Epigenetics, Nutrition and Human Health

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Imagine yourself at the scene of a crime where you need to determine the age of a victim or perpetrator. If you are lucky, you will have access to skin or dental tissue, or perhaps anthropometry measures, all of which may help determine an approximate age. However, recent research suggests that you could instead obtain an astonishingly accurate measure of chronological age with an "epigenetic clock" that uses a very small number of epigenetic marks in the genome.[1] This would allow you to pin down a sample's age to within a few months, irrespective of the tissue from which it was obtained.

The field of epigenetics is currently attracting a lot of attention from scientists and the wider public. Epigenetic processes describe changes to the genome that can alter gene expression without changing the underlying DNA sequence[2] (**Figure 1**). One such mechanism is DNA methylation of cytosine bases at CpG dinucleotide sites, and there is strong evidence that this can be influenced by a diverse array of intrinsic and environmental factors, including age, disease, stress, exposure to pollutants, and nutrition. Furthermore, epigenetic marks have been associated with a range of diseases affecting health throughout the life course, including cancers, and neurological and metabolic disorders.[3] Together, these observations suggest that our epigenomes carry a "cellular memory" of environmental insults, with the potential for lasting effects on health and disease. Epigenetic changes at certain locations are also believed to be heritable, raising the possibility of trans-generational effects that cannot be explained by standard Mendelian genetics.[4]

Diet and epigenetics in The Gambia

Our group is exploring human diet-epigenome interactions by exploiting an "experiment of nature" in rural Gambia whereby

FIGURE 1: Epigenetic mechanisms of DNA modification. Reproduced with permission from Yan MS-C, Matouk CC, Marsden PA.[5]

