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REVIEW ARTICLE

Epigenetics provides a bridge between early nutrition and long-term health and a target for disease prevention

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Abstract

Exposure to nutritional imbalance during early life can influence disease risk lifelong and across generations. In this long-term conditioning, epigenetics constitutes a key mechanism. They bridge environmental cues and the expression of genes involved in the setting of long-standing biological regulations in numerous organs and species. Epigenetic marks are proposed as innovative diagnostic biomarkers and potential targets in the prevention of diseases. However, a number of uncertainties make them difficult to use in clinical approaches in the context of early exposure to nutritional challenge. In conclusion, active investigations in this field are still needed before clinical applications are considered.

KEYWORDS
early nutrition, epigenetics and long-term health

1 | INTRODUCTION

Alterations in the nutritional or dietary balance are one of the most common challenges for an organism over a lifetime. They can be the root of a wide range of diseases, including metabolic, cardiovascular and neurological diseases, as well as cancer.[1] While in adulthood, the health impact of a transient challenge can be reversed by restoring the nutritional balance, this is more deleterious early in life. Early developmental challenges can induce both short and long-term consequences.[2] In the short term, maternal undernutrition during pregnancy is associated with negative outcomes, such as increased risk of preterm delivery, haemorrhage, anaemia and birth defects, as well as death at the maternal and offspring levels.[3] Meanwhile, maternal nutritional excess is associated with an increased risk of gestational diabetes and preeclampsia. Over the long term, permanent changes leading to chronic diseases are also induced.[3] The concept of the developmental origins of health and disease (DOHaD) proposed by Barker et al. describes how a challenge during early life modifies developmental trajectories to cause maladaptation to the environment faced later in life. The hypothesis of the thrifty phenotype explains how this mismatch increases the susceptibility to diseases.[4] Epidemiological and animal studies highlighted the foetal and perinatal periods as windows of sensitivity, when qualitative or quantitative alterations to maternal nutrition influence the offspring's health later in life.[5,6] This involves remarkably similar mechanisms, despite differing initial conditions. Moreover, increasing evidence points to the role of the paternal nutrition in the offspring's health, as it regulates offspring adiposity and metabolic and vascular functions.[7,8] The factors at play in situations of parental over-nutrition during preconception, pregnancy and early infancy periods are represented in Figure 1. Based on meta-analyses of genome-wide association studies, genetic factors also have been implicated in the programming of long-term health.[9,10] Indirect maternal and direct foetal genetic factors have been found to influence the relationship

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Abbreviations: DNA, deoxyribonucleic acid; DNMT, deoxyribonucleic acid methyltransferase; RNA, ribonucleic acid.

between lower birthweight and higher blood pressure later in life. These associations were attributable to genetic effects, but not to intrauterine programming. However, the analyses were limited to birthweight variation within normal range. Thus, they did not reflect effects of extreme environmental challenges such as famine, environmental toxicants, or socio-economic factors, which could introduce confounding. Remarkably, epigenetics added a new dimension in the understanding of non-mendelian inheritance of acquired traits and are currently considered as a bridge between nutrition and health. However, even though the direct causal role of epigenetic mechanisms in the inheritance of diet-induced health changes has been demonstrated in animal models,[11] only associations have been made in humans after early exposure to nutritional challenges.

Key Notes

- Early developmental exposure to nutritional challenges impacts health and influences lifelong disease susceptibility, which can be inherited.
- Epigenetic regulations are influenced by nutrition and represent a key mechanism for long-term programming of health and disease.
- Even though epigenetic marks constitute potential biomarkers of disease and targets for prevention and therapy, still numerous limitations in knowledge and in the level of evidence stress the need for further research before clinical applications are considered.

2 | EPIGENETIC MECHANISMS

Epigenetics describes how all cells of an organism that carry the same deoxyribonucleic acid (DNA) present differential gene expression profiles to fulfil specific functions. In the 1940s, Waddington used the term epigenetics to explain how the environment and the genes interact to modulate development and phenotype. He utilized a developmental landscape diagram to illustrate how development can be canalised to follow different routes, depending on environmental influence.[12] Epigenetic regulations rely on three main mechanisms that are tightly interrelated: DNA methylation and hydroxymethylation, histone post-translational modifications, including phosphorylation, acetylation and methylation, and regulation by non-coding ribonucleic acid (RNAs) such as microRNAs, Piwi-interacting RNAs, transfer RNAs and long non-coding RNAs (lncRNAs). These mechanisms are already at play during early embryonic development and gametogenesis. During these periods, they carry out epigenetic reprogramming through a dynamic process of erasing and re-establishing epigenetic marks in two waves in blastocysts and primordial germ cells. In some regions, epigenetic reprogramming ensures the expression of only one of the two inherited alleles of imprinted genes, either from the paternal or maternal side. The imprinted genes include Insulin-like growth factor 2 (*IGF2*), *H19* (coding for a lncRNA), and *GNAS* (a locus), which are critical for growth.

