Review

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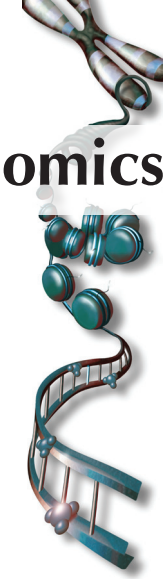
Epigenomics



The relationship between early-life environment, the epigenome and the microbiota

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Children exposed to early-life adversity carry a greater risk of poor health and disease into adulthood. This increased disease risk is shadowed by changes in the epigenome. Epigenetics can change gene expression to modify disease risk; unfortunately, how epigenetics are changed by the environment is unclear. It is known that the environment modifies the microbiota, and recent data indicate that the microbiota and the epigenome interact and respond to each other. Specifically, the microbiome may alter the epigenome through the production of metabolites. Investigating the relationship between the microbiome and the epigenome may provide novel understanding of the impact of early-life environment on long-term health.

Keywords: early-life adversity • environment • epigenetic • epigenome • histone modification • metabolite • methylation • microbiome

Exposure to early-life adversity fuels the risk of poor health and disease later in life. The risk appears particularly high if the adversity occurs during the prenatal or early postnatal life. This observation was initially supported by investigating the long-term health effects of perinatal exposure to famine during the Dutch Hunger Winter of 1944 [1–3]. Subsequent studies in both humans and animals have found similar results confirming long-term alterations in health as a result of early-life adversity [4–8]. Yet despite supportive studies, the mechanism by which early-life adversity impacts adult health remains unclear. Furthermore, a mechanism through which to decrease the risk of early-life adversity affecting long-term health is also not established. Epigenetics and the microbiota may provide such a mechanism.

Changes in epigenetic patterns often follow early-life adversity [4,9–10]. Each cell in our body consists of a relatively stable DNA genome and an adaptable epigenome. The epigenome can change the structure of chromatin and gene expression through modification of DNA and associated proteins. The epigenome can be modified in a cell type specific manner throughout development and by the environment. Environmental epigenetics is the study of how normal developmental processes are affected by external environmental influences [11–13]. Epigenetic modifications occur through DNA methylation, chromatin modifications and noncoding RNAs. These changes in the epigenome can be transitory or be passed on through cellular division and affect health even across generations. By affecting the normal developmental epigenetic processes, the impact of early-life adversity may be realized over a lifetime. Early life is also a critical time for the establishment of the microbiome, and similar to the epigenome, disruptions during early life can alter microbial colonization [7,14–16].

Our microbial community, or microbiota, regulates our health. The microbiome consists of the genetic material of all the microbes on and in our body, most of which reside in the large intestine [17]. Microbial genes outnumber human genes and produce a large proportion of active metabolites [17–19]. Bacteria play an impor-

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tant role in many biological processes, including aid in the digestion of our food [20,21], the development of our immune system [22,23] and alter neurological processes [24,25]. The microbiome is established through early-life events, though it is continually evolving through environmental influences [14,26–28].

We believe that the epigenome and the microbiome record our environmental histories. Both are environmentally adaptive, changing with factors such as diet [4,9–10,12,29–30]. Both can be modified by underlying genetic information, but can also modify gene expression [31–33]. Finally, and perhaps most critically, both may modify disease risk and play a critical role in the development of our health [8,34–36].

The epigenome and the microbiome react to the early-life environment to influence our health. Evidence exists to suggest that their responses may be interrelated and influenced by each other [36–38]. However, the relationship between early-life environment, changes in the epigenome, the microbiome and the development of disease is unknown. Additionally, our appreciation of how the microbiome affects the epigenome is at its infancy. Finally, while understanding how the environment directly impacts developmental epigenetics remains a challenge, our understanding of environmental influences on the microbiota are growing. We propose that understanding the early-life environmental influences on the epigenome can be facilitated through the microbiome. This review will explore how early-life environment can alter both the epigenome and the microbiota, as well as how the two interact with each other and contribute to long-term changes in health and disease.

