Early Nutritional Influences on Human Developmental Epigenetics

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Summary  Transient nutritional exposures during critical ontogenic periods can cause persistent changes in gene expression, metabolism, and risk of various diseases. We have been investigating whether such 'developmental programming' occurs via nutritional influences on developmental epigenetics. Our studies in agouti viable yellow and axin-fused mice showed that developmental establishment of DNA methylation at 'metastable epialleles' is especially sensitive to maternal nutritional status around the time of conception. At metastable epialleles, DNA methylation is established stochastically in the early embryo and subsequently maintained during differentiation of diverse lineages, resulting in systemic interindividual epigenetic variation that is not genetically mediated. Lately, using a multiple-tissue screen for interindividual variation in DNA methylation, we have identified human genomic regions that appear to be metastable epialleles. Stochastic establishment of DNA methylation at these loci is affected by maternal nutrition around the time of conception, consistent across multiple tissues, and stable for many years. Most recently, our studies using genome-wide bisulfite sequencing have identified candidate metastable epialleles that are associated with human disease, providing exciting opportunities for epigenetic epidemiology.

Key Words  DNA methylation, epigenetic development

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