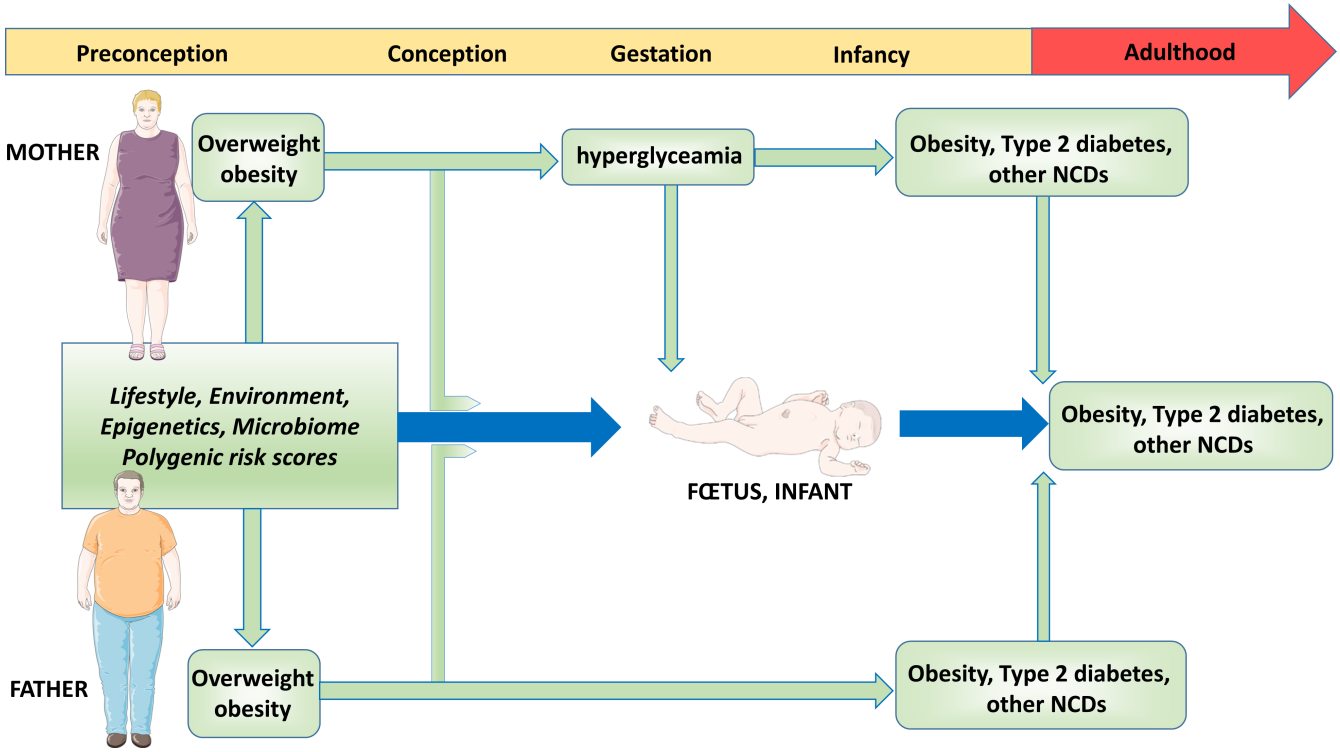

FIGURE 1 Parental factors influence offspring long-term health. Factors such as parental overweight or obesity, lifestyle, environment, epigenetics, microbiome and polygenic scores influence offspring risk to develop obesity, type 2 diabetes or other non-communicable diseases (NCDs). These parental factors are at play during preconception, conception, gestation and infancy