Early-life adversity alters epigenetics & disease risk

Early-life adversity contributes to adult disease [39]. Early-life adversity can occur in many forms, including over or under nutrition, alterations in maternal care or separation as well as other forms of stress. These disruptions in early life, including during gestation or lactation are associated with an increased risk of several diseases including obesity [40,41], diabetes [42,43], cardiovascular disease [44] and neurobehavioral disease [3]. Early-life-associated disease risk is often accompanied by shifts in epigenetic patterns.

Historical events that coincide with a women's pregnancy or an infant's early life, provide opportunities to study long-term effects of early adversity on epigenetics and health. The most frequently investigated events are historical famines, including the Finnish famine of 1866–68 [45], the Guernsey occupation of 1940–1945 [46], the Greek Famine of 1941–1942 [47], the Dutch Famine of 1944–1945 [1–3,48–49], the Chinese Famine of 1959–1961 [50–52] and the Biafran Famine of 1967–1970 [53]. Close examination following all these events indicates that early-life environment influences adult health [1–3].

Data collected from each of these events are unique and inform in different ways. The Guernsey occupation and Chinese famine occurred over a longer period of time providing more data. However, the length of time also makes it difficult to distinguish effects of *in utero* exposure versus exposure in the first or second year of life. Additionally, a longer duration and severity may alter mortality and reproductive success. By contrast, the Greek and Dutch famines were shorter, though still affected a large number of people. The Biafran famine is relatively recent and demonstrates the power of differentiating environments on health, specifically famine conditions and the recent introduction of urbanization and a westernized diet [53–56]. Data from the Finish famine demonstrated that individuals who experienced low crop yields early in life showed lower survival during the later famine, indicating the long-term effect of early environment [45]. However, despite their differences, all these studies demonstrate that early-life adversity, including poor perinatal nutrition and stress can contribute to adult diseases [1–3,46–49,51–53,57].

Data from historical events also provide an opportunity to examine long-term epigenetic effects. Further investigation, six decades after the Dutch Famine, reveals epigenetic changes associated with the disease phenotype. Altered epigenetic patterns were detected in individuals exposed in utero compared with unexposed individuals. Methylation analysis of exposed offspring showed changes in DNA methylation in imprinted genes as well as genes important for growth and metabolic disease. For example, periconceptual exposure to famine altered methylation *IGF-1*, and *GNASAS* and *LEP*. These changes in DNA methylation differed according to the timing of the exposure as well as the gender of the offspring [9,10]. Changes in the expression of these genes through epigenetic modifications could contribute to long-term changes in metabolism and health. A subsequent study of the Dutch Hunger Winter provided further evidence of long-term epigenetic effects associated with environmental adversity. Hughes *et al.* found that exposure to famine during adolescence and young adulthood was associated with persistent epigenetic changes that influence the development of colorectal cancer [4].

Animal studies similarly demonstrate changes in epigenetic patterns following early-life adversity. Animal models that alter the early-life environment and result in intrauterine growth restriction of offspring have consistently shown alterations in epigenetic pat-

terns long after delivery including changes in DNA methylation and histone modifications [58–62]. Similar to these studies, investigations in disruption of early-life environment by changes in maternal diet also result in alterations in epigenetic patterns [63,64].

Maternal diet disrupts epigenetic patterns and health in offspring. For example, Marco *et al.* demonstrated that offspring from dams on a high-fat diet had altered methylation in the promoter of a gene important for the control of food intake, the *Pomc* gene. Importantly, they also found that this change in methylation persisted into adulthood and was associated with increased body weight and vulnerability when challenged with a high-fat diet [63]. This study demonstrates lasting effects of maternal diet on offspring body weight and appetite possibly through epigenetic modifications of the *Pomc* gene. Suter *et al.* similarly found that maternal high fat diet altered histone modifications in offspring, some of which persisted to 5 weeks of age [64]. These studies and others consistently illustrate that early-life environment, like changes in maternal environment can have long-lasting epigenetic and phenotypic consequences in offspring. Unfortunately, the mechanisms by which environment manipulates epigenetics and disease risk is unknown. The studies described here suggest that one mechanism may be through diet. To understand how diet can alter epigenetics, we must understand microbial breakdown of food into bioactive molecules. Some environmental influences on the microbiome are known, and similar to changes in the epigenome, microbial changes can influence disease risk [7,8].

