FOCUS

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Why Are Genetics Important for Nutrition? Lessons from Epigenetic Research

by Frank M. Ruemmele and Hélène Garnier-Lengliné

Key insights

This article summarizes the molecular mechanisms behind nutritional imprinting, i.e. where specific and early nutritional modifications may impact the regulation of gene expression either in the short or long term.

Current knowledge

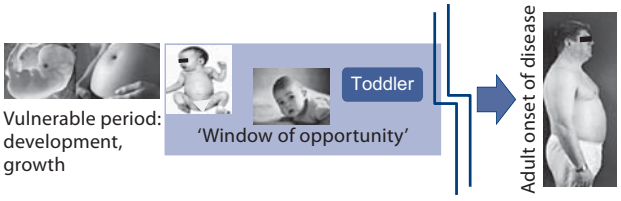
Targeted nutritional intervention can modify gene expression on a permanent manner, as evidenced by epigenetic histone modifications or targeted DNA methylation. In addition, a very complex and rather new epigenetic regulatory mechanism by the way of non-coding microRNAs exists, meaning that the regulation is on a post-DNA level or 'epigenetic'. Epidemiological data, such as the Dutch famine studies, suggest that targeted nutritional intervention might be causative for long-term effects on health, such as the increased risk of cardiovascular diseases and metabolic syndrome in this cohort. To date, the potential of positive nutritional modification on phenotype has been demonstrated solely through experimental animal models.

Practical implications

Based on the current understanding of the epigenetic regulation of gene expression, a new concept has emerged, indicating that specific early nutritional interventions during a short time frame might set the initial insult for the development of chronic disease decades later.

Recommended reading

Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French TA, Tai ES, Milner J, Koh WP, Xie L, Zucker M, Buckley M, Cosgrove L, Lockett T, Fung KY, Head R: Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. J Nutrigenet Nutrigenomics 2011;4:69–89.



Targeting early intervention: nutritional imprinting and disease prevention (see text for details).

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Why Are Genetics Important for Nutrition? Lessons from Epigenetic Research

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Key Messages

- Targeted nutritional intervention can modify gene expression on a permanent manner: this can be yielded by epigenetic modification (i. e. of histones or targeted DNA methylation).
- A very complex and rather new epigenetic regulatory mechanism is by non-coding microRNAs.
- Based on the understanding of epigenetic regulation of gene expression, a new concept emerges indicating that specific early nutritional interventions during a short time frame (nutritional imprinting) might set the initial insult for the development of diseases decades later.

Key Words

DNA methylation · Epigenetics · Famine cohort · Gene expression · Nutrigenetics · Nutrigenomics · Nutritional imprinting · Pediatric nutrition

Abstract

Marked advances were made over the last decade in deciphering the molecular mechanisms on how external, nutritional factors can impact on the regulation of genes and ultimately their function without modification of the genetic code. This field of nutrigenomic research is literally exploding. With the understanding of epigenetic control mechanisms, such as DNA methylation, histone acetylation, methylation or phosphorylation, as well as the posttranscriptional regulation of gene expression via non-coding microRNA, many different experimental and analytic approaches were possible to elucidate how varying nutritional support might impact on specific functions, with short- and potently long-term effects. This review highlights the major principles of epigenetic control mechanisms and their link to particular nutritional influences. Epidemiological data, such as the Dutch famine studies, suggest that targeted nutritional intervention might be causative for long-term effects on health, such as the increased risk of cardiovascular diseases and metabolic syndrome in this cohort. However, to date most of the knowledge comes from experimental and animal data, which cannot be easily transferred to human situations. It is anticipated that within the next few years, major advances will be made to translate this knowledge of nutritional intervention on gene regulation and expression into health preventive programs.

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Introduction

Are genetics and the knowledge of genetics important for nutrition? There is one clear answer: yes. Behind this answer, we find interesting new concepts, such as genetic imprinting/programming and long-term effects of particular nutritional interventions as well as individualized nutrition. Over the last decade, major advances were made in the field of genetics, opening new areas of investigations; deep insight was gained into the effects of nutrition on signaling pathways under physiological as well as pathological situations. One main question is: does targeted nutritional intervention have the potential to prevent adverse health outcomes, or, in contrast, to enforce positive effects in the short term as well as in the long term? If this is the case, how could this be achieved and what is the best time point for targeted nutritional intervention? Does a window of opportunity exist and is there a critical (and probably also vulnerable) period in life, where changes in nutritional support can cause effects beyond the simple energy supply, and, potentially, at a distance from the nutritional intervention (months or years later)? To address these interesting questions in this review article, we performed a literature research focusing on particular situations in humans and also on representative animal and experimental studies. However, it will be difficult to extrapolate from experiences and knowledge gained in animal models to particular situations in humans without any criticisms.

