Impact of Epigenetic Dietary Compounds on Transgenerational Prevention of Human Diseases

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Abstract. The etiology of most human diseases involves complicated interactions of multiple environmental factors with individual genetic background which is initially generated early in human life, for example, during the processes of embryogenesis and fetal development *in utero*. Early embryogenesis includes a series of programming processes involving extremely accurate time-controlled gene activation/silencing expressions, and epigenetic control is believed to play a key role in regulating early embryonic development. Certain dietary components with properties in influencing epigenetic processes are believed to have preventive effects on many human diseases such as cancer. Evidence shows that *in utero* exposure to certain epigenetic diets may lead to reprogramming of primary epigenetic profiles such as DNA methylation and histone modifications on the key coding genes of the fetal genome, leading to different susceptibility to diseases later in life. In this review, we assess the current advances in dietary epigenetic intervention on transgenerational human disease control. Enhanced understanding of the important role of early life epigenetics control may lead to cost-effective translational chemopreventive potential by appropriate administration of prenatal and/or postnatal dietary supplements leading to early disease prevention.

INTRODUCTION

The mammalian embryogenesis process involves complicated regulations that are mainly controlled by genetic and epigenetic mechanisms. Early embryonic developmental processes are controlled by highly conserved and accurate developmental genetic/epigenetic programs leading to precisely time-controlled tissue-specific gene expression, global gene silencing, and subsequent diverse phenotypes between cells, organs, as well as individuals. Recent studies have shown that epigenetic regulations such as DNA methylation and histone modification play a crucial role on genomic reprogramming during early development including gametogenesis, embryogenesis, and fetal development (1–4). Aberrant chromatin modification can result in dysregulation of normal developmental processes such as X chromosome inactivation and genomic imprinting leading to various congenital disorders as well as other human diseases in later life (5–7). It is well known that epigenetic processes are frequently influenced by environmental factors. Nevertheless, the vulnerability to environmental exposure during embryogenesis provides an excellent opportunity to re-program epigenetic profiles leading to a beneficial outcome such as disease prevention in the offspring.

An emerging theme from recent studies focused on certain groups of botanic components with bioactive properties in influencing epigenetic processes has attracted considerable attentions. These bioactive components can be consumed as part of the human diet which collectively are referred to as the "epigenetic diet" (8,9). Studies have shown that these particular diets are believed to have effects on prevention of various human diseases such as cancer and diabetes if proper dietary guidelines are followed. Many human foods contain epigenetic dietary components, such as genistein, a natural isoflavone in soybean products, sulforaphane (SFN), an isothiocyanate from

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ABBREVIATIONS: DNMT, DNA methyltransferase; HDACs, Histone deacetylases; HATs, Histone acetyltransferases; SFN, Sulforaphane; EGCG, (−)-Epigallocatechin-3-gallate; SAM, *S*-adenosylmethionine; NTDs, Neural tube defects; ER, Estrogen receptor; NCDs, Noncommunicable diseases.

cruciferous vegetables such as broccoli sprouts or cabbage, and (−)-epigallocatechin-3-gallate (EGCG), the major polyphenol in green tea, which have been found to be associated with a lower risk of developing many common cancers (10–12). These dietary epigenetic compounds are considered as potent dietary epigenetic modulators that affect key tumor-related gene expression through epigenetic regulation (13–16). In addition, some human epidemiological and animal studies have shown that early consumption of certain epigenetic diets may lead to phenotype alterations of the offspring through epigenetic modulations and therefore reduce the risk of developing certain diseases later in life (17–19). These results indicate that early-life consumption of certain diets may exhibit transgenerational effects leading to different individual health/disease outcomes later in life. Although studies on epigenetic mechanisms in dietary-associated transgenerational human disease prevention are just emerging, understanding the process of epigenetic reprogramming during embryogenesis and how maternal epigenetic dietary regimens affect this process will lead to beneficial health outcomes in the next generation.

EPIGENETIC REGULATIONS DURING EMBRYOGENESIS

DNA Methylation During Embryonic Development

DNA methylation is the best characterized epigenetic modification of chromatin. It is a stable and heritable component of epigenetic regulation that represents an important memory mechanism during embryogenesis. In mammals, DNA methylation primarily occurs on cytosine residues of CpG dinucleotides (20). A high density of CpGs frequently clustered into a certain region of genomic DNA is referred to CpG islands, and DNA methylation of these islands correlates with transcriptional repression (20). DNA methylation plays important roles during embryogenesis including genomic imprinting, regulating chromatin structure, maintaining gene expression, or silencing and X chromosome inactivation (1,2,20).

