What You Eat Matters to Your Grandchildren - Epigenetic Inheritance

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The recent evidence has suggested that chronic metabolic stress alters physiological condition not only of an individual who is exposed to, but also of one's next generations. Although it emerges that the transgenerational inheritance occurs even in the absence of the changes in DNA sequences, its underlying mechanism remains unclear. Epigenetic modulation has gained much attention in recent years as a possible molecular mechanism of transgenerational inheritance. Epigenetic regulation, mediated by chemical modifications to DNA and histones, dictates gene transcriptional status by toggling between a condensed or de-condensed state without the changes of DNA codes. We hypothesized that metabolic stress i.e. high fat diet to male mice leads to altered expression of fat metabolic genes in the offspring the liver and adipose and the alterations are mediated by epigenetic mechanism, especially dynamics of DNA methylation and demethylation. We observed that high fat diet-fed male mice (F0 HFD) transmitted metabolic alterations to the next generations, but to a lesser extent. F2 male mice from F0 HFD through maternal transmission (F2 HFM) showed greater body weights and higher hepatic TG levels than F2 male mice from F0 CD (F2 CFM). In addition, F2 HFM showed higher fasting glucose levels compared to F2 CFM. Interestingly, F2 female mice from F0 HFD through maternal transmission (F2 HFF) had significantly lower body weights F2 female mice from F0 CD (F2 CFF), although showed significantly higher hepatic TG levels and impaired glucose response. These physiological changes were accompanied by transcriptional changes of multiple genes such as Gck and Glut4 involving fat metabolism in the liver and adipose tissues, respectively. ER stress genes were upregulated and phosphorylated IRS-1 increased. Intriguingly, the list of differentially expressed genes includes Ten-eleven translocation methylcytosine dioxygenase 2 (Tet2). TET2 is an enzyme to convert 5-methylated cytosine (5mC) to 5-hydroxymethyl cytosine (5hmC) in DNA that is an intermediate for oxidative demethylation. Recently, 5hmC and TET proteins are known to be involved in lineage decision of embryonic stem cells. Since Tet2 expression was altered in the offspring, we further investigated whether Tet2 plays a role in adipogenesis. We showed that it was required for Pparγ induction upon initiation of adipogenesis in 3T3-L1 cells. Its expression increases during adipogenesis and its knockdown resulted in suppression of Pparγ expression due to reducing 5hmC and at the locus. In addition, CAC metabolites and vitamin C influence the rate of adipogenesis via controlling the TET protein activity. The findings are novel and suggest that

Tet2-mediated epigenetic changes might be involved in not only fat metabolism but also transgenerational effects of metabolic stress.