Early-life environment alters microbiota & disease risk

Maternal environment can alter microbial colonization in offspring. Though the fetus was once thought to be sterile prior to birth, it is now recognized that bacterial transfer may begin earlier. Maternal bacteria can be shared with offspring through four routes: transplacental transfer [28,65]; fetal ingestion of amniotic fluid in utero [26,66–67]; delivery [14,15] and maternal milk [27,68–70]. Consequently, maternal microbial colonization is important for offspring. Additionally, disruptions in maternal environment that alter microbial colonization could potentially affect offspring health.

Early-life environment changes microbial patterns. Children born to obese mothers have alterations in their microbiome even at 2 years of age [71]. Importantly, these children are also at an increased risk for obesity themselves. Childhood obesity has also been associated with maternal weight and mode of feeding in infancy [71]. Collado *et al.* found that overweight mothers had differences in the bacteria present in their breast milk. Some of these differences correlated to changes in inflammatory cytokine concentration [72].

Changes in the maternal environment also may hold an opportunity to beneficially alter microbial colonization of offspring. Maternal prebiotic and probiotic usage has been shown to beneficially affect the colonization of the GI tract in offspring [73–75]. Gronland *et al.* demonstrated mother–infant associations in gut colonization following maternal probiotic use [76]. Maternal probiotic use significantly increased the infants' microbial diversity indexes and the mother–infant similarity indexes in offspring at both 1 and 6 months of age. These data suggest that changes in maternal environment may provide a relatively unexplored route of influencing health of future generations.

Maternal environment patterning microbial colonization in offspring is also evident in animal studies. Using a primate model, Ma *et al.* demonstrated that exposure to a high-fat diet during gestation and lactation alter the microbial pattern, including changes in *Campylobacter*, 6 months after weaning even if the offspring is on a low-fat diet [16]. Tormo-Badia *et al.* found that offspring of pregnant mice treated with antibiotics had changes in the microbiota, including changes in composition and diversity. Interestingly these changes were associated with changes in T-cell populations, immune function and disease risk [5,7]. Paralleling human studies data from rats demonstrate that maternal diet, including high protein or high prebiotic fiber diet, alters microbial colonization as well as milk content [77].

Hansen *et al.* performed an interesting study examining the incidence of diabetes in offspring and maternal diet [8]. In this study, pregnant nonobese diabetic mice were fed a gluten-free diet through weaning. The offspring of gluten-free dams had a dramatic decrease in the incidence of diabetes and insulitis as well as changes in the gut microbiota. Specifically, the authors found an increase in *Akkermansia*, Proteobacteria and TM7 in dams and offspring exposed to the diet. Additionally, anti-inflammatory immune cells like Foxp3$^+$ Tregs were increased, and inflammatory intestinal gene expressions, such as the cytokines, *Ifng*, *Il12b* and *Il18* were decreased in offspring exposed to a gluten-free maternal diet [8]. These intriguing animal studies highlight the connection between environment, microbiota and disease. However, additional work is needed to determine how these interventions affect relevant epigenetic characteristics in these animals.

The epigenome & the microbiome interact

The epigenome and the microbiota are critically important to our health. Recent studies have fur-

ther indicated that the establishment of these two dynamic environmental records during early life plays a role in adult health [38]. However, our understanding of the interaction between the epigenome and the microbiome remains limited. Filling this gap in knowledge may provide novel insights into health and disease.