During early embryogenesis, a wave of genome-wide DNA methylation reprogramming is established. Firstly, both maternal and paternal chromosomes undergo progressive demethylation by a passive mechanism, which erases most of the epigenetic marks in the zygote (21). After implantation, global embryonic *de novo* methylation patterns are reestablished, which is then maintained throughout life in the somatic cells (21,22). This dynamic methylation reprogramming including global demethylation and remethylation processes is essential for fetal development during early embryogenesis. The genome-wide demethylation processes might lead to chromatin decondensation contributing to the transcriptional activation in the zygotic genes that are essential for early development. Subsequent *de novo* methylation processes might facilitate development of gene-specific methylation patterns, which determine tissue-specific transcription through a global silencing state. Although most genomic DNA undergoes genome-wide demethylation and *de novo* methylation processes during early embryogenesis, the methylation marks on imprinted genes escape from this prevailing reprogramming and thus are preserved as parental imprints leading to the differential expression of several dozen imprinted genes in the paternal and maternal alleles during development (20,23). Therefore, incorrect development of DNA methylation patterns during this critical period may lead to embryonic lethality, developmental malformations, and increased risk for certain diseases (4,24).

Maintaining DNA methylation patterns is dynamically mediated by at least three independent DNA methyltransferases (DNMTs), DNMT1, DNMT3a, and DNMT3b, which are required for cellular differentiation during early embryonic development. DNMT1 maintains genomic methylation patterns in a DNA replication-dependent manner, while DNMT3a and DNMT3b act primarily as *de novo* methyltransferases after DNA replication by adding a methyl moiety to the cytosine of CpG dinucleotides that are not previously methylated (25–29). Recent studies have found a new DNMT family member, DNMT3-like (DNMT3L), which encodes a protein that shares homology with DNMT3a and DNMT3b but lacks the highly conserved methyltransferase motifs and has no enzymatic activity (30). DNMT3L is believed to cooperate with DNMT3a and DNMT3b to regulate the gamete-specific methylation and genomic imprint (31).

Since DNA methylation plays important roles during early embryogenesis and development, appropriate exposure to epigenetic modulators from the diet that target DNA methylation reprogramming processes or DNMTs may lead to beneficial intervention of early epigenetic reprogramming and disease prevention in later life (Fig. 1).

