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The epigenetic basis of the developmental origins of health and disease

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One mechanism by which maternal diet during pregnancy may lead to stable changes in gene expression within the offspring is through the altered epigenetic regulation of genes. Epigenetic processes stably alter gene activity without altering gene sequence. The two major epigenetic mechanisms are DNA methylation and histone modification. Methylation of CpG rich clusters (termed CpG islands) which span the promoter regions of genes is associated with transcriptional repression, while hypomethylation of CpG islands is associated with transcriptional activation (1-4). These methylation patterns are largely established *in utero*. We have shown for the first time that feeding pregnant rats a protein-restricted (PR) diet alters promoter methylation patterns in a gene-specific manner in the offspring (5). We found decreased methylation of the 5' region of the PPARα (20%) promoter and glucocorticoid receptor (GR) 1_{10} promoter (23%) genes in the liver after weaning of the offspring from dams fed a PR diet during pregnancy (5). Hypomethylation of the 5' CpG islands in the promoters of GR and PPARα correlates with the increase in expression of these genes that we previously observed. These epigenetic changes were associated with increased expression of acyl-CoA oxidase (AOXa) (5), the rate-limiting enzyme in peroxisomal fatty acid β-oxidation and with dyslipidemia (6). Supplementation of the PR diet with folic acid prevented these epigenetic changes in GR and PPARα expression, and normalised AOX expression (5). Thus altered gene methylation may provide a causal mechanism to explain how maternal diet can stably reset gene expression within the offspring.

Histone modification, like DNA methylation, can also affect gene activity. In each cell, DNA is wrapped around a core of histone proteins (H2A. H2B, H3 and H4), in general acetylation of specific amino acid residues in histone proteins causes a decrease in the strength of interaction between DNA and histones which facilitates access to gene promoters by the transcription machinery (7). Prenatal under-nutrition also induced hyperacetylation of histone H3 and H4 at the GR (8). Together these data reveal, for the first time, a causal molecular mechanism linking impaired fetal nutrition with long-term modification of the phenotype of the offspring.

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Epigenetic basis of cancer

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In recent years, increasing evidence has demonstrated the role of epigenetic alterations in the etiology of many diseases. Epigenetics -the stable and heritable (or potentially heritable) changes in gene expression that do not entail a change in DNA sequence- are characteristic of different cell types and, in fact, play a key role in defining the transcriptome, which determines the identity of each cell type (1). Two major groups of changes contribute to defining the epigenome of a cell: DNA (cytosine) methylation and histone modifications.

The early onset of epigenetic changes and the growing view that stem cells are the target cells for cancer, together with the idea that epigenetic changes probably distinguish stem cells from somatic cells, make it likely that epigenetic disruption of stem cells is a common unifying theme in cancer etiology (2). Great advances have been made in characterizing epigenetic alterations in cancer. Two major alterations occur concerning DNA methylation patterns. First of all, there is a global loss of 5-methylcytosine or demethylation, in many cases in repetitive sequences. In parallel, CpG islands, CG–rich regions coincident in most cases with the promoter of protein coding genes, suffer from a process of hypermethylation that leads to gene silencing. This mechanism is now considered to be a key event leading to the inactivation of many tumor suppressor genes in a tumor-type specific fashion. More recently, alterations in histone modifications have also been recognized to occur in cancer cells. Histone modification changes are intimately associated with alteration in the DNA methylation pattern. The dependence of histone modifications and DNA methylation pattern can be recognized in a global context of architectural organization. Also, histone deacetylation and specific alterations in the histone methylation profile are specifically associated with transcriptional silencing of many tumor suppressor genes. Finally, it has been demonstrated that histone modification changes can also be detected at a global scale in a cancer cell. In particular, loss of acetylated Lys16 and trimethylated Lys20 residues of histone H4 are a common hallmark of human cancer (3). These changes are associated with the hypomethylation of DNA repetitive sequences, a well-known characteristic of cancer cells that is involved in genomic instability.

External influences on epigenetic processes are seen in the effects of diet on long-term diseases such as cancer (4, 5). On the other hand, it is possible that small defects in transmitting epigenetic information through successive cell divisions, or maintaining it in differentiated cells, accumulate in a process that could be considered as an epigenetic drift. Identification of proteins that mediate these effects has provided insight into this complex process and diseases that occur when it is perturbed (6, 7). Accumulation of epigenetic defects would probably occur at a faster

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