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Comment

Maternal Genistein Alters Coat Color and Protects A^{vy} Mouse Offspring from Obesity by Modifying the Fetal Epigenome

The 'fetal basis of adult disease' or 'early origins hypothesis' postulates that nutrition and other environmental factors during prenatal and early postnatal development influence developmental plasticity, and alter susceptibility to adult cardiovascular disease, type 2 diabetes, obesity, and other chronic diseases [1, 2]. Recently, human epidemiologic and animal model data have suggested that developmental plasticity is influenced by persistent epigenetic adaptations that occur early in development in response to environmental and nutritional factors [3-5]. The epigenome is particularly susceptible to deregulation during gestation, neonatal development, puberty, and old age. Nevertheless, it is most vulnerable to environmental factors during embryogenesis because the DNA synthetic rate is high, and the elaborate DNA methylation patterning required for normal tissue development is established during early development.

Recently, we have shown that maternal dietary supplementation of mice with genistein, the major phytoestrogen in soy, at levels comparable to humans consuming high soy diets, shifted the coat color of heterozygous viable yellow Agouti (A^{vy}/a) offspring toward pseudoagouti. This marked phenotypic change was significantly associated with increased methylation of six CpG sites in a retrotransposon upstream of the transcription start site of the *Agouti* gene. The extent of this DNA methylation was similar in endodermal, mesodermal, and ectodermal tissues, indicating that genistein acts during early embryonic development. Moreover, this genistein-induced hypermethylation persisted into adulthood, decreasing ectopic *Agouti* expression and therefore protecting offspring from obesity. Thus, we provide the first evidence that mouse *in utero* dietary genistein affects gene expression and alters susceptibility to obesity in adulthood by permanently altering the epigenome.

The results of our study have a number of other important implications. Firstly, the biological importance of establishing genomic methylation patterns during early development suggests that it is essential to determine the effects of environmental factors on the epigenome during prenatal and early postnatal development, rather than just in adults. Secondly, phytoestrogen content in laboratory animal feed is highly variable [6]. Therefore, genistein's effect on fetal DNA methylation patterns could significantly influence the interpretation of hormone and other rodent assay studies [7-9] as well as confound the interpretation of gene expression arrays and DNA methylation studies. Finally, it needs to be determined whether the relatively high genistein intake of infants consuming soy formulas is beneficial or has unintended deleterious effects on the human epigenome, especially in the U.S. and other countries where the food supply is fortified with methyl donor compounds such as folic acid. Elucidating the potential for epigenetic modifications during pre and early postnatal development is especially pressing given recent research correlating nurturing maternal behavior with offspring demethylation within hippocampal glucocorticoid receptor (*GR*) gene promoter[10, 11]

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