Histone Modifications During Embryonic Development

In addition to DNA methylation, changes in gene expression governed by the plasticity of chromatin add another layer of epigenetic control in embryogenesis (Fig. 1). The dynamic structure of chromatin is maintained by modification of core histones at their amino-terminal tails through adding molecular groups such as acetylation, phosphorylation, methylation, and ubiquitylation (32). Prior to fetal development, the zygotic genome is reprogrammed by changes in the epigenetic landscape mediated by key genes and histone marks that dictate correct lineage specification and terminal differentiation (33). Methylation of histone H3 lysine and arginine residues in conjunction with protein complexes such as trithorax (trxG) and polycomb (PcG) group influences the epigenetic landscape required for imprinting of genes and programming of cells (34–39). Trimethylation of histone H3 lysine 27 (H3K27me3) with PcG complex and trimethylation of histone H3 lysine 4 (H3K4me3) with trxG establish inactive and active chromatin states, respectively. Histone H3 lysine 9 acetylation and trimethylation (H3K9me3) constitute active and repressive marks, respectively (40,41). Transcriptional regulators of cell differentiation lineages are marked by H3K4me3 and are repressed in the presence of H3K27me3 in the embryonic stem cells (ESCs) (39,42). The progressive loss of H3K27me3 can activate these regulators that are marked by H3K4me3. Therefore, such bivalent marks regulate the differential potential of ESCs. Genes of pluripotent cells derived from the blastocyst require the activation of pluripotent factors: octamer-binding transcription factor 4 (*Oct4*), sex-determining region Y-box 2 (*Sox2*), and *NanoG* (43). However, monomethylation states of histone H3 lysine residues (H3K4me1, H3K9me1, and H3K27me1) direct changes from multipotent to differentiated unipotent cells; an example of this is the differentiation into
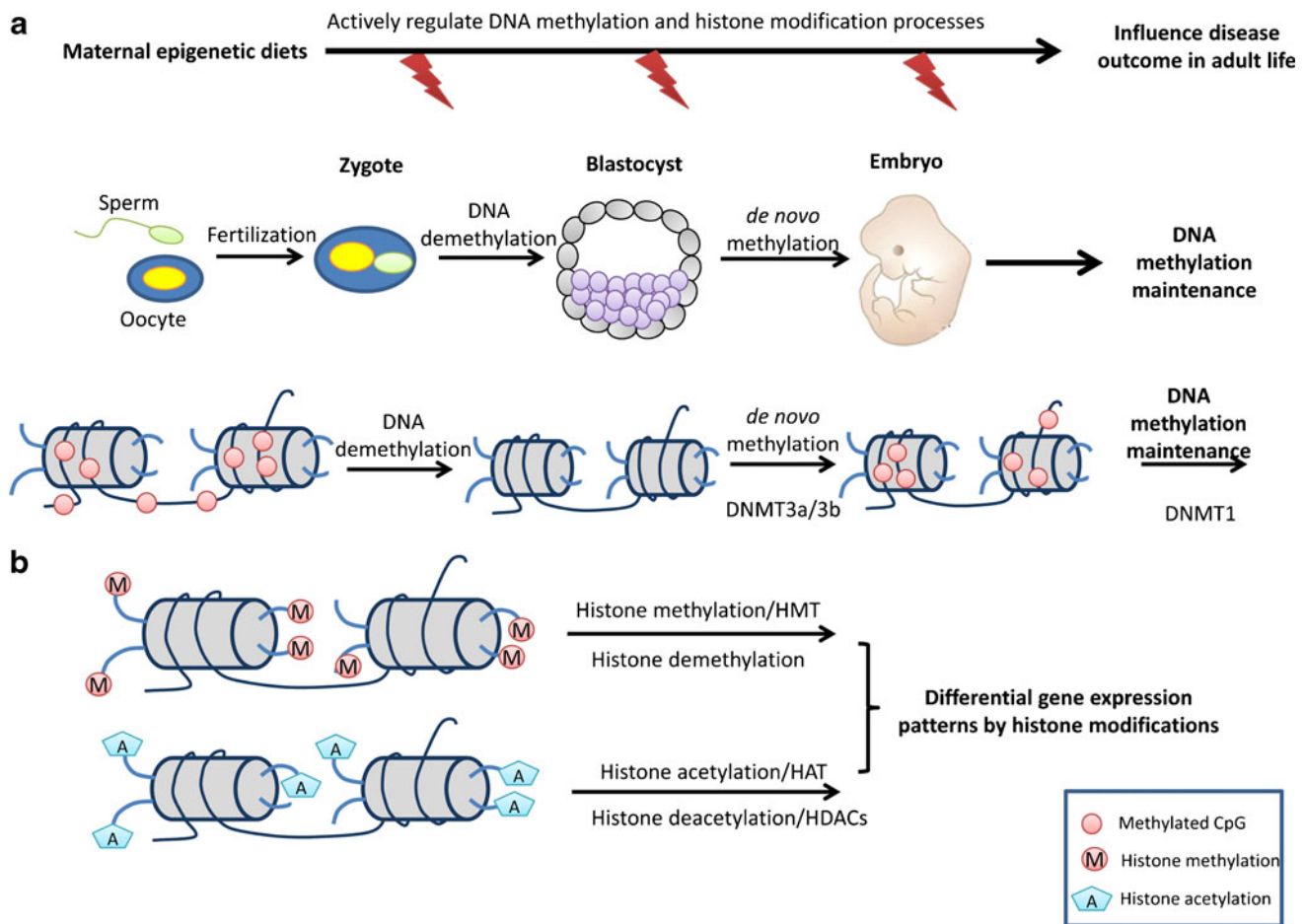
Fig. 1. Maternal epigenetic diets regulate DNA methylation and histone modifications during embryogenesis. **a** DNA methylation reprogramming during early embryonic development. After fertilization, genomic DNA undergoes a passive demethylation process and parental DNA methylation markers are erased except imprinting genes. The methylation level of a blastocyst reaches the lowest point. After implantation, a genome-wide remethylation phase occurs through an active *de novo* methylation regulated by DNMT3a/3b. Cellular and organ-specific methylation patterns are maintained by DNMT1 throughout life in the somatic cells. **b** Histone modification during embryogenesis. Transcriptional regulators of cell differentiation lineages are mainly regulated by histone methylation and acetylation. Histone methylation is mediated by HMT, and either gene activation or repression by histone methylation is dependent upon the particular lysine residue that is modified. Histone acetylation is mediated by HAT and deacetylation is catalyzed by the HDAC family. Histone acetylation causes an open chromatin structure leading to active transcription, whereas histone deacetylation is always associated with transcriptional repression. *DNMT* DNA methyltransferases, *HAT* histone acetyltransferases, *HDAC* histone deacetylase, *HMT* histone methyltransferase

erythrocyte precursors from human primary hematopoietic stem cells/progenitor cells (44). The epigenetic landscape changes as developmental and differentiation potentials decrease from totipotent to unipotent cell populations. Therefore, specific histone marks may correlate to defined embryonic stages governed by the expression or repression of pluripotent factors or lineage regulators.

