Gut microbiota and obesity-related gastrointestinal cancer: a focus on epigenetics

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Abstract: Changes in DNA methylation and histone modifications are important in the development of many diseases including cancer. These epigenetic alterations drive the formation of cancer by altering the expression of critical genes such as those controlling proliferation, survival and cell migration. The microorganisms that colonise the gastrointestinal tract (gut microbiota) are potentially a source of localised microbial-induced epigenetic change. Recent evidence shows that obesity is associated with dramatic differences in the composition of gut microbiota when compared with normal-weight individuals. This review explores the evidence for microbial-induced epigenetic changes and hypothesizes that this may contribute to the pathogenesis of obesity-related colorectal cancer.

Keywords: Cancer; colorectal cancer; epigenetics; inflammation; microbiota

Submitted Sep 25, 2013. Accepted for publication Oct 08, 2013.
doi: 10.3978/j.issn.2224-4778.2013.10.03
Scan to your mobile device or view this article at: http://www.amepc.org/tgc/article/view/2862/3780

Introduction

As adults our microbial census exceeds the total number of our own human cells by about 10-fold (1). The vast majority of these commensal bacteria reside within the gastrointestinal tract to form a complex and delicately balanced symbiotic relationship with the host. Bacterial phyla in the gut such as firmicutes, bacteroidetes, actinobacteria and proteobacteria metabolise dietary components that remain undigested in the small intestine and therefore contribute to the 'energy harvest' of the host diet (2).

Changes in the composition of the gut microbiota, termed dysbiosis, can be associated with diseases such as obesity and CRC (3-7). The gut microbiota produces a broad range of metabolites and the spectrum of these metabolites can change depending on the relative abundance of each microbial species. Some of these metabolites can modulate the epigenetic state of the host (8). Epigenetics refers to the stable heritability of a phenotype that results in changes in a chromosome without alterations in the DNA sequence (9). Epigenetic changes regulate the function of DNA and play an important role in development and disease by regulating DNA accessibility and gene expression.

This review proposes that dysbiosis contributes to the pathogenesis of obesity-related CRC by causing microbial-induced epigenetic changes.

Obesity and cancer risk

Obesity is defined as a body mass index (BMI) ≥30 kg/m^2 and is recognised as an important and potentially preventable cause of cancer (10). It is estimated that approximately 3.2% and 8.6% of all incident cancers in men and women respectively are attributable to excess body weight (11). Obesity is a risk factor for the development of cancer throughout the gastrointestinal and hepatobiliary tract from the oesophagus to the rectum (10). Though there are organ and gender-specific differences for specific cancers, obese individuals show around 1.5-2.0 times the relative risk of gastrointestinal cancer compared with normal weight individuals (10). In addition to increasing the risk of cancer,

obesity is also associated with a worse prognosis following diagnosis of gastrointestinal cancers (12). Furthermore, some studies have shown that weight loss following bariatric surgery correlates with a reduction in the risk of breast, endometrial and CRCs (13-15) and that weight loss is associated with a reduction in proinflammatory gene expression in human colorectal mucosa (16). However, many studies investigating the anticancer benefit of weight loss have proved inconclusive (10) and further research is needed.

The mechanisms by which obesity increases cancer risk are unclear at present but it is likely to be multifactorial. Obesity is associated with increased serum levels of insulin and insulin-like growth factor (IGF-1), both of which have a demonstrated role in cancer (17). The adipokine leptin, a hormone that regulates satiety and energy balance, is also increased in obesity and is thought to promote cancer through activation of multiple signalling pathways including the phosphatidylinositol 3-kinase (PI3K) pathway, the mitogen-activated protein kinase (MAPK) pathway and the signal transducer and activator of transcription 3 (STAT3) pathway (18).

