CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Epigenetic Signatures of Obesity

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The prevalence of obesity is continuing to increase at an alarming rate in both the developed world and the developing world. This is of major concern not only because of the well-established detrimental health consequences for the obese person but also because obese parents are likely to have obese children, thus perpetuating a cycle of obesity.

This transmission of phenotype from parent to offspring is in part a consequence of shared genes and current environment. However, there is also evidence that the transmission of susceptibility to obesity can occur as a consequence of "developmental programming."[1] This concept suggests that the environment encountered at the point of conception and during fetal and neonatal life permanently influences the structure, function, and metabolism of key organs, thus leading to an increased risk of diseases such as type 2 diabetes and cardiovascular disease later in life.

Most evidence for such developmental programming has come from studies in mammals, which have focused initially on transmission through the maternal line as a consequence of suboptimal nutrition during pregnancy. However, evidence suggests that the transmission of traits, such as the phenotype for diet-induced obesity,[2] can also occur through the paternal line. Epigenetic mechanisms that influence gene expression have been proposed to mediate the effects of both maternal and paternal dietary manipulation on disease susceptibility in the offspring (these mechanisms include alterations in DNA methylation, histone modifications, and the expression of microRNAs).

Ost et al.[3] recently described a model of intergenerational metabolic programming using the fly *Drosophila melanogaster* (Fig. 1). Male flies were fed a diet with a defined sugar content, which ranged from very low to very high. The flies that were fed the diet with the highest sugar content for 2 days before mating had an increase in their triglyceride content that was three times as high as the level at baseline.[3] These males were then mated with females, and the F1 offspring were fed either normal fly food or an obesogenic high-sugar diet. No effect of paternal diet was observed in the F1 male flies raised on the normal food. However, when the F1 males were fed a high-sugar diet, an effect of paternal diet was observed: F1 male offspring of the fathers who were fed either a low-sugar diet or a high-sugar diet had increased triglyceride content. These data are consistent with evidence from mammalian models showing that suboptimal nutrition at either end of the spectrum (i.e., parental overnutrition or parental undernutrition) causes an increased risk of metabolic dysfunction in the offspring.

Having established that changes in paternal diet lead to programmed effects on metabolism in the offspring in the *D. melanogaster* model, Ost and colleagues then addressed the potential mechanisms through which this could occur, focusing on effects on chromatin. (Chromatin is the complex of DNA, RNA, and protein of which chromosomes are composed; changes to chromatin can affect gene expression.) They were able to use position-effect variation, a genetic phenomenon that can be used as a quantitative readout of the chromatin state and therefore of transcriptional silencing at specific chromosomal loci. The authors found an effect of paternal sugar-feeding on the chromatin structure at a specific region of the X chromosome.

Further evidence for the effects of paternal diet on the chromatin structure came from a transcriptome analysis of embryos generated from fathers fed a high-sugar diet, which revealed dysregulation of transcripts encoding two proteins — one of them is called Su(var) — that are involved in the dynamic shaping of chromatin conformation. This dysregulation involved down-regulation of enzymes known to change chromatin structure and gene regulation.