IN UTERO EPIGENETIC DIET EXPOSURE

Aberrant patterns and dysregulation of DNA methylation and histone modifications may cause stable, heritable transcriptional abnormality of the associated gene during embryogenesis. Epigenetic variability appears to be susceptible to modulation by nutritional changes such as diets (45). Epigenetic diets refer to a broad range of diets that have been identified to mediate epigenetic processes (8,9). The epigenetic diets such as green tea, broccoli sprouts, and soybean and the bioactive compounds extracted from these diets have received extensive attention due to their profound actions on the prevention of various human diseases such as cancer, diabetes, and cardiovascular diseases by altering aberrant epigenetic profiles in cells (13–16,46). Recent studies have shown that epigenetic diets may also have an impact on developmental processes leading to disease prevention in later life (17–19) (Table I). Although the precise epigenetic mechanism-regulated developmental pathways and target genes are not fully understood, better understanding the effects of epigenetic diets on embryogenesis shows promising prospects in developing a novel maternal dietary regimen to prenatally prevent human diseases.

Folate

Folate, a water-soluble B vitamin, which must be obtained from dietary sources or supplements, is of fundamental importance

Table I. Transgenerational Effects of Epigenetic Dietary Compounds

Dietary components	Food resource	Epigenetic effects	Transgenerational effects	References
Folate	Leafy vegetables; egg yolk; liver products	Methyl donor diet (providing methyl group for SAM synthesis)	Folate insufficiency increased the risk for neural tube defects in the fetus and genome-wide DNA hypomethylation and genomic instability in *agouti* mice	(47–49,51,52)
Genistein	Soybean products	DNMT inhibitor; HDACs inhibitor	Maternal genistein may cause diverse effects of breast cancer development in later life; maternal genistein leads to genome-wide DNA hypermethylation in *agouti* mice	(61,66–68)
Sulforaphane	Cruciferous vegetables such as broccoli sprouts and cabbage	Potent HDAC inhibitor; DNMT inhibitor	Early-life consumption of cruciferous vegetables exhibits more effective prevention effects against cancers	(18,73)
EGCG	Green tea	Potent DNMT inhibitor; HDAC inhibitor	Maternal ingestion of green tea may provide transplacental protection against carcinogenesis and chronic diseases	(82)
Butyrate	Cheese	HDAC inhibitor	*In utero* exposure to butyrate delays the developmental switch from γ- to β-globin gene expression in sheep fetuses	(87)
Indole-3-carbinol	Cruciferous vegetables	Regulate microRNA expression	Maternal ingestion of indole-3-carbinol provides transplacental protection against carcinogen-induced lung cancer	(88)

DNMT DNA methyltransferases, *HDAC* histone deacetylase, *SAM* S-adenosylmethionine

for normal DNA synthesis and repair (47). Folate is essential for the transfer of one-carbon units and believed to act as a methyl donor diet for synthesis of *S*-adenosylmethionine (SAM), the universal methyl donor of biological methylation (48). Folate deficiency leads to a decrease in SAM and is associated to genome-wide hypomethylation both in humans and in animal models (45,48–51).

Evidence has indicated that folate deficiency is associated with developing several human tumors (50), which may be due to the abnormal process of DNA synthesis and methylation caused by low folate status. More importantly, it is well recognized that folate insufficiency during pregnancy increases the risk for development of NTDs in the fetus and may also influence risk for the other human diseases in later life owing to the critical role of folate in DNA methylation and synthesis of purines and pyrimidines (51). The *agouti* mouse model system has been successfully used to detect the methylation status in mammals when administrating folate-deficient dietary supplementation (52,53). The coat color of mice carrying the *agouti* viable yellow gene varies from yellow to mottle to pseudoagouti, which is dependent on the methylation status of the transgene. Studies have shown that *agouti* dams fed with methyl donor supplementation (folate, methionine, choline, and vitamin B$_{12}$) during pregnancy prevent the ectopic expression of agouti protein due to the methylation of intra-cisternal A particle retrotransposon inserted upstream of the agouti gene. The expression of agouti results in yellow coat color, obesity, diabetes, and tumor susceptibility in the offspring and absence of the protein shifts towards the production of the pseudoagouti phenotype (54,55). Therefore, maternal diet enriched with methyl donors possibly through folate supplementation can have a significant effect on DNA methylation.