The loss of imprinting of these genes, driven by aberrant methylation, results in congenital growth disorders.[13] The established epigenetic landscape is relatively stable and heritable through mitosis beyond adulthood. However, environmental changes in utero and during early postnatal life can induce changes in the epigenetic profile that may promote the adaptation of the individual to the environment experienced in later life. When these adaptations do not match the later life environment, they can increase susceptibility to diseases.[14] As such, in observational studies, nutritional perturbations during early development have been shown to threaten thriftiness by causing genetic/epigenetic reprogramming. The alterations in the methylation patterns of imprinted genes, which persist into adulthood, potentially predispose the individuals to non-communicable diseases in later life. In animal models of early exposure to nutritional challenges, common features such as cardiac inflammation, hypertrophy, fibrosis and metabolic dysfunctions have been associated with changes in DNA methylation levels, histone marks and microRNA profiles.[5,6,15] Epigenome-wide association studies are a powerful approach to identify epigenetic variations associated with environmental exposures. In particular, variations in DNA methylation have been extensively studied.[16] Perinatal nutritional status has been associated with permanent changes in *IGF2* methylation following maternal exposure to a nutritional challenge. In a Dutch cohort, children who were prenatally exposed to wartime famine in 1944–1945, exhibited lower DNA methylation of *IGF2*, which is a modulator of a newborn's foetal growth and development.[17,18] A genome-scale analysis performed in the same cohort after periconceptional exposure to famine highlighted differential DNA methylation in whole blood. Changes occurred preferentially at regulatory regions mapped to genes related to growth and metabolism.[19] The comparison of exposure timing highlighted the critical role of gestational timing. From a mechanistic point of view, the impact of diets on epigenetic regulations relies, at least in part, on their role as providers of methyl groups used in the methyl activation cycle, or on their potential to modify the activity of enzymes involved in these pathways, for example, DNA methyl transferases (DNMTs). This is the case with methionine, vitamin B (choline, pyridoxine, folate and cobalamin), betaine (trimethylglycine), zinc and polyphenols.[20] Therefore, by influencing DNA or histone methylation processes, deficiency in these compounds, especially during development, has been associated with altered gene expression and diseases, like impaired cognitive function.[21] Even seasonal nutritional variations naturally occurring in rural Gambia influence methyl-donor nutrient intake of mothers around the time of conception, leading to modifications in DNA methylation patterns in neonates.[22]

3 | EPIGENETIC MECHANISMS BRIDGE EARLY NUTRITION AND LONG-TERM HEALTH

The long-term impact of early nutritional challenges involves multiple levels of regulation, including effects on different biological systems, like placental function, brain development, and breast milk and microbiome composition. At each level, epigenetics is a critical player.

3.1 | Role of the placenta

The placenta is described as a critical mediator in the long-term effects of maternal dietary challenges on offspring health (Figure 2). Indeed, the placenta is involved in the regulation of offspring growth, and a maternal dietary challenge can affect placental development and function. Epigenetic changes in the placenta provoked by maternal over- or undernutrition have been shown to mediate changes in an infant's metabolism or food preference after birth. Notably, epigenetic regulation of genes that are involved in nutrient supply or hormonal regulation have been observed. In particular, leptin, a key regulator of energy homeostasis, presents lower methylation levels at its promoter in the placenta when the mother is exposed to nutritional excess.[23] A study performed in calves highlighted that DNA methylation occurs in the placenta when there is a maternal methionine supply, which was associated with altered placenta metabolism and sex-specific body mass changes.[24] Maternal intake of olive oil and fish can modify histone acetylation in the placenta, regulating immune regulatory genes in humans.[25] Drug consumption also influences epigenetic marks in the placenta. For instance, metformin, which is used for diabetes treatment during pregnancy, has been shown to stimulate placental mitochondrial biogenesis and inhibit the aberrant epigenetic alterations occurring in maternal diabetes. Thereby, metformin confers protective effects on offspring.[26]

3.2 | The central control of energy homeostasis

Maternal dietary challenges influence foetal brain development and behaviour, and by this way, they can affect the offspring health in the long term.[27] In particular, a perinatal nutritional challenge can induce permanent changes in the foetal central appetite regulatory pathways. Indeed, in the hypothalamus, Proopiomelanocortin (*POMC*) neurons play a critical role in feeding behaviour and energy homeostasis. Epigenetic regulation of *POMC* has been involved in obesity and metabolic disease. Hypermethylation of *POMC* has been described in the rat brain after postnatal or maternal overnutrition, which may predispose the animals to metabolic disorders in later life.[28] Similarly, increased methylation levels have been reported in the *POMC* gene in blood cells of obese children,[29] which highlights *POMC* methylation level as a potential non-invasive biomarker. In addition, an individual's preference for palatable foods can involve reward circuitry. Notably, deregulated reward circuitry in offspring exposed to maternal high-fat diet, has been associated with global hyper-acetylation of histone H3 and alteration of methylation in the hypothalamus.[30]