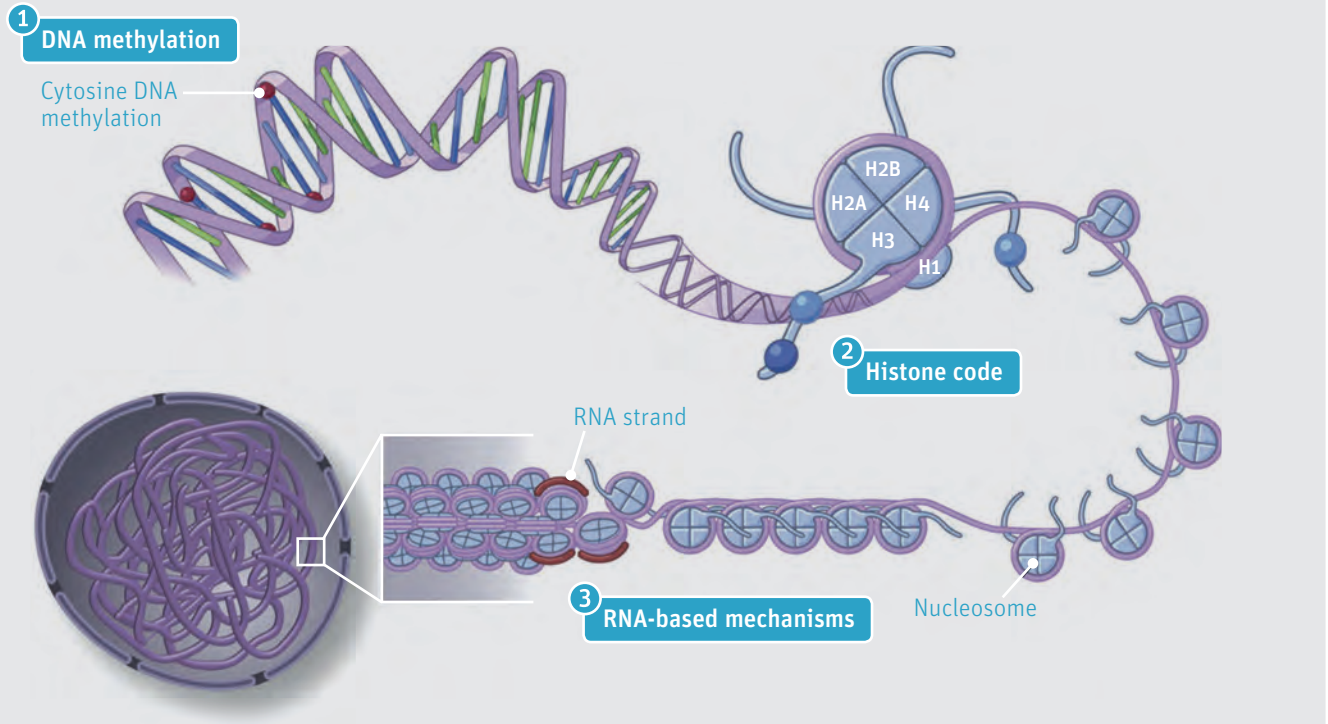


FIGURE 2: Keneba in the rainy and dry seasons

fluctuations in energy balance and maternal nutrition show a distinct bimodal seasonal pattern (**Figure 2**). Our study population experiences a rainy ("hungry") season from July to September, with increased energy expenditure through agricultural work, depleted food stores, and peaks of malarial and diarrheal diseases. The dry ("harvest") season occurs from February to April, when harvesting takes place, leading to improved food security.

> "Epigenomes carry a 'cellular memory' of environmental insults, with the potential for lasting effects on health and disease"

Almost 20 years ago, we uncovered strong evidence that the season when a child is born has a profound effect on lifelong health. Gambian children born during the rainy season are up to 10 times more likely to die prematurely in young adulthood.[6] Since then, pieces of the puzzle are starting to fall into place, with nutrition-related epigenetic regulation in the early embryo emerging as a highly plausible candidate mechanism.

Five years ago, in partnership with Rob Waterland at Baylor College of Medicine in Houston, we demonstrated that season of conception predicts DNA methylation at certain genomic loci known as metastable epialleles (MEs). These are CpG sites whose methylation state varies between individuals, but where variation is correlated across tissues originating from all germ layers in a single individual[7] – indicating that the marks must have been laid down in the first few hours after conception before cell types start to specialize. This period in the very early embryo is when the methylome is globally reprogrammed – a period crucial to development.[8] We therefore use MEs as a device to study the influence of a mother's nutrition on the epigenome of the baby at the time of conception.

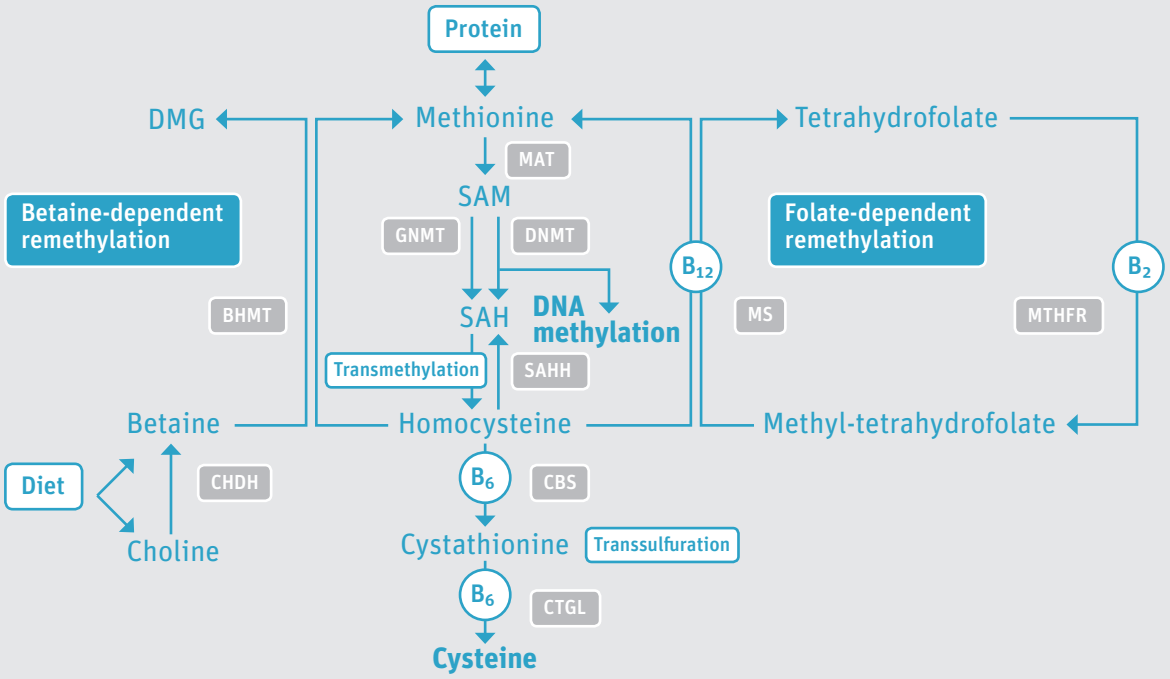
> "We use metastable epialleles as a device to study the influence of a mother's nutrition on the epigenome of the baby at the time of conception"