Although extensive evidence has indicated the vital roles of folate in regulation of epigenetic profiles during development *in utero*, studies on how folate supply during development affects chronic human diseases in later life are still under investigation. Thompson *et al.* have reported a case–control study indicating that folate supplementation in pregnancy reduces the risk of common acute lymphoblastic leukemia in the child (56). However, an animal study in sheep has shown periconceptional restriction of maternal folate intake leads to widespread changes in the fetal epigenome and the offspring are more resistant to insulin and have higher blood pressure by adult age (57). These results indicate that early-life exposure to folate may be beneficial to changing the susceptibility to certain human chronic diseases in adulthood.

Soybean Genistein

Soy products have been of particular interest because of their bioactive roles on inhibiting various human cancers and other chronic noncommunicable diseases. Genistein is a botanical isoflavone enriched in soybean products, such as soymilk and tofu (58). Genistein is believed to act as a phytoestrogen to compete with estradiol and interact with the ER-associated signal pathway (59). Epidemiological studies also indicate that the incidences of breast and prostate cancer in Asian countries, where the genistein-rich soy products are their traditional daily diet, are much lower than in the USA suggesting that genistein is a potent dietary chemopreventive compound against human breast and prostate cancers (59,60). Besides, its notable effects on suppressing carcinogenesis, early exposure to genistein *in utero* has recently been found to alter multiple phenotypes of the offspring of the *agouti* mice such as reduction of prevalence of obesity and brown coat due to hypermethylation of the *agouti* gene (61). This result suggests that soybean genistein can act as an epigenetic modulator to interfere with early epigenetic reprogramming leading to altered phenotypes such as different susceptibility to diseases in the offspring. Our work on genistein also confirmed that genistein can influence key gene expression

and signal pathways through dynamic regulation of epigenetic pathways via both DNA methylation and histone modification pathways (13,14,62).

Although strong evidence has shown a clear correlation of postnatal consumption of soybean genistein with a low incidence of human cancer, an appropriate exposure window has been considered as a crucial factor for genistein to implement its effects on inhibiting tumorigenesis. For example, most existing literature suggests that consumption of soy isoflavone genistein during childhood and adolescence in women reduces later mammary cancer risk, whereas adult exposure to soy genistein is not protective but considered dangerous due to a weak estradiol character of genistein (63–65). There has also been controversy with respect to whether maternal (*in utero*) exposure to soybean genistein can actually affect breast cancer incidence of the offspring in adult life. The findings obtained in rats exposed to purified genistein during the fetal–perinatal period vary from study to study (66–68), indicating appropriate exposure window during pregnancy could be a key factor for transgenerational effects of genistein on mammary cancer prevention (Fig. 2). However, little evidence is available for a correlation of a maternal genistein diet to incidence of chronic noncommunicable diseases such as cardiovascular disease and diabetes. The result showing a change of obesity status in the offspring of the *agouti* mice fed with a maternal genistein diet (61) suggests that early exposure to genistein may influence adipogenesis process in later life; however, this speculation requires further investigation.

Cruciferous Vegetable Sulforaphane

SFN ($CH_3-SO-(CH_2)_4-N=C=S$), an isothiocyanate from cruciferous vegetables such as broccoli sprouts, cabbage, and kale, is a common dietary natural plant product that can reduce the risk of developing many human cancers (11). SFN mediates chemoprevention through several mechanisms including cell cycle arrest, induction of apoptosis, and phase 2 detoxifying enzymes (69,70). Recent studies on investigation of epigenetic regulation by SFN in chemoprevention have drawn extensive attention due to its inhibitory property on histone deacetylase (HDAC) enzymatic activity (8,9,71) which leads to an increase in the global and local histone acetylation of a number of genes (15,72). In addition, both animal work and human studies indicate that SFN is a potent HDAC inhibitor and is readily bioavailable to prevent various human diseases.

