We are what we eat

The link between diet, evolution and non-genetic inheritance

The old adage that pregnant women eat for two might be more true than ever before in the light of recent research into diet and the control of gene expression. The link between the diet of pregnant women—and, to some extent, men—during pre-conception and the health of the fetus has been viewed mostly in terms of major risk factors such as smoking or substance abuse. However, epidemiological and molecular research is revealing a more complex and subtle picture of how a pregnant woman's eating behaviour influences the expression of her own—and possibly her fetus's—genes, and thus the long-term health of her children. "Type II diabetes, heart disease due to obesity, insulin resistance, and hypertension are the diseases most strongly associated with maternal diet during pregnancy," said Karen Lillycrop,

who specializes in perinatal nutrition at the University of Southampton in the UK.

In addition, there is growing evidence that dietary effects, which can alter the expression and control of genes, might even have been a driving force for human evolution. A recent study revealed that the greatest divergence between the genomes of humans and chimpanzees is found among genes that control metabolism and are closely associated with diet (Somel *et al*, 2008).

The mechanisms that allow the genome to interact with environmental factors, such as diet, are epigenetic changes—a concept first proposed by the British biologist Conrad Waddington (1905–1975) in 1942 to describe the interplay between genes and the environment in determining the phenotype of an organism.

Further research since Waddington's time has shown that epigenetic changes not only take place during embryonic development, but also throughout the lifetime of an organism. The same mechanisms—notably DNA methylation and histone modification—have a role in the acquisition and maintenance of epigenetic changes induced by dietary or other environmental factors. In fact, they are a prerequisite for multicellular life; the epigenetic changes that take place in the embryo during cellular differentiation allow organs and cell types to form and retain their specific gene expression profiles. For this to happen, the epigenetic modifications must be preserved during cell division. Furthermore, the ability to modify gene expression in response to environmental factors must have pre-dated the evolution of multicellular life because it occurs in single-celled eukaryotes and

prokaryotes. Therefore, it is likely that these mechanisms were co-opted by multicellular life to facilitate cellular differentiation.

For a long time, scientists assumed that these environmentally induced changes lasted, at most, for the lifetime of the individual organism, but did not influence its offspring because gametogenesis would 'wipe the slate clean' and the offspring would inherit a completely unadulterated set of genes. However, the specific mechanisms that cause the epigenetic modification of gene expression are now known to be involved in non-Mendelian—i.e. non-genetic—inheritance.

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Epigenetic mechanisms are also involved in another form of non-Mendelian inheritance, genomic imprinting, which is most prevalent in mammals and flowering plants, in which the female devotes substantial resources to its offspring. Genetic imprinting occurs in only a small number of genes, when the allele inherited from a specific parent—most often the mother—is silenced. The mechanism seems to have evolved, at least in part, through sexual competition and is not itself affected by environmental factors. However, as only one copy of each imprinted gene is inherited, they are particularly sensitive to environmentally induced epigenetic reprogramming. Furthermore, imprinted genes, which have probably evolved as a result of sexual conflict over the allocation of resources to offspring, are involved in various metabolic functions and the processing of nutrients.

It is therefore not surprising that some of the most serious conditions resulting from deleterious environmental or dietary effects involve epigenetic modification of imprinted genes, for example, the insulin-like growth factor 2 gene. Yet, most of the genes modified by dietary effects, especially in cases where the impact is less marked, are not imprinted. Genetic imprinting is completely determined by the parents, unlike epigenetic modifications, which are induced by diet or other environmental factors, some of which can also be inherited.

During the past decade, epidemiologists have been piling up examples of heritable epigenetic changes that are induced by diet. For instance, several studies have reported that mothers who are diabetic or overweight during pregnancy—which depends, in part, on diet—are more likely to have obese children (Mayer-Davis *et al*, 2006). This and other work has an immediate relevance for public health as it helps to explain some human health problems that result from modern nutrition, especially in industrialized countries. Although people in developed countries might be living longer than ever before, the modern lifestyle has also spawned several problems, many of which, as is now becoming clear, involve epigenetic effects. Foremost among these is a growing epidemic of obesity—particularly childhood obesity—which afflicts every country in the industrialized world and causes severe problems for public health and health care systems, and the people suffering from it.

Obviously, the genetic make-up of a whole population cannot change within a single generation, which apparently leaves only two possible explanations for childhood obesity: either it is caused by a change in diet—in particular, the consumption of addictive high-calorie junk foods; or children take less exercise than they used to; or a combination of both. However, this does not account for the full extent of the obesity epidemic; indeed, it seems that the diet and health of the mother play a big part too.

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This might be good news for therapeutic intervention because the epigenetic component of a phenotypic trait—such as susceptibility to childhood obesity—might be easier to change than actual genetic defects. Indeed, epigenetic modifications are, by definition, fairly susceptible to change because they respond to environmental factors; thus, a reversal of the conditions that lead to childhood obesity—bad maternal diet during pregnancy—could solve the problem. In fact, it turns out that a mother can administer good medicine herself by breast-feeding, especially if she takes particular care of her

diet. A US study found that breast-feeding reduced the risk of childhood obesity regardless of the mother's diet during pregnancy (Mayer-Davis *et al*, 2006). In other words, the mother has the chance to reverse some of the damage caused by bad diet if she continues to breast-feed her child for as long as possible.

There is additional epidemiological evidence that the mother's diet is relevant to the health of her offspring during lactation (Godfrey & Barker, 2001). This is reinforced by several experiments in animal models: a study at the University of Rio de Janeiro in Brazil, for example, found that the offspring of rats that were fed a diet restricted in protein or energy during lactation took longer to reach puberty (da Silva Faria *et al*, 2004).

