an independent trait or even a predisposition for the development of obesity later in life. Interestingly, Tsuduki and colleagues [5] previously reported that feeding a high fat diet during lactation also increases serum insulin levels at weaning. However, this effect was only observed transiently as no differences in serum insulin levels were observed later in life.

Fernandez-Twinn and colleagues focused their study on the early consequences of maternal obesity on the offspring, thus it will be interesting to see if in this mouse model insulin levels normalize over time too. This is of great interest as a transient insulin resistance early in life could cause a predisposition to obesity or other components of the metabolic syndrome later on and most likely would not be recognized if not specifically tested. However, a direct translation of these findings from mice to humans is complex as mice are born at a developmental stage comparable to the beginning of the third trimester in humans. Therefore the lactation period in mice overlaps with the final developmental/ growth phase in-utero in humans.

The adverse effects of maternal obesity on the offspring later in life have been previously demonstrated and linked to a dysregulation of key signaling molecules of the insulin signaling pathway in the liver and skeletal muscle [1,4,6]. However, these studies were performed after the development of obesity and impaired glucose tolerance. Thus, any molecular changes could be a consequence of the maternal obesity or the metabolic syndrome in the offspring.

As the authors were investigating mechanisms to explain the obesity independent hyperinsulinema in their mouse model, they turned to molecular changes in visceral adipose tissue. White adipose tissue is critically dependent on insulin action during its development and function and itself is essential to maintain whole body lipid and glucose homeostasis as a site of energy storage and as an important endocrine organ [7]. Dysfunctional adipocytes lead to local and systemic inflammation as well as lipid spill over into other organs like the liver and skeletal muscle and have been proposed as one possible explanation for the development of insulin resistance [8]. However, not all fat is equal, as increase in subcutaneous adipose tissue is inert to, or in some studies has even been shown to protect against the development of insulin resistance. In contrast, increase in visceral adipose tissue is generally associated with a higher risk to develop insulin resistance and other characteristics of the metabolic syndrome [9]. A better understanding of the underlying principles associated with the different risk associations of adipose tissue depots are therefore of great significance to understand and utilize the beneficial effects of one adipose tissue depot while inhibiting the adverse effects of the other.

In the present study Fernandez-Twinn and colleagues focused on the molecular changes in visceral adipose tissue, where they identified a significant reduction in the protein levels of various components of the insulin signaling pathway prior to the development of obesity. A more detailed analysis revealed IRS-1 as the most downregulated protein in their panel. Subsequent experiments showed no alterations in mRNA expression or protein stability, but the authors identified miR126, directly targeting IRS-1, to be overexpressed in visceral adipose tissue as well as in primary in vitro differentiated adipocytes from mice of obese dams. Thus, maternal obesity either during pregnancy or lactation results in an upregulation of miR126 in visceral adipose tissue, which in turn downregulates IRS-1. The cell autonomous upregulation of miR126 that persists upon differentiation of preadipocytes in vitro suggests some sort of epigenetic regulation of this miRNA. Children born either before or after gastrointestinal bypass surgery show differences in DNA methylation at ~3% of all CpG sites, indicating a strong impact of maternal obesity on the DNA methylation of the offspring [10]. However, the consequences of these altered DNA methylations were only studied with respect to gene expression and did not investigate the expression of miRNAs. Therefore, epigenetic regulation of miRNAs could provide a novel mechanism by which the physiological state of the dam alters the posttranscriptional regulation of target genes. This hypothesis would

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require additional experiments to see if the upregulation of miR126 is indeed due to epigenetic changes and if these changes are confined to miR126 or indicative for a more general phenomenon. Furthermore, it remains to be seen if the observed downregulation of insulin signaling components and the upregulation of miR126 is also evident in subcutaneous fat or restricted to visceral adipose tissue, as these changes might contribute to the different risk associations of individual fat depots.

A challenging but exciting question is if the observed hyperinsulinemia is indeed caused by the downregulation of insulin signaling components and thereby presumptive reduced insulin sensitivity in visceral adipose tissue? In addition to IRS-1, many other components of the insulin signaling cascade, including the insulin receptor, were downregulated in mice from obese dams. Thus, future experiments will need to identify the regulatory mechanism of these proteins and their contribution to the overall phenotype.

Rapid progress is currently being made in understanding the complex interactions between obesity, insulin resistance and the development of type 2 diabetes, affecting multiple tissues and a magnitude of different signaling cascades. These studies will undoubtedly lead to the discovery of novel drugs that will help to treat these diseases or stop the progression from one step to the next in this complex cascade of events. However, if the ultimate goal is to prevent these diseases we can not only start to educate or treat children but we now know that we need to ensure a healthy uterine environment or at least aim to correct this "environmental heritage" before it causes any harm. Fernandez-Twinn and colleagues highlighted that the initial metabolic insult is not the development of obesity but rather insulin resistance. More specifically the authors show that insulin resistance in adipose tissue due to downregulation of key insulin signaling components precedes the development of obesity. These data imply that in addition to the role of insulin action in skeletal muscle and liver, white adipose tissue is a central player in the early events leading to insulin resistance, obesity and eventually type 2 diabetes. Therefore much greater attention needs to be paid on the early molecular changes in distinct white adipose tissue depots regulating insulin sensitivity to develop novel strategies against the development of obesity and type 2 diabetes.

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