Environmental factors play a major role in the interaction between genomic background and individual phenotypes through epigenetic regulations. Epidemiological studies have also suggested that early-life consumption of SFN through dietary cruciferous vegetables is more effective than later-life consumption (18,73). Asian populations who consume more cruciferous vegetables at earlier ages than Caucasians have less incidence of certain diseases such as breast cancer and prostate cancer, suggesting that maternal consumption of cruciferous vegetables during pregnancy may reduce the subsequent risk of cancer in their children (74). A recent study shows that *in utero* exposure to SFN prevents skin blistering associated with keratin 14 mutations in epidermolysis bullosa simplex, a rare inherited condition in which the epidermis loses its integrity after mechanical trauma (75). Our pilot study shows that maternal SFN diet can prevent the onset of breast tumorigenesis in a spontaneous breast cancer mouse model. Although the chemopreventive mechanisms for early exposure to broccoli sprout sulforaphane during pregnancy are currently not clear, the key characteristic of HDAC inhibitor of SFN may represent an attractive target for epigenetic reprogramming during embryogenesis. Further studies aimed towards elucidating the detailed
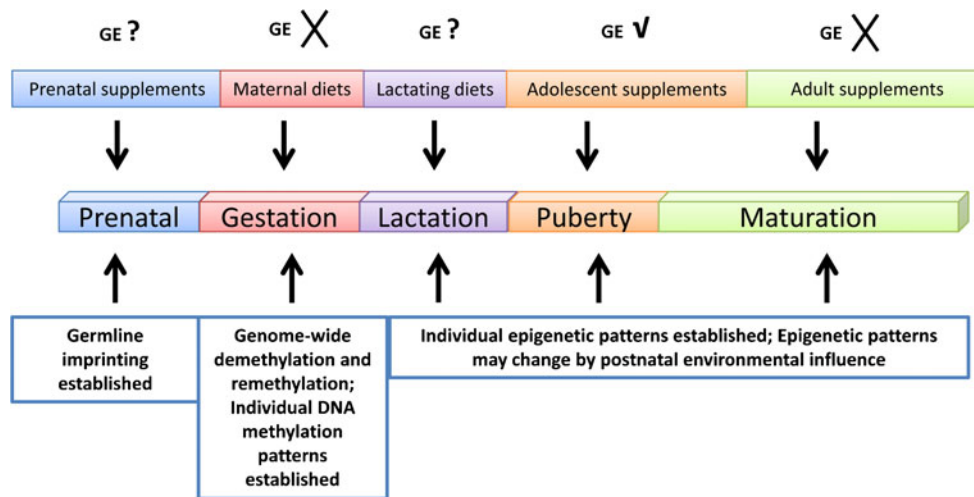

Fig. 2. The timing of epigenetic diet exposure throughout life. The *top row* indicates the importance of different epigenetic dietary exposure that may affect the epigenome and have later-life consequences. For example, early consumption of genistein during childhood and adolescence in women reduces later mammary cancer risk, whereas maternal/adult exposure to GE may be considered to be a risk factor to induce breast cancer. The *middle row* represents different lifetime periods including prenatal, gestation, lactation, puberty, and maturation periods. The *bottom row* indicates important epigenetic events in different stages of life. *GE* genistein; *check mark* indicates potential protective effects of GE consumption on prevention of breast cancer; *cross* indicates the potential risk factors of GE consumption to the development of breast cancer; *question mark* indicates an unknown effect of GE consumption on breast cancer development

mechanisms for how SFN interferes with early developmental processes are urgently needed.

Green Tea Polyphenols

Tea is consumed worldwide and has shown many beneficial effects on human health. EGCG, the most abundant polyphenol, is considered the most effective content for prevention of various human diseases in green tea (12). Green tea EGCG has been extensively studied as a bioactive dietary component against various types of human diseases such as cancer, cardiovascular diseases, hypertension, and hyperlipidemia through multiple mechanisms such as anti-oxidation and induction of apoptosis (76–78). Recently, studies indicate that EGCG can modulate gene expression by influencing epigenetic processes such as DNA methylation and/or histone modification (79–81). EGCG can alter DNA methylation patterns by directly and indirectly inhibiting the enzymatic activities of DNMTs. Furthermore, it is believed that EGCG-induced remodeling of chromatin structure is a key epigenetic mechanism for regulating tumor-related gene transcription (16,79).

However, there has been some controversy with respect to consumption of tea products during pregnancy due to the adverse effects of caffeine from the tea for fetal development. Recent studies, however, have proven that consumption of green tea in a small amount (<2 cups per day) is safe during pregnancy (82), and maternal ingestion of green tea during pregnancy and nursing may provide transplacental protection against carcinogenesis (82). Studies from Yang *et al.* have indicated that maternal green tea EGCG prevents hyperglycemia-induced embryonic vasculopathy and malformation via inhibition of oxidative stress signaling (83). A similar work by Long *et al.* indicated that consumption of green tea prevents ethanol-induced embryonic growth retardation (84). These studies provide insights that a diet rich in chemopreventive compounds consumed early in life may modulate the genetic/epigenetic profiles to confer beneficial effects against the risk of developing several types of diseases later in life. However, the epigenetic mechanisms for these changes and the role of green tea in these processes are not known.