3.3 | Hormones

Hormones play a pivotal role throughout life in the regulation of numerous mechanisms such as growth, development and metabolism. Some compounds called endocrine disruptors, which are

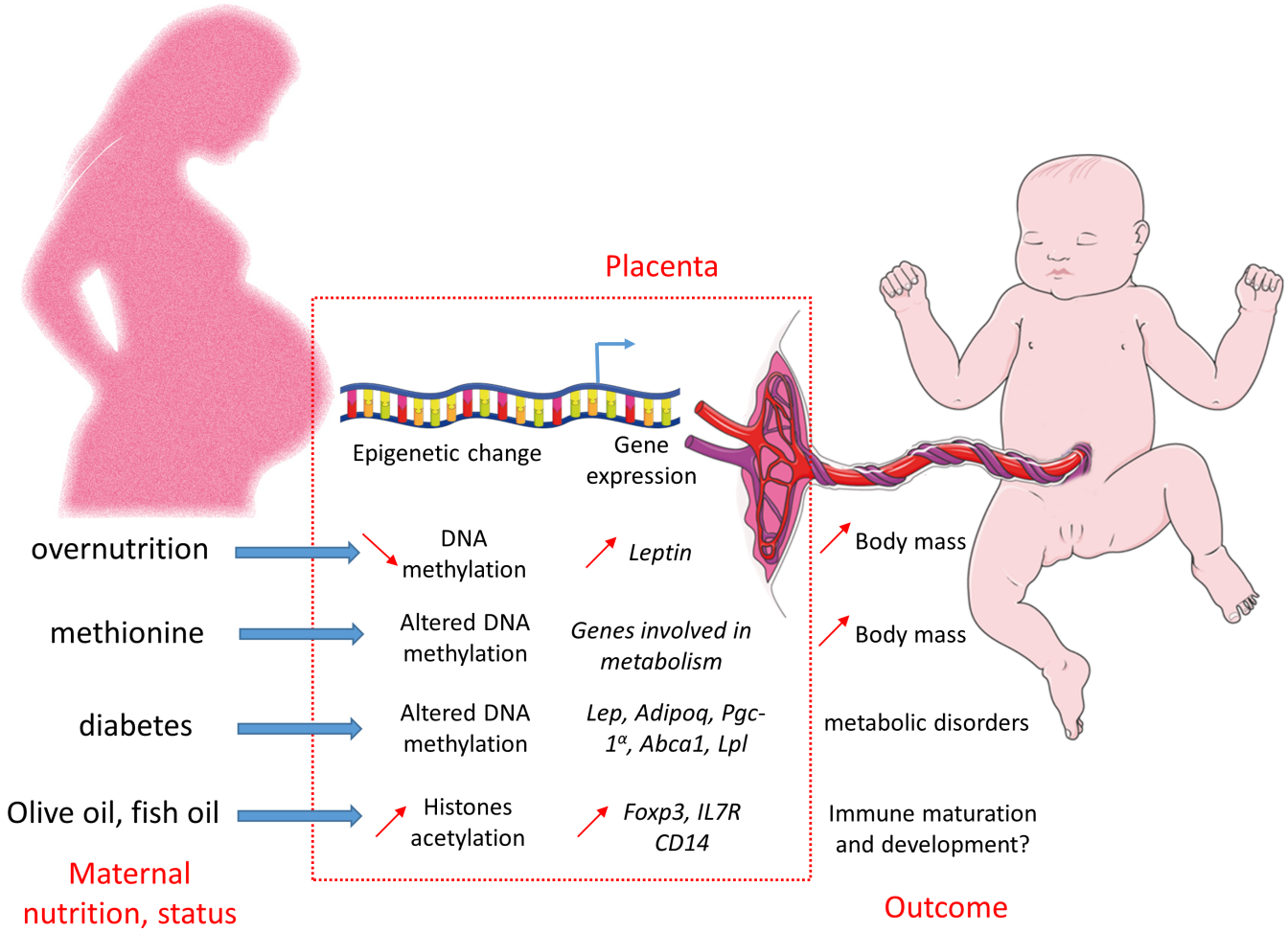

FIGURE 2 Maternal nutrition or status influences offspring health through the induction of epigenetic changes in the placenta. Studies performed in human or animal models highlighted changes in epigenetic marks (DNA methylation and histones acetylation) in the placenta, which were associated with changes in gene expression (involved in metabolism, growth and immune regulations) and specific outcomes in the offspring