One of the crucial dietary factors that can trigger childhood obesity seems to be the level of, and ratio between, two critical fatty acids: α -linolenic acid and γ -linolenic acid—along with longer-chain derivatives of these. The theory is that childhood obesity is encouraged by a maternal diet high in α -linolenic acid derivatives in the n-6 chain and low in γ -linolenic acid derivatives in the n-3 chain, as this leads to an inflammatory response in adipose tissue, which, in turn, causes fatty acids to accumulate in the liver and muscle. Childhood obesity could therefore be prevented by a diet high in γ -linolenic acid derivatives—such as those contained in breast milk—even when the mother still has a bad diet (Todoric *et al*, 2006; Carpentier *et al*, 2006). These findings have led some nutrition scientists, such as Manisha Talim at Shushrusha Hospital in Mumbai, India, to advocate a correction of the balance between n-3 and n-6 fatty acids in foods as an urgent global health priority (Talim, 2007).

Although epidemiology is contributing evidence for diet-induced epigenetic effects in humans themselves, observing and understanding the underlying epigenetic changes at the molecular level requires animal models. Much of this research has so far focused on the impact of protein restriction during pregnancy; Lillycrop and colleagues, for example, reported that this leads to altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats, which increases the risk of diabetes and other problems later in life (Lillycrop *et al*, 2007).

Animal models have also revealed that these diet-induced epigenetic changes are

not limited to one generation, but can ripple down to descendants. Females with an increased disposition to metabolic problems during pregnancy can transfer this to their offspring. Mammals in particular are prone to developing temporary diabetes during pregnancy as a result of an increased resistance to insulin caused by hormonal changes. "It is known that the offspring of mothers who do develop gestational diabetes with elevated blood glucose levels are in turn more prone to metabolic complications, including gestational diabetes themselves," commented Andreas Plagemann, Head of Experimental Obstetrics at the Charité University Hospital in Berlin, Germany. "In female individuals this leads to gestational diabetes and therefore exposure of the next generation to intra-uterine hyperglycemia again, and so on," he explained. "In this way, intergenerative transmission of acquired conditions is possible over successive generations of the maternal line, and this can even influence evolution."

Plagemann's reference to an evolutionary role is indeed interesting, given that epigenetic modifications do not directly affect genes. Indeed, the evolutionary rationale for epigenetic inheritance could have been to provide a means of adapting rapidly to short-term environmental changes without having to wait for the underlying genes to change by mutation and selection. However, epigenetic changes that ripple through many generations could exert selective pressure on some genes. In the case of gestational diabetes, for example, it could encourage selection of alleles that reduce the incidence of diabetes during the lifetime of the individual. The point is that, in the event of persistent gestational diabetes, individuals with the appropriate alleles would have a selective advantage because they would be less prone to die before reaching reproductive age.

So far, there has been relatively little research to find direct evidence of a link between diet and mammalian evolution. However, a recent study at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, provided some clues as to how nutrition might have had a crucial role in the divergence of humans and chimpanzees (Somel *et al.*, 2008). The researchers compared the epigenetic effects of typical human and chimpanzee diets—although, of course, it was not possible to feed humans on a chimpanzee diet, which is much lower in animal protein, nor was it permissible to give chimpanzees a human diet. Consequently,

the research was conducted on mice in the hope that this would yield some conclusive results. However, it was not at all clear at the outset how relevant a mouse model would be, as the study's corresponding author, Mehmet Somel, conceded: "When we started the experiments, we were not at all sure whether the effects of different diets in mice would be of any relevance to human and chimpanzee differences." Yet, it turned out that many of the genes, the expression of which in the liver is affected by diet, are common to humans, chimpanzees and mice. Of course the genes are not identical in the three species but, according to Somel, the study's authors found candidates with sufficiently similar DNA sequences and genomic locations to suggest that they evolved from a common ancestor and retained the same metabolic functions throughout evolution.

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In fact, one of the main conclusions was that the genes for which expression did vary in response to diet had diverged significantly since the time when chimpanzees and humans shared a common ancestor. The logical implication is that genes that are directly affected by dietary changes come under strong selective pressure, which eventually leads to crucial morphological and functional changes. "The role of diet in human evolution is still rather a speculative topic," Somel noted, adding that, "[o]ne popular hypothesis [the expensive-tissue hypothesis] about how a switch to a high-quality diet affected our evolution was that the dietary change allowed a reduced gut size and an increased brain size" (Aiello & Wheeler, 1995).

According to one publication, a smaller gut size combined with a switch to a high-calorie diet—made possible by the introduction of cooking—allowed the brain to increase in size, driving human evolution (Wrangham & Conklin-Brittain, 2003). The authors argue that a diet of raw food could not be digested quickly enough to sustain the high-energy requirements of the human hunter-gatherer, who had evolved the ability to run faster and travel much greater distances than other great apes. At the same time, cooking would

have allowed a reduction in tooth and jaw size, as well as a smaller gut, thus creating the capacity for brain enlargement. The authors noted that cooking had been discovered independently by various human populations a sufficiently long time ago for the current phenotypes to evolve.

These developments could have been mediated by epigenetic modifications of gene expression, which allowed the creation of new phenotypes that, in turn, stimulated long-term genetic changes. Epigenetic inheritance can therefore be seen not just as an evolutionary 'third way' that complements mutation and natural selection, but actually as an engine of evolution that creates long-term genetic changes and might thus have an important role in species divergence.

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