Other Epigenetic Diets

Most *in vitro* and *in vivo* studies analyze the effect of single epinutrients on disease outcome. Maternal diet varies, and the altered state would depend on nutrient–nutrient interactions, nutrient–gene interactions, placental transport, and concentration. Therefore, the influence of epimolecules in embryonic development contributing to altered physiological and diseased states is complex. The impact of the epigenetic maternal diet on embryogenesis occurs at the pre-pregnancy and gestational stage, both of which influence *in utero* environment and availability of nutrients through the placenta. A study of female rats fed with a high-fat diet showed that changes in the uterine environment affected developmental outcomes, and in the study, impaired bone developmental was observed due to hypermethylation of homeobox protein Hox-A10 (*HOX-A10*) promoter and down-regulation of the gene (85). Diets that contain molecules that target histone deacetylases such as butyrate (cheese), diallyl sulfide (garlic), indole-3-carbinol (cruciferous vegetables), and histone acetylases such as curcumin (turmeric, an Asian spice)

can potentially influence histone markers, thus affecting embryological development and further different risk against diseases (86–89). Therefore, the time of consumption of foods rich in the aforementioned biomolecules and the placental availability of these compounds determine the phenotypic outcome during embryogenesis.

TRANSGENERATIONAL PREVENTION OF HUMAN DISEASES

Early evidence has revealed that developmental plasticity is affected, at least in part, by epigenetic changes that are established in early life and modulate gene expression during embryogenesis. It is thought that maternal dietary epigenetic modulations acting as fetal environmental factors that can be transmitted maternally to the embryo, fetus, and breastfeeding neonates can influence subsequent susceptibility to certain congenital birth defects as well as chronic disorders in later life (Table II).

Congenital Birth Defects

Although the potential mechanisms that cause congenital disorders can be complex, the intrauterine environment such as maternal dietary intake is considered as one of the most important factors that can influence embryogenesis and fetal development leading to either beneficial prevention or adverse effects contributing to certain birth defects. Folate is by far the most effective prenatal supplement to prevent neural tube defects such as spinal bifida and anencephaly in fetus (51). It also has been shown that folate can reduce the risk of other congenital disorders such as congenital heart defects and urinary tract anomalies (90,91). Despite its major roles on DNA and RNA synthesis for cellular proliferation, folate is essential to carry one-carbon units and plays an important role on DNA methylation. The direct evidence for maternal folate influencing methylation status in the offspring comes from the *agouti* mouse model as we discussed previously (52), which suggests that folate-induced epigenetic reprogramming during early embryonic development may contribute to its preventive properties of certain congenital disorders. Early exposure to another epigenetic diet, soybean genistein, results in alterations of multiple phenotypes of the *agouti* offspring such as reduction of prevalence of obesity and brown coat due to hypermethylation of *agouti* gene (61). However, direct pieces of evidence including animal experimentation and epidemiological data connected to other important epigenetic dietary components, such as soybean genistein, broccoli sprout sulforaphane, and green tea polyphenol EGCG, to prevention of congenital defects are largely lacking.

Noncommunicable Diseases

Turbulent epigenetic rewriting occurs during early embryogenesis, whereas global demethylation and subsequent *de novo* remethylation processes as well as concomitant histone modification changes establish a new epigenetic pattern in the offspring, most of which will be maintained throughout life in the somatic cells. Therefore, the early impact on epigenetic profile induced by maternal epigenetic diets could be stably inherited and then influence genetic

Table II. Transgenerational Prevention of Human Diseases by Epigenetic Maternal Diet

Diseases	Diet	Findings	References
Congenital diseases	Folate; SFN	Maternal folate prevents neural tube defects, congenital heart defects, and urinary tract anomalies; *in utero* exposure to SFN prevents a rare inherited condition, epidermolysis bullosa simplex	(51,75,90,91)
Cancer	Folate; GE; SFN; EGCG; I3C	Maternal folate reduces the risk of acute lymphoblastic leukemia in the child; maternal GE may promote carcinogen-induced breast cancer development in rats; early-life consumption of cruciferous vegetables exhibits more effective prevention effects against cancers; maternal ingestion of green tea may provide transplacental protection against carcinogenesis; maternal ingestion of I3C provides transplacental protection against carcinogen-induced lung cancer	(18,56,68,82,88)
Diabetes	Folate; genistein; EGCG	Restriction of maternal folate may increase risk of diabetes by adult age; studies in *agouti* mice suggest that early exposure to genistein may influence the adipogenesis processes and obesity-related diseases such as type 2 diabetes; maternal green tea extract attenuates a high-fat diet-induced insulin resistance in adult male offspring	(57,61,100)
Cardiovascular diseases	Folate	Restriction of maternal folate may increase risk of high blood pressure in adulthood	(57)