Early evidence investigating the relationship between early-life environment, the epigenome and microbiota is enticing, yet the connection requires much further investigation. For example, blood DNA methylation profiles from pregnant women were found to be associated with gut microbiota profiles and disease risk [38]. This association with changes in health of the offspring is unknown. However, by using a mouse model, Myles *et al.* demonstrated that maternal high-fat diet led to changes in microbial colonization and immune function including allergy and infection responses. Importantly, maternal diet was also associated with alterations in epigenetic patterns which were consistent with transgenerational inheritance [35]. Specifically the authors found that pups exposed to western diet had increased H3K9Me3 histone modifications associated with the lipopolysaccharide (LPS)-binding protein (*LBP*) loci. LPS-binding protein binds bacterial LPS to stimulate an immune response. Changes in *LPB* expression by epigenetic modifications could contribute to an altered immune response. Additionally, the authors demonstrated an increased ratio of Firmicutes to Bacteroidetes, greater representation of *Lachnospiraceae* and *Clostridiales* and lower diversity in pups exposed to western diet. This study endorses the idea of early-life environment changing epigenetic and microbial patterns then subsequently altering long-term health.

A thoughtful method of investigating cooperation between the epigenome and microbiota is through examining the effects of a methyl-donor diet. In particular, a maternal methyl-donor diet is critical in fetal development. Schaible *et al.* investigated the effects of maternal methyl-donor supplementation on colitis in offspring. Interestingly, maternal methyl-donor supplementation increased susceptibility to colitis in offspring [78]. Additionally, the colitis was associated with colonic mucosal DNA methylation and gene-expression changes as well as a prolonged effect on the mucosal microbiota in the offspring. Interestingly, the authors found that the methylation of the X chromosome was particularly sensitive to maternal methyl-donor diet supplementation, demonstrating decreased methylation independent of gender. The authors also found persistent species-level microbial alterations in microbial composition particularly in *Staphylococcus saprophyticus*.

Collectively, these studies indicate that early-life environment is associated with changes in the epigenome and the microbiome. Importantly, these changes are also associated with changes in long-term health. These exciting studies provide the first steps in understanding the connection between early-life environment and adult health. The next goal is to understand the molecular relationship between the epigenome and the microbiome. Understanding this relationship may provide novel techniques to monitor, predict and improve health.

Mechanism of epigenome–microbiota interactions

The microbiota and the epigenome adapt to current environmental conditions to effect health. These two dynamic systems then allow for direct communication between our environment and our molecular response. Additionally, emerging evidence indicates that the microbiome and the epigenome interact [36,37]. This includes the epigenome regulating bacterial colonization as well as commensal bacteria effecting epigenetic patterns through active metabolites. Understanding this interaction provides a path for effecting health and disease across generations.

Evidence of epigenetic regulation of microbiota comes from animal studies. Alenghat *et al.* demonstrated that mice with an intestinal epithelial-cell specific deletion of *HDAC3* exhibit dysregulation of intestinal epithelial cell gene expression including decreased expression of genes associated with antimicrobial defense [36]. Perhaps most interesting, however, these mice also demonstrated a loss of Paneth cells, impaired epithelial cell function and alterations in the composition of intestinal commensal bacteria when conventionally housed. These changes were associated with increased susceptibility to intestinal damage and inflammation [36]. This important study highlights how epigenetic mechanisms can alter microbial colonization, which can have far reaching consequences on health.

Human and animal studies have demonstrated that changes in environmental factors can affect the colonization of commensal bacteria as well as the pattern of epigenetic marks. This is particularly evident in dietary studies. The breakdown of dietary components into individual nutrients requires gastrointestinal bacteria. Importantly, some metabolites of this process are epigenetically active. Epigenetic modifications can then be driven by bacteria and the diet they metabolize.

Certain microbial-derived metabolites are epigenetically active and can alter gene expression [79]. Epigenetically active bacterial metabolites include folate [80], choline [81,82], short-chain fatty acids (SCFA) [37,83],

isothiocyanates [84–86] and polyphenols [87]. Dietary sources of these epigenetically active metabolites include folate, eggs, fiber, cruciferous vegetables and fruit. Epigenetically active metabolites can alter DNA methylation, histone acetylation and expression of noncoding RNA [37,79,81–83,85–87]. Folate and choline have perhaps the best understood epigenetic potential, however, SCFA, isothiocyanates and polyphenols also strongly influence epigenetics.