We have since shown that a mother's levels of several key nutrients vary by season and predict DNA methylation at six MEs in their offspring.[9] These nutrients play a role in 1-carbon metabolism, a biological pathway crucial for the provision of methyl (CH3) groups required for DNA methylation (**Figure 3**). The two main carriers that activate, transport and transfer these methyl groups are tetrahydrofolate (THF) and S-adenosylmethionine (SAM). While 1-carbon units are used as substrates for a whole range of intricate biochemical processes (including cellular biosynthesis, redox status regulation and genome maintenance through the regulation of nucleotide pools), it is their role in cytosine and histone methylation that is central to the interplay between diet and the epigenome.

Linking diet, epigenetics and health

Our latest research has identified another ME that is sensitive to the periconceptional environment in Gambian infants.[11] The associated gene has been implicated in the regulation of immune function and is a putative tumor suppressor, suggesting a potential epigenetic pathway linking a nutritional insult affecting the very early embryo to some serious outcomes in later life. This requires rigorous testing, but work in animal models has already demon-

FIGURE 3: An overview of 1-carbon metabolism. Reproduced with permission from Dominguez-Salas P, Moore SE, Cole D et al.[10]



BHMT, betaine-homocysteine methyltransferase; B_2, vitamin B_2; B_6, vitamin B_6; B_{12}, vitamin B_{12}; CBS, cystathionine-β-synthase; CHDH, choline dehydrogenase; CTGL, cystathionine-γ-lyase; DMG, dimethylglycine; DNMT, DNA methyltransferases; GNMT, glycine N-methyltransferase; MAT, methionine adenosyltransferase; MTHFR, methylenetetrahydrofolate reductase; MS, methionine synthase; SAH, S-adenosylhomocysteine; SAHH, S-adenosylhomocysteine hydrolase; SAM, S-adenosylmethionine

strated that maternal diet can influence the offspring epigenome, with subsequent dramatic effects on phenotype. In the case of the Agouti mouse, pregnant dams fed a diet rich in methyl donor micronutrients (vitamin B_{12}, folic acid, betaine and choline) produced offspring with increased methylation at the agouti locus, leading to fewer obese yellow offspring and more lean brown offspring (**Figure 4**) – characteristics that persisted into adult life, with associated differences in appetite, adiposity and glucose tolerance.[12,13]

Implications for the future

Our Gambian studies offer the first-in-human evidence that periconceptional nutrition can affect the epigenome of the fetus. Just as the epigenetic clock shows that our genome carries an epigenetic signature of the ageing process, it seems that it also bears the hallmark of nutritional exposures at the very start of life.

> "Our Gambian studies offer the first-in-human evidence that periconceptional nutrition can affect the epigenome of the fetus"

The next task is to characterize more clearly how this affects phenotype. To what extent does disrupted methylation affect gene expression? How might these effects influence lifelong risk of morbidity and mortality? Most importantly, from a translational perspective, can epigenetic errors be corrected by optimizing the maternal metabolome through periconceptional nutritional supplementation?

The best known periconceptional nutrition supplement to prevent neural tube defects is folic acid. While the mechanism in this particular example has not yet been conclusively described, epigenetics is a strong contender. Given current research, we believe it is possible to speculate that other forms of periconceptional supplementation might positively influence the epigenome of the unborn child, leading to lifelong health gains across a whole variety of phenotypes.

Clearly the process of validating key findings, further delineating the mechanisms involved, and translating the science into practical public health policy requires a large collaborative effort, along with advances in technology and access to funding. While it is not possible to predict the precise direction research will take in this rapidly evolving field, it seems likely that nutritional considerations will remain paramount in the development of epigenetic therapies to improve health over the life course.

FIGURE 4: The effect of maternal diet on offspring phenotype of the Agouti mouse. Coat color corresponds to methylation levels at the agouti locus. Reproduced with permission from the American Society for Microbiology, Waterland et al.[12]

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