present in diet, can interfere with endogenous hormones. Such molecules are natural or man-made and are ubiquitous in the environment. Phytoestrogens naturally present in fruits, vegetables and whole grains bind oestrogen receptors and modulate their activities. Phytoestrogens include flavonoids, coumestans, lignans and stilbenes. Their consumption during early life has been shown to influence health both in a negative and positive way.[31,32] The health effects of phytoestrogens rely on different bases, including their interaction with oestrogen signalling through oestrogen receptors, or their binding to membrane receptors, for example, G protein-coupled oestrogen receptor 1 or aryl hydrocarbon receptor. High perinatal consumption of phytoestrogens has been shown to induce permanent epigenetic changes which have consequences on characters such as sexual maturation[31] or erythropoiesis.[33] They also have been described as regulators of non-coding RNAs. For instance, treatment of umbilical vein endothelial cells with phytoestrogens down-regulates miR-34a and miR-155 levels, which subsequently inhibits inflammation.[34] In areas with poor food handling and storage methods, mycotoxins can parasitise agricultural crops and contaminate food at significant levels. Some of them, such as zearalenone, are detected in baby and infant cereals.[35] Zearalenone acts as an oestrogen-like compound and maternal exposure to this mycotoxin has been shown to modify tri-methylation levels of H3K4, H3K9 and H3K27 in oocytes, which may be detrimental to female reproductive capability.[36] However, the long-term effects of phytoestrogens on epigenetic marks remain poorly investigated.

3.4 | Microbiome

The human intestine microbiome forms a symbiotic relationship with the host by providing essential nutrients, metabolising dietary fibres into short-chain fatty acids. In this way, the gut microbiome influences the host metabolism by regulating appetite, lipogenesis and gluconeogenesis, as well as ensuring proper development of the immune system.[37] It is currently under debate whether the bacteria found in the placenta and in the meconium before birth originate