Folate & choline

The microbiota is known to produce many vitamins, including water-soluble vitamins of the B group. Whereas dietary intake of vitamins occurs in the small intestine, absorption of microbial vitamins takes place in the colon [88]. The colon is a major depot of folate and colonic folate production by bacterial exceeds dietary intake. Additionally, folate production by intestinal bacteria is absorbed and used by the host and affects the folate status in the host [80]. This is supported by probiotic studies. Humans administered probiotics consisting of *Bifidobacterium* had significantly increased fecal folate concentration 48 h later [89]. Similar results were also found in rats administered *Bifidobacterium* [90].

DNA methylation also depends on dietary intake of methyl groups, including choline. Choline is commonly consumed in meat and eggs. Recently choline metabolism was found to be dependent on commensal gut bacteria [91–93]. Choline is catabolized to trimethylamine by gut microbiota. Irregularities in choline and trimethylamine metabolism are associated with nonalcoholic fatty liver disease, and cardiovascular disease including atherosclerosis [91,94]. Interestingly, these diseases are also associated with disruptions in early-life environment [44,46,53]. Mice fed a methionine-choline-deficient diet were found to have decreases in *Bifidobacterium* and *Lactobacillus* in their feces [95]. Additionally, methyl-deficient diets disrupt epigenetic modifications including DNA and histone methylation [81–82,96]. These studies highlight the role of gastrointestinal bacteria on dietary methyl groups and their downstream epigenetic targets. While bacteria may alter methylation through folate and choline, bacterially produced SCFA are known to alter histone acetylation.

Short chain fatty acids

Dietary carbohydrates that are resistant to digestion in the stomach can undergo colonic fermentation resulting in the production of SCFA [97,98]. SCFA have 1–6 carbon atoms and are mainly produced by anaerobic bacteria. SCFA are critical contributors to normal intestinal function. The most abundant SCFA produced through fermentation are acetate, butyrate and propionate.

The SCFA butyrate is of particular interest due to the multiple health benefits both in the intestinal track and peripheral tissues ascribed to it. One mechanism by which butyrate may contribute to health and disease is through regulatory effects on gene expression. Butyrate is a member of an important class of epigenetic modifiers that inhibit the removal of histone acetyl groups by HDAC enzymes called HDAC inhibitors [99–103].

Butyrate's epigenetic function may contribute to changes in health. An intriguing study by Gao *et al.* demonstrated the powerful effects of butyrate on obesity. Obesity is growing at an alarming rate, and has been associated with early-life adversity. Interestingly, mice on a high-fat diet and supplemented with butyrate did not develop insulin resistance or obesity [37]. Specifically, fasting blood glucose, fasting insulin and insulin tolerance were all preserved in the supplemented mice, and body fat content was maintained at 10% without a reduction in food intake. Additionally, butyrate concentrations were increased in circulation and histone deacetylate activity was reduced by 50% in the supplemented mice. Finally, obese mice supplemented with butyrate also showed increased insulin sensitivity and decreased adiposity [37]. This study demonstrates butyrate's effects on obesity and highlights its epigenetic function as a possible mechanism.

In addition to butyrate, another short-chain fatty acid, propionate can modulate epigenetics. A recent study by Lukovac *et al.* demonstrated that propionate and butyrate produced by *Akkermansia muciniphila* could modulate the expression of several genes including *HDAC3* and *HDAC5*. Interestingly, these same results were not found with another commensal short-chain fatty acid producing bacteria, *Faecalibacterium prausnitzii* [83]. These results indicate that there may be important specificity in which bacteria produce the metabolite. While less in known about the specific bacteria that produce isothiocyanates and polyphenols, these bacterial metabolites can similarly alter epigenetic patterns.