One main question is: does targeted nutritional intervention have the potential to prevent adverse health outcomes or to enforce positive effects in the short term as well as in the long term?

One approach to address these questions is via cohort and epidemiological studies. Insights in the importance of nutritional supply during a critical period on long-term outcome were gained from the Dutch famine cohort. During the Nazi occupation in Winter 1944, food supply was extremely shortened in parts of the Netherlands, a real humanitarian disaster. This extreme food shortage occurred during a short period and showed to have a major impact on particular situations, such as ongoing pregnancies. The Dutch cohort studies analyzed the outcome of pregnancies occurring during this famine period and the consequences of massive maternal undernutrition on offspring on a long-term scale. Many data were collected from the long-term follow-up of this cohort [1–3]: there was an increased risk of cardiovascular diseases 4–5 decades later in those children born to mothers who experienced extremely severe undernutrition during the first trimester of pregnancy [4]. The incidence of cardiovascular diseases was 2 times higher in this group compared to the control cohort [4]. But not only was the risk for cardiovascular diseases increased in this particular cohort, the nutritional insult also increased the risk for metabolic disorders, including obesity, and breast cancer decades later [5–7]. However, depending on the moment of food starvation (early versus late pregnancy, and preconceptional undernutrition or after birth) marked differences were observed, indicating the first trimester of pregnancy as a particularly vulnerable period. What may be the molecular basis explaining these observations?

Nutrigenomics and Nutrigenetics

In recent years, we learned from excellent experimental models that complex machinery exists, which tightly controls the regulation of gene expression and the function of genes and their products. Indeed, experimental data showed to what extent this machinery is influenced by endogenous and exogenous factors and therefore particularly prone to nutritional imprinting [8–11]. The interaction between nutrition and genes can be separated into two dimensions: the impact of nutritional factors on gene regulation and expression, which is summarized by the term 'nutrigenomics', and the fact that genetic variants predefine nutritional requirements and tolerance under physiological as well as particular pathophysiological situations. This interaction is now termed 'nutrigenetics'. This second topic is not developed in this review article but covered by several excellent reviews [12–15].

Epigenetic Regulations: Molecular Mechanisms

Molecular analyses revealed that the regulation of genes is controlled by 3 different mechanisms: histone modification, DNA methylation, and microRNA. Histone modification refers to the way DNA is densely packed around protein complexes, by the so-called histones. This DNA packing is not only a mechanical way to stock and protect the DNA, but it is also a very efficient way to switch on or off genes depending on their geometric location, allowing stereometric access of transcrip-

tion factors to the corresponding promoter regions. Any modifications of this DNA packing can lead to changes in the accessibility of different genes for transcription, thereby directly impacting on gene functions. It is well known that the structures of histones can be modified by active methylation, acetylation or simple phosphorylation [16–19], a highly efficient system to control gene expression. DNA methylation refers to the fact that human DNA contains many areas that are rich in CpG elements, so-called CpG islets, which are characterized by a cytosine residue followed by guanine in the 5′ to 3′ direction [20, 21]. These islets can be easily methylated. The methylation status of CpG islets in promoter regions of specific genes efficiently interferes with the transcription of the corresponding gene (fig. 1). High methylation means reduced access of specific transcription factors to the promoter region, whereas low or absent methylation results in an enhanced accessibility and transcriptional activity [22, 23]. Usually CpG residues are methylated, while promoter regions of house-keeping genes are completely unmethylated. This DNA methylation process is tightly regulated by a complex enzyme machinery. It is easily understandable that depending on the presence or absence of CH_3 elements, the degree of methylation is enabled or not. MicroRNAs are small non-coding RNA molecules. This is a rapidly increasing family of molecules, and, to date, already more than 1,000 microRNAs are described [24–26]. Intense research over recent years identified that about one third of coding genes are regulated by microRNAs. This regulatory process is downstream from transcriptional regulation and nicely eludes the complexity of controlling the expression and function of genes and their ultimate products.

