epigenoom komt tot stand door middel van DNA-methylering en histonmodificatie. Epigenetische merktekens zijn inherent labiel en vormen de basis van celdifferentiatie en ouder-specifieke effecten door middel van 'imprinting'. Het epigenoom geeft ook instructies door vanuit de omgeving naar het genoom. Deze merktekens vormen een 'geheugen' waarmee gegevens van de omgeving potentieel kunnen worden overgedragen op de volgende generatie(s). Folaat is één van de vele omgevingsfactoren die het fenotype moduleren door middel van epigenetische mechanismen. Het erven van twee chromosomen van één ouder en geen van de ander, en mutaties in de epigenetische machinerie zijn klassieke voorbeelden van epigenetische ontsporing. Enkele zeldzame ziektes ontstaan door mutaties, epigenetische ontsporingen of combinatie hiervan, die een enkele locus aantasten. Een recente studie legde een verband tussen epigenetische mechanismen en de hypothese van de 'ontwikkelingsoorsprong van ziekte'. Een disbalans tussen de verwachte en werkelijke omgeving kan het ontstaan van typisch Westerse ziekten verklaren. Veel vooruitgang is geboekt in de epigenetica van kanker. Tumorgenesemodellen met elkaar wederzijds versterkende epigenetische disregulatie en mutatie zijn o.a. gepostuleerd. De kortetermijnaanpassing aan de omgeving geschiedt door middel van 'sensoren'. Zo zijn peroxisoom-proliferator geactiveerde receptoren (PPARs) bijvoorbeeld nucleaire transcriptiefactoren die functioneren als sensoren voor vetten. Indien geactiveerd door vetzuren uit de voeding, induceren ze de gecoördineerde expressie en repressie van eiwitten die betrokken zijn in het intermediair metabolisme, groei en differentiatie, en ontstekingsreacties. Harmonie tussen ons miljoenen jaren oude genoom en de omgeving kan het aantal jaren in gezondheid doen toenemen. Voor de klinische chemie vereist het bereiken van deze toestand van 'optimale homeostase' een heroverweging van het gebruik van referentiewaarden en het gebruik van algoritmen die een vroege interventie mogelijk maken. Ook *Homo sapiens* dient zich aan te passen aan de leefomstandigheden gedurende welke haar genoom tijdens de evolutie vorm heeft gekregen.

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Fundamentals of epigenetics and its relevance to human disease

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The term 'epigenetic' is used to refer to heritable patterns of gene expression that occur without changes in the DNA sequence. Epigenetic regulation plays an important role in animal and plant development, and is required in particular to achieve stable repression of genes in specific cell types and at defined developmental stages (1). In mammals, there are many examples of epigenetic inactivation of one of the two alleles of genes. These include X-chromosome inactivation in female somatic cells (2), and imprinted genes, a subset of about a group of essential genes whose expression depends on whether they are inherited from the mother or the father (3).

The allelic repression of imprinted genes depends on epigenetic marks, the imprints, which are placed onto the gene upon passage through either the female or the male germ line (3). Some eighty imprinted genes have been identified in humans and mice to date. These rather unusual genes are clustered in the genome. They are organized in evolutionarily conserved chromosomal domains, some of which are more than a thousand kilobases in size. Mouse studies have shown for several imprinted genes, including the insulin-like growth factor 2 (*IGF2*) gene, that they play key roles in the regulation of growth and cellular proliferation, both in the embryo and in the extra-embryonic lineages. Deregulation of the epigenetic marks that regulate imprinted genes is causally involved in different disease syndromes of aberrant growth, such as the Silver-Russell Syndrome (SRS), Beckwith-Wiedemann Syndrome (BWS), and Transient Neonatal Diabetes Mellitus (TNDM) (4). The somatic maintenance of imprinting is frequently perturbed in cancer as well, and is thought to be an early event in tumourigenesis.

The somatic maintenance of imprinting is a highly complex process that involves DNA methylation, covalent histone modifications, and recruitment of non-histone proteins to the chromatin (3). Different kinds of environmental stress, including embryo culture and assisted reproduction technologies, may perturb the maintenance of these epigenetic marks (5, 6). Also dietary changes may disrupt the maintenance of epigenetic marks, and can thus heritably affect gene expression (6). Recent studies in the mouse suggest that genomic imprinting is particularly susceptible to perturbation in the early embryonic cells that give rise to the extra-embryonic tissues. Possibly, this could be explained by the finding that, in contrast to the embryo and the adult animal, imprinting of certain genes in the placenta does not require DNA methylation for its somatic maintenance (7, 8). Our current studies address to which extent this kind of imprinting is evolutionarily conserved in humans, and could contributes to imprinting disorders such as the Silver-Russell and Beckwith-Wiedemann Syndromes (9).

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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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