Isothiocyanates

Cruciferous vegetables such as cabbage, broccoli, cauliflower, collards, mustard, horseradish and Brussels sprouts are important sources of glucosinolates. Glucosinolates are metabolized into isothiocyanates (ITCs) by the plant enzyme myrosinase or bacterial thioglucosidases. ITCs have been suggested to be protective against many diseases including cancer and obesity [104–107]. Cooking either by boiling,

steaming, microwaving or stir-frying deactivates myrosinases, so gut bacteria are important for ITC production [108]. Several bacterial species have been identified with the ability to convert glucosinolates to ITCs including *Escherichia coli*, *Bacteroides thetaiotaomicron*, *Enterococcus faecalis*, *Enterococcus faecium*, *Peptostreptococcus* species and *Bifidobacterium* species [109,110].

Studies have suggested that some of the health benefits of ITCs may occur through their effects on epigenetics. For example, Wong *et al.* recently showed that treatment with an ITC family member decreased DNMT expression and altered genome-wide promoter methylation levels in prostate cell lines. Interestingly they also found a reversal of some aberrantly methylated cancer genes following ITC treatment [84]. Liu *et al.* additionally found that treatment with another member, ITC family member, altered site- and promoter-specific H3 histone tail modifications [85]. Finally, Izzotti showed alterations in microRNA expression with ITC treatment [86]. Collectively these studies show that ITCs can effect several epigenetic mechanisms and support their importance in gene expression and health.

Polyphenols

Dietary polyphenols are found in many foods such as tea, fruit and vegetables and are associated with health benefits. Consumption of polyphenols is associated with a reduced risk of cancer [111], cardiovascular disease [112] and obesity [113,114]. A large number of polyphenol classes exist including flavonoids, stilbenes, coumarins, lignans, lignins, cinnamic, and benzoic acids. Polyphenols are found in a wide variety of foods to varying concentrations, however, some common sources include berries (blueberries, blackberries, raspberries, strawberries), dark chocolate, tea (green and black) and red wine. Intact forms of dietary polyphenols have limited bioavailability and must undergo digestive and microbial transformation [115,116].

Ellagitannins are polyphenols found in some fruits (strawberries, raspberries, blackberries, pomegranate) and walnuts. Dietary ellagitannins are digested in the stomach and small intestine to ellagic acid. Intestinal bacterial metabolism converts ellagitannins to urolithins. Ellagitannins have many important benefits on health, including as antioxidants [117,118], antimicrobial properties [119], antitumor activities [120] and anti-inflammatory properties [121,122]. Recently, Zou *et al.* administered an ellagitannin commonly found in pomegranates to rats on a high-fat diet. Ellagitannin supplementation significantly reduced diet-induced hyperlipidemia and hepatic lipid deposition [123]. Additionally, expression of serum inflammatory cytokines was restored to baseline levels with ellagitannin supplementation. In a complementary study, Kiss *et al.* found that physiological concentrations of ellagic acid and urolithins alter the inflammatory process through epigenetic modulation [87]. They found that inflammatory stimulation of an immune cell resulted in decreased cell viability, reduced HDAC activity and increased HAT activity. Interestingly, coincubation with either ellagic acid or urolithins restored cell viability and reversed the inflammatory effect on HDAC and HAT activity. These results suggest that ellagitannins can affect inflammation through epigenetic mechanisms.

Collectively these studies demonstrate that the function of the epigenome and the microbiome depend on each other. Additionally, this dynamic interaction is facilitated through microbial metabolites affecting the epigenome. Understanding this relationship also provides a path for environmental influence on the epigenome through the microbiome.

Microbiome: an access point to epigenetics

Our ability to influence the epigenome through the microbiome may provide an access point to change our health. Specifically, through modifying the epigenome, gene expression can be changed. Unfortunately, *in vivo* manipulation of the epigenome has proven to be difficult. Gene-, site- and modification-specific changes remain a challenge. Additionally, understanding the coordination of each epigenetic modification and how they partner with specific cell types and precise developmental timing remains a struggle and a goal. Finally, the effect of environment also exists as a gap in our knowledge. Teleologically, the microbiome and the epigenome have been interacting across millennia, suggesting that such an interaction has been evolutionarily crafted to avoid extremes that lead to significant morbidity. Moreover, some of the unanswered questions about the epigenome may be answered more easily through microbiota due to accessibility. We propose that through microbial influences we may be able to affect the epigenome. The microbiota continuously and uniquely responds to our environment. Further understanding of the microbiome's influence on the epigenome may provide novel access to the epigenome which may be used as an effector and marker of our health.