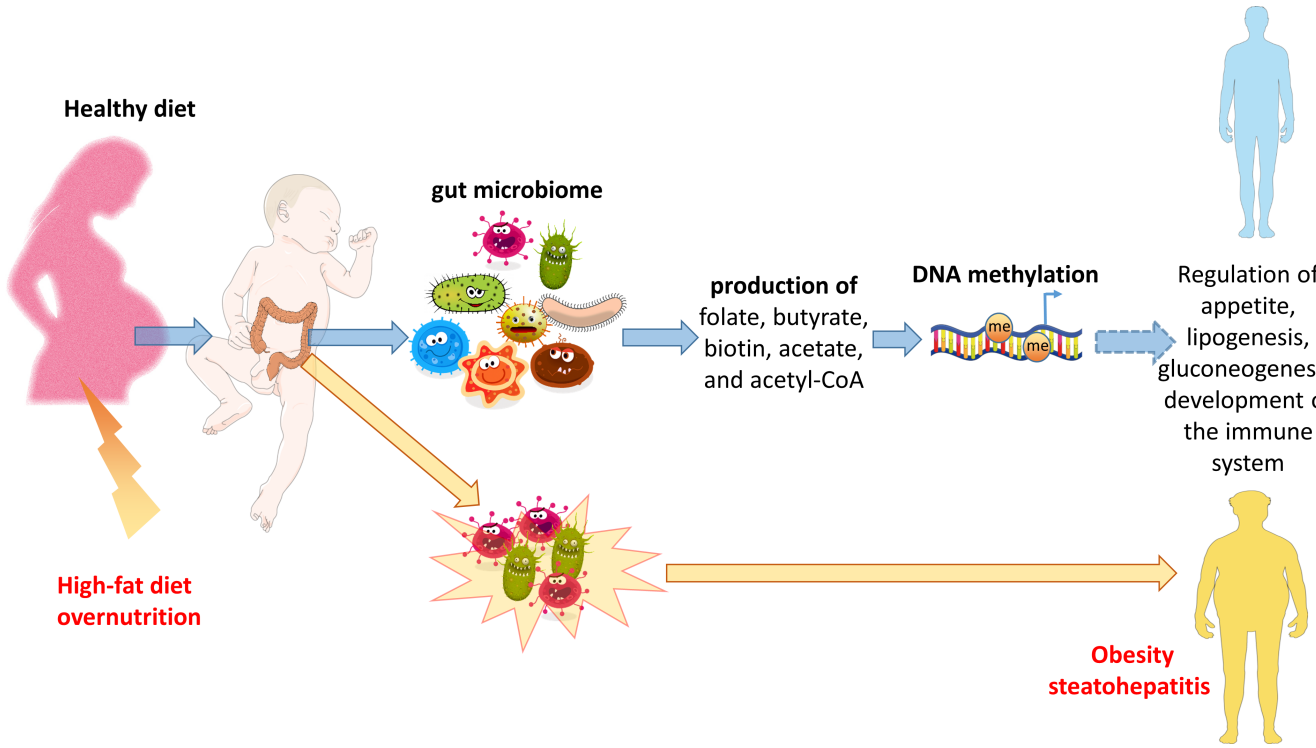

FIGURE 3 Maternal nutrition affects offspring health by influencing the offspring's gut microbiome composition. The gut microbiome regulates metabolism and the immune system, through at least in part, the production of compounds used in DNA methylation processes. Maternal high-fat diet and overnutrition induce changes in offspring microbiome profile associated with obesity and steatohepatitis

from external contaminations. Gut colonisation is described as an early developmental event and early exposure to challenges, including maternal diet, influences the composition of the neonatal gut microbiota.[38] In animal studies, maternal high-fat diet has been shown to permanently modify the commensal microbiome profiles in the offspring, which has been proposed to contribute to obesity development and steatohepatitis (Figure 3).[39] In human studies, similar observations indicate that maternal over-nutrition alters the gut microbiome in the offspring, which may increase the risk of obesity in children with obese mothers.[40] Therefore, the gut microbiota is considered a crucial factor for proper early life development and lifelong health. Among the mechanisms involved in the effects of the microbiome on the host is the production of substrates used in epigenetic modifications, such as folate, butyrate, biotin, acetate and acetyl-CoA.[41] For instance, *Bifidobacterium* strains promote the production of folate and butyrate involved in DNA methylation and histone modification processes.[42]

4 | POTENTIAL OF EPIGENETICS IN CLINICAL APPLICATIONS

4.1 | In diagnostics

Periconceptional and perinatal nutrition affix marks on the epigenome which can be indelible and which can orchestrate pathogenic events. Those marks can be also detected in non-invasive tissues, including body fluids. In clinics, epigenetic tests studying the DNA methylation level of specific genes have been already approved by the Food and Drug Administration for early detection of colorectal cancer. However, most identified epigenetic differences in diseases are still under clinical trial evaluation or preclinical states. MicroRNAs represent valuable biomarkers of diseases and exposure to challenges that can be used in diagnostics because they are stable (e.g., resistant to freeze and thaw, change in pH), easy to measure by common methods (e.g., polymerase chain reaction), and sensitive.[43,44] For example, different circulatory microRNAs profiles have been described between piglets fed with human milk and animals fed with dairy-based formula.[45] These differences were still detected at postnatal day 51, indicating a persistent effect of the neonatal diet on circulating microRNAs.

Pathway analyses indicated the potential benefits of human milk on microRNAs regulating the immune response. Another study performed in lambs has shown that maternal supplementation with fish oil modulates inflammation-related microRNAs (miR-33a and miR-146b) and genes (interleukin 1 Beta and nuclear factor kappa-light-chain-enhancer of activated B cells) in suckling offspring's peripheral blood mononuclear cells.[46] However, in both studies, the association with long-term health outcomes has not been explored. DNA methylation levels, which were investigated more intensively, are of high interest. In this sense, DNA methylation of the leptin promoter in lymphocytes was reduced in male preschool-age children when they were exposed in utero to maternal hyperlipidaemia. These changes in DNA methylation levels in the blood have been associated with

increased birth weight and elevated blood pressure.[47] In a randomised control trial, maternal dysglycaemia was found to induce changes in DNA methylation profiles in the cord blood, which were modified by diet and physical activity intervention during pregnancy.[48] Here again, the possible medical implications of the findings remain to be investigated. Additionally, in contrast with the genome, the epigenetic profile is expected to be cell specific. Thus, the value of epigenetic profile as biomarkers of diseases in non-invasive tissue could be questionable. Concerning their value in therapy, studies showed the new perspectives opened by epigenetics.