GE genistein, *SFN* S-adenosylmethionine, *EGCG* (−)-epigallocatechin-3-gallate, *I3C* indole-3-carbinol

susceptibility to certain human disease in the adult life. Noncommunicable diseases (NCDs) refer to noninfectious and non-transmissible medical condition, and most of NCDs are chronic human diseases such as cancer, diabetes, and cardiovascular diseases with defined genetic predisposition. Although direct evidence on how epigenetic diets affect chronic human diseases in later life is still insufficient, many epidemiological studies provide first-hand evidence indicating a tight correlation of maternal epigenetic diet consumption with disease prevention in the progeny. For example, maternal consumption of folate supplementation, a methyl-donor diet, has been shown to reduce the risk of common acute lymphoblastic leukemia in later life (56); whereas long-term consumption of cruciferous vegetables enriched SFN is correlated with low incidence of breast cancer in their children (73). In addition, study shows that deficiency of maternal folate leads to genome-wide changes in the fetal epigenome and the offspring are more prone to develop diabetes and high blood pressure by adult age (57), indicating a potential role of maternal folate on prevention of diabetes and cardiovascular diseases in adult life.

Animal studies have demonstrated that when pattern changes in DNA methylation or histone modification on obesity- or adipogenesis-related genes such as *leptin*, *leptin receptor*, *glucocorticoid*, and *peroxisome proliferator-activated receptor* γ, a proclivity towards an obese phenotype is observed in adult life (92–96). Diet enrichment of methyl donors (folic acid intake, selenium choline, vitamin B_{12}, diallyl sulfide) has been shown to prevent transgenerational obesity (97). Dietary inhibitors of histone acetylases (HATs) and HDACs such as curcumin and diallyl sulfide may influence chromatin states as well affect genes of the adipogenic pathways (98,99). In addition, a change of obesity status in the offspring of the *agouti* mice fed with another epigenetic diet, soybean genistein, suggests that early exposure to genistein may influence the adipogenesis processes in later life, thus influencing the susceptibility to certain human diseases that are closely related to obesity, such as type 2 diabetes (61). Evidence also indicates that maternal green tea

attenuates a high-fat diet-induced insulin resistance in adult male offspring suggesting a transplacental prevention effect of green tea EGCG against diabetes (100). Further investigation focused on determining actual transgenerational epigenetic alterations and precise epigenetic loci changes that are connected to disease incidence is highly needed.

WINDOW OF EPIGENETIC DIET EXPOSURE

The importance of the exposure period to soybean genistein during pregnancy and lifetime on prevention of mammary cancer is well illustrated by experimental animal and human epidemiological studies (63–65). In postnatal life, early consumption of genistein during childhood and adolescence in women reduces later mammary cancer risk, whereas adult exposure to soy genistein is not considered as a protective factor (63–65). Although the findings obtained in rats and mice exposed to maternal genistein on later breast cancer prevention vary from study to study, our recent pilot study indicates a clear adverse effect of maternal genistein exposure during pregnancy on breast cancer development in a spontaneous breast cancer mouse model, indicating that an appropriate exposure window could be a key factor for prevention of human diseases (Fig. 2). Although the precise mechanisms that cause these differences are still not clear, two important factors including interfering with estrogen signaling and epigenetic pathways may contribute to diverse effects of genistein on prevention of mammary cancer. Further investigation focused on determining accurate exposure time that maximizes beneficial effects of epigenetic diets will provide key evidence for guiding optimal maternal dietary regimens in humans.

CONCLUSIONS

The available data provide a molecular basis for epidemiological and experimental evidence that shows that the early period of life is critical in determining susceptibility to many human diseases. Early embryogenesis involving

accurately designed sequential epigenetic reprogramming provides an excellent opportunity for later intervention on several human diseases when there is appropriate exposure to epigenetic diets such as folate, soybean genistein, broccoli sprout sulforaphane, green tea polyphenols, etc. (Fig. 1). Although our knowledge of the role of epigenetic mechanisms in early dietary prevention on human diseases is relatively limited at the present, further studies will likely provide more precise interpretation. Moreover, better understanding the transgenerational effects of bioactive dietary compounds as well as the precise mechanisms during this process will facilitate the discovery of the novel approaches linking early dietary or pharmaceutical interventions to human disease prevention.

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Conflict of Interest The authors declare that they have no competing interests.

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