Several studies have begun to investigate the potential of bacteria on altering epigenetics and health. One way to alter the microbiome is through the use of diet and probiotics. Probiotics are bacteria that are consumed and believed to confer a health benefit. Research investigating the effects of probiotic is ongo-

ing, including how they alter the epigenome. Ghadimi *et al.* investigated the effects of two common components of probiotics, *Bifidobacterium* and *Lactobacillus* on inflammation and epigenetics [124]. Administration of these bacteria decreased LPS-induced expression of proinflammatory cytokines involved in the pathogenesis of inflammatory bowel disease. Importantly, DNA methylation was increased and histone acetylation was decreased on cytokine genes [124]. These data indicate that some bacterial health effects may be initiated through alterations in epigenetics and subsequent gene expression.

The effect of dietary fiber on microbiota, the epigenome and colorectal cancer was recently investigated by Donohoe *et al.* Their study utilized mice with a defined gut microbiota fed either a high- or low-fiber diet [125]. Some of the mice were additionally colonized with a butyrate-producing bacterium. This allowed the authors to control genetic background, microbial colonization and diet to investigate the effects of induced colorectal carcinoma. Interestingly they found that mice on a high-fiber diet and colonized with the butyrate-producing bacterium were better protected from tumor development. The authors then went on to show that the effect of butyrate is mediated through epigenetics. They showed that altered metabolism by colon cancer cells (Warburg effect) lead to the accumulation of butyrate which then acted as an HDAC inhibitor, increasing histone H3 acetylation and effecting apoptosis and cell proliferation. Lastly, the authors applied their results to human colorectal carcinoma samples which contained increased levels of butyrate and H3 acetylation compared with normal tissue [125].

These powerful studies indicate that we may be able to influence epigenetics through bacteria, and thus alter our gene expression and health. This provides an exciting new path to understand how the environment influences our health across multiple generations.

Conclusion

The environment is a powerful force in shaping our health particularly during vulnerable periods of development. In particular, the microbiome is sensitive to the environment and can alter epigenetic patterns. Understanding the relationship between the epigenome and microbiome may provide novel insight into preventing, predicting and treating disease.

Future perspective

Awareness of the role for early-life environment, epigenetics and the microbiota in long-term health and disease is increasing. Data support the view that maternal environment is an important contributor to offspring health. An exciting new role for epigenetics and the microbiome is now being explored not just as a contributor to health, but also a possible vehicle for treatment and prevention.

A future challenge and goal is to utilize the epigenome and microbiome as a record of environmental exposures to monitor and predict disease. Exciting works using epigenetics as a novel tool for diagnostic and prognostic biomarker in cancer are already underway [11]. These studies could provide a blueprint for studies of the environment, epigenetic and microbial interactions. Additional research needs to address questions surrounding the effect of maternal intervention through diet, pro- and pre-biotics, antibiotics and bacterial metabolites on offspring gene expression and health. Additionally, identification of the molecular pathways, the microbiome and epigenome, used to respond to the early-life environment is of great importance. Understanding the dynamic interaction between the early-life environment, the epigenome and the microbiome can uncover novel approaches to improve health.

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Executive summary

- Early-life adversity influences adult health.
- The epigenome and the microbiome dynamically respond to the environment to effect health.
- The epigenome and the microbiome molecularly interact with each other and influence each others response.
- Microbial metabolites can influence epigenetic patterns and change gene expression.
- The microbiome may provide novel access to affect epigenetic modifications.
- Understanding the relationship between the epigenome and the microbiome may allow for novel ways to prevent, predict and treat disease.

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