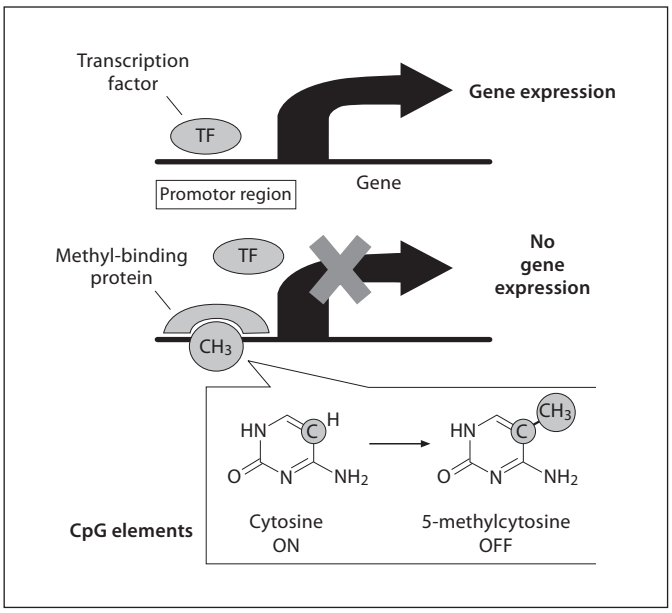

Fig. 1. Epigenetic modification of gene expression. Via methylation of CpG-rich islets in promoter regions of a specific gene, this can be potently (and permanently) switched off (or on).

There is excellent evidence that an efficient way to silence a gene is by methylation of lysine residues on histone H3 at position K9 or K27, whereas demethylation at the same sites results in activation of the associated gene.

These complementary modifications on different levels impacting on gene expression and functions without modification of the genetic code is now summarized by the term 'epigenetics' or 'epigenetic modification' – meaning that the regulation is at post-DNA level. There is excellent evidence that an efficient way to silence a gene is by methylation of lysine residues on histone H3 at position K9 or K27, whereas demethylation at the same sites results in activation of the associated gene. In addition, acetylation of histones was also shown to result in gene activation [27, 28]. These epigenetic modifications are important mechanisms implicated in the differentiation of cells and tissues during development and also to adapt to internal or external influences requiring differential functions [23]. It is of note that epigenetic modifications can be permanent and they are mitotically inheritable.

Lessons from Animal Models: How Nutritional Modifications Can Impact Phenotype and Health Conditions

The potential of nutritional modification on phenotype can be nicely shown in experimental models, such as in *agouti* mice [29]. Depending on the maternal diet (high- or low-CH_3 diet) before or during pregnancy as well as during the suckling period, the phenotype of the pups markedly differs. This well-known, but longtime unexplained phenomenon was recently elucidated at the molecular level due to the increasing understanding of

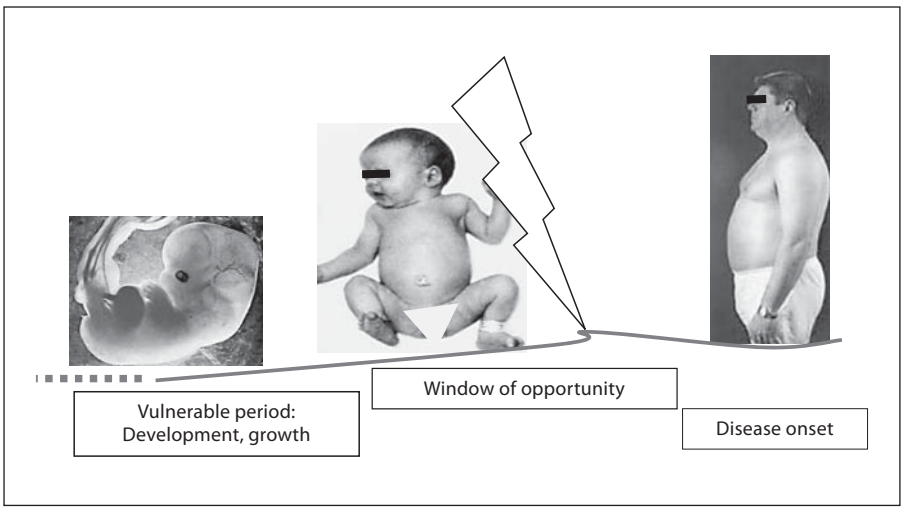

Fig. 2. Photographs highlighting the concept of early nutritional intervention during a window of opportunity (nutritional imprinting) on long-term health outcome.