4.2 | In therapy

Whereas alterations in the genome are difficult to reverse, changes in the epigenome can be prevented by nutritional or pharmacological approaches as well as lifestyle modifications.[49] For instance, altered DNA methylation levels associated with neural tube defects induced by maternal high-fat diet can be inhibited by maternal intake of green tea polyphenol Epigallocatechin 3-gallatecan.[50] The targeting of the histone deacetylase Sirtuin 1 has shown to be beneficial in models of early exposure to a high-fat diet. Indeed, overexpression of Sirtuin 1 attenuates offspring metabolic and liver disorders,[51] and the compound SRT1720, a Sirtuin 1 activator, attenuates obesity and insulin resistance.[52] Another possibility that has been studied recently is the targeting of the microbiome. Through changes in the microbiota, a high-fibre diet could alleviate cognitive and social deficits induced by maternal obesity. Faeces microbiota transplantation experiments revealed a causal relationship between the reshaped microbiota and the behavioural changes.[53] The microbiome has also been highlighted as an interesting target in treating generational stress. Strikingly, the development of memory and extinction in offspring of rats exposed to maternal separation has been reversed by probiotic supplementation. This was effective either as an active treatment, when administered to infant F1 rats, or as prophylactic, when administered to F0 fathers before conception.[54] Even though the role of epigenetics was not evaluated here, these studies highlight the importance of identifying bacterial species driving individual physiological responses to diet to develop personalised microbial therapies. One more controversial way to regulate microbiota under study is dietary supplementation of microRNAs. Indeed, a few studies highlighted some exogenous dietary RNAs that may resist the extreme conditions encountered in the gastrointestinal tract and could enter the host intestines to exert regulatory effects on the gut microbiota.[55]

4.3 | Limitations

While epidemiological observations and experimental studies point at the key role of epigenetics in the programming of health and disease by early nutrition, a number of questions remain to be answered. First, human studies are often observational, and their design hardly offers both early and late time points. Because nutritional challenges are typically associated with co-variates such as socio-economic status, exposure to toxicants or stress, their contribution to the phenotype must be delineated. In fact, uncertain access to food, in the case of undernutrition, represents an important source of stress. In rats, perinatal undernutrition has been shown to regulate sympathoadrenal and hypothalamic–pituitary–adrenal axis responsiveness to restraint stress.[56] Similarly, exposure to excess saturated fat during early life has been shown to alter gene expression in hippocampus and to increase the risk for anxiety and impaired stress-coping abilities in adulthood.[57] Then, it is not mechanistically clear how early changes in epigenetic marks can be transmitted through cell divisions and persist until adulthood, or across generations. In addition, while there is well-documented potential to target epigenetics in disease prevention, epigenetic-targeted therapies have been applied in practice only in the treatment of haematological malignancies, and in preclinical and clinical trials to treat solid tumours.[58] While in animals a few studies suggested the potential value of epigenetics in diseases prevention and therapy, their causal link remains to be identified. Thus, their value as therapeutic targets in other pathologies as well as following early exposure to dietary challenges remains to be investigated. One point that makes the epigenetic targeting drugs difficult to be used in clinics is the lack of specificity of their action. Even though pharmacological approaches have demonstrated their efficiency in animal models, their application would likely be questionable in pregnancy/ childhood due to limitations, such as side-effects.[59] Developing epigenetic drugs with a specific target and selectivity is critical. Recent advances in clustered regularly interspaced palindromic repeats (CRISPR)/Cas-based epigenome editing technologies have enabled the rewriting of the epigenetic signature at a particular *locus* of interest in such a way that the effects might be mitotically stable across cell divisions.[60] Further investigations may open the potential of epigenome-editing to treat and prevent diseases related to developmental exposure to nutritional challenges.

5 | CONCLUSION

Epigenetic changes induced by early nutrition has proven its key role in health and disease programming. However, given the infinite potential combinations of epigenetic marks acquired during early development, their numerous possible downstream alterations, and their identifiable impacts on health throughout life, identifying epigenetic links to specific diseases remains a major challenge. While the potential of epigenetics as a preventative or therapeutic target is of extreme importance, only a few applications have attained a sufficient level of evidence to be applied to promote health or cure a disease, underlining the necessity for research in this area.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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