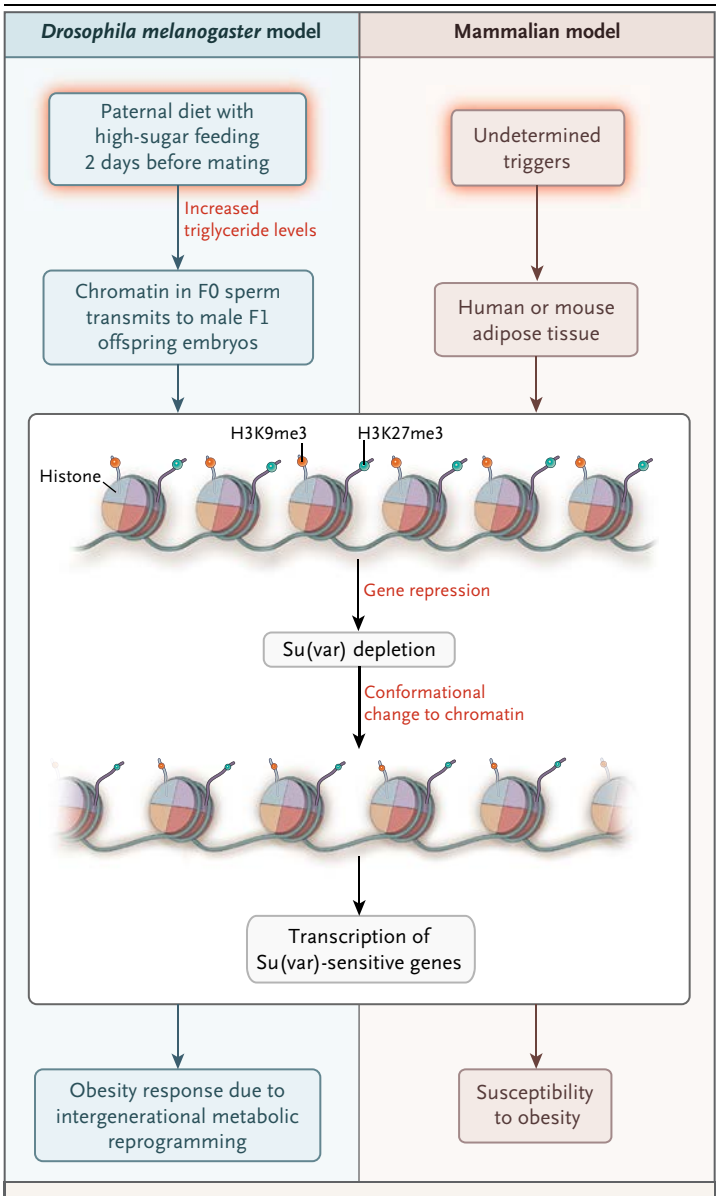

Figure 1. Epigenetic Transmission of Obesity.

In a recent study of *Drosophila melanogaster*, Ost et al.[3] found that features of obesity can be transmitted from the father to male offspring. Fathers fed a diet with a high sugar content 2 days before mating had dramatically increased triglyceride levels and gave rise to male offspring with excess triglyceride reserves, relatively large lipid droplets and adipose reserves, and increased body weight. Further investigations suggest that changes to chromatin in the father's sperm represent the vehicle of a transgenerational transmission of phenotype. The data support the involvement of several pivotal chromatin-modifying proteins, such as Su(var), and a general increase in gene expression in the affected F1 progeny. Analyses of adipose tissues from mice and from humans suggest that a deficit in orthologous chromatin-modifying proteins is associated with obesity in mice and humans. H3K9me3 denotes trimethylation of lysine 9 on histone 3, and H3K27me3 trimethylation of lysine 27 on histone 3.

In a final set of experiments, Ost and colleagues explored the possibility that similar changes in chromatin structure are associated with obesity in mammals. Using existing microarray data sets obtained from adipose tissue from lean individuals and from obese individuals, they found a depletion of the Su(var) proteins in three data sets from humans and in two data sets from mice. One of the human data sets was obtained from adipose-tissue samples from monozygotic twin pairs, in which one twin was obese and the other was of normal weight, thus showing that depletion of the Su(var) pathway was associated with obesity in genetically identical persons. This finding is consistent with the possibility that the depletion of the Su(var) pathway may be brought about by an environmental insult to the genome that is associated with obesity.

Ost et al. have therefore identified a clear and conserved epigenetic signature that is associated with obesity across species. The key challenges now will be to establish whether the early environment can modulate this epigenetic signature in humans and whether the signature is present before the development of the phenotype (i.e., obesity) and therefore could be used as a biomarker of disease risk. To maximize its therapeutic potential, tissue specificity of this signature would need to be established to enable identification of the most suitable clinically accessible tissue for diagnostic use. Once these knowledge gaps are filled, the use of epigenetic signatures for diagnostic purposes could become a realistic possibility.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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