epigenetic regulation. Indeed, varying maternal diet is able to influence gene expression during development, such as demonstrated for the *agouti* gene in these mice, resulting in a particular phenotype on birth, i.e. yellow hair color [30]. This particular gene is expressed in hair follicles of mice during a brief stage of hair development and growth and it encodes a paracrine signalling molecule responsible for the production of a yellow pigment. In normal wild-type mice, a yellow band appears on the otherwise brownish hair. A spontaneous insertion into the *agouti* gene of an intracisternal A partial (IAP), a retrotransposon common in the mouse genome, results in the viable yellow agouti (A^{vy}) mice [29]. Due to a cryptic promoter within IAP, a permanent and constitutive *agouti* expression in all tissues occurs in A^{vy} mice, leading on one side to a yellow coat. On the other side, these mice are extremely obese, due to ectopic *agouti* expression in the hypothalamus. The agouti protein binds antagonistically to the melanocortin-4 receptor in the hypothalamus, responsible for massive hyperphagia observed in these pups. The insertion of IAP into the *agouti* gene causes epigenetic dysregulation, resulting in spontaneous inter-individual variability in CpG methylation at the A^{vy} locus. Thus, within a single litter of genetically identical A^{vy}/a mice, due to differing methylation states, pups can present with all possible phenotype variants from completely yellow and obese to brownish and slim (the normal 'agouti' phenotype). The normal agouti phenotype reflects a high methylation status leading to complete repression of the *agouti* gene. Now, it becomes easily understandable how supplementation with choline and vitamins (B_{12} and folic acid) before and during pregnancy impacts on the phenotype of the offspring. Waterland et al. [30] demonstrated at the molecular level that differences in maternal food supplementation results in differences in the methylation status of A^{vy}. There was a clear correlation between the degree of methylation and the definite adult phenotype of the offspring [30]. This is one of the best-studied experimental models making a molecular link between external (nutritional) modification (of the mother) during a particular period (early pregnancy) and a definitive change of a long-term outcome parameter (hair color and body size). Various other experimental models confirm these observations, such as the effect of maternal methyl donor intake on the aspect of the tail (tail kinking) of their offspring due to the high degree of epigenetic plasticity of the metastable axin fused [Axin(Fu)] epiallele [29, 31] or the effect of low-protein diet during pregnancy on the methylation status of hepatic peroxisome proliferator-activated receptor-γ and glucocorticoid receptor expression in rats [32]. However, besides the quality of these molecular data, the functional outcome of epigenetic modifications is not always clear and, even more important, an extrapolation to the situation of humans is not yet possible – even if the cited epidemiological data might suggest so.

Nevertheless, there is increasing evidence to believe that complex diseases, such as atherosclerosis and coronary heart disease, metabolic syndrome and obesity as well as cancers, are related to important changes in lifestyle and diet, along with smoking and other environ-

mental factors [10, 33–36]. Based on the evidence of experimental and animal studies, it is very likely that these might impact on cellular functions and their epigenetic regulation. In the focus of interest is the current concept that changes in diet, lifestyle, physical activity and environmental factors create a chronic stress on the single cell, but also at the tissue level, thereby significantly overloading the tissue repair machinery with the risk of permanent lesions. This concept might completely change the view how to prevent coronary heart diseases or the occurrence of a metabolic syndrome. Since the starting point to disease susceptibility might occur years if not decades prior to the onset of the first symptoms (fig. 2). With the understanding of the molecular and epigenetic mechanisms this concept is more and more plausible.

Over the last decade, major advances were made in the understanding of gene expression and regulation of gene functions. One rather unexpected finding was that external factors can markedly impact on the expression of genes, potentially with long-term consequences, however without modifying the genetic code of the DNA. This mechanism of gene regulation is now called 'epigenetic' and this concept is validated in multiple experimental models. In particular, nutrition interventions are very potent modifiers via epigenetic modification of gene expression and thereby contributing to long-lasting effects. Several experimental models were designed in recent years; however, substantial research needs to be done before extrapolation to humans will be possible. This is an exciting field of research: and over the next few years, scientists will probably translate these discoveries into clinical and, hopefully, everyday situations as well.

Disclosure Statement

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