In addition to the mechanisms described above, two prime candidates for the increased risk of cancer in obese individuals are dysbiosis (discussed below) and chronic inflammation. Chronic inflammation is a hallmark of cancer (19) and cancer risk accumulates with increasing duration of chronic inflammation (20). Adipose tissue is an active endocrine organ that secretes many different types of cytokines and growth factors including interleukin (IL)-6, IL-8, C-reactive protein (CRP), tumour necrosis factor (TNF) and macrophage migration inhibitory factor (MIF) (10,21,22). IL-6 in particular is an important inflammatory marker known to activate the MAPK and PI3K pathways, amongst others (18). Therefore increases in adipose tissue lead to increased systemic levels of these proinflammatory markers in obese individuals, which are thought to promote low-level chronic inflammation. However, elevated levels of intestinal proinflammatory markers, such as faecal calprotectin, can act locally rather than systemically to promote intestinal inflammation in obese individuals (23). Inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis confer an increased risk of developing CRC (24,25). Inflammation can promote tumourigenesis by increasing cell proliferation, invasion, migration and angiogenesis. For example, inflammation-induced activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and STAT3 transcription factors results in the suppression of apoptosis and accelerated progression through the cell cycle (26). Furthermore, in a mouse model with constitutive Wnt pathway hyperactivation, it has been shown that proinflammatory signalling through the NF-κB pathway acts synergistically with Wnt signalling to drive the de-differentiation and expansion of tumour-initiating cells (27).

Inflammation, the gut microbiota and obesity-related cancer

Recent evidence shows that the gut microbiota can play an important role in obesity-related inflammation. For example, obesity-induced gut microbial metabolites can promote liver cancer by inducing the secretion of a signature profile of inflammatory cytokines, chemokines and proteases (28). In this interesting study, mice fed on a high-fat diet showed altered composition of the gut microbiota leading to increased production of deoxycholic acid (DCA), a microbial metabolite known to cause DNA damage. Enterohepatic circulation of DCA stimulated the production of proinflammatory cytokines in hepatic stellate cells upon exposure to chemical carcinogens and promoted the development of hepatocellular carcinoma (HCC) (28). In a separate study the loss of *IL-10* (*IL-10*$^{-/-}$), a gene involved in regulating inflammation in the colonic mucosa, is associated with colitis in mice (29). *IL-10*$^{-/-}$ mice show increased abundance of commensal *Escherichia coli* (*E. coli*) bacteria in the intestine compared to control mice. Interestingly, when *IL-10*$^{-/-}$ colonised with the *E. coli strain* NC101 were treated with azoxymethane (a potent carcinogen often used to induce CRC in mice and rats), 80% developed CRC; However mice colonised with the human commensal *Enterococcus faecalis* rarely developed tumours (29). Finally, there is also evidence to suggest that the gut microbiota may contribute to chronic inflammation in obese individuals through raised systemic levels of lipopolysaccharides (LPS) due to increased gut permeability (30). Together, these findings suggest that inflammation, the gut microbiota and obesity-related cancer are inextricably linked.

The relationship between the gut microbiota and obesity

Dysbiosis can impact on host metabolism and energy storage (energy homeostasis) (1) and may actually play a causative role in the development of obesity (31). A study of stool samples from 68 obese individuals and

47 controls revealed that elevated levels of the bacteria species *Lactobaccillus reuteri* were associated with obesity, whereas species such as *Bifidobacterium animalis* and *Methanobrevibacter smithii* were associated with normal weight (6). Sterile mouse models lacking gut microbiota are protected from obesity caused by a high-fat diet (32,33). Furthermore, inoculation of lean germ-free mice with gut microbiota from obese mice results in significantly higher fat gain in the recipients (33). In humans, faecal microbiota transplantation (FMT) from lean to obese volunteers lead to improved insulin sensitivity in recipients concomitant with acute changes in the gut microbiota (34).

Epigenetic regulation of gene expression

Epigenetic regulation of gene expression involves a dynamic multi-layered network of chromatin modifications. This includes chemical modification of the DNA itself, namely the methylation of cytosine to create 5-methylcytosine and 5-hydroxymethylcytosine. The vast majority of DNA methylation in mammalian cells occurs in the context of CpG dinucleotides. These are enriched at regions known as CpG islands, which are found at the promoter regions of around 70% of human genes (35). The function of DNA methylation is context dependent (36) but 5-methylcytosine at gene promoter regions is usually associated with transcriptional silencing. In addition to DNA methylation, there are a number of other chromatin modifications that control the packaging of DNA. The functional unit of chromatin is the nucleosome, consisting of a histone octamer containing one histone $(H3\text{-}H4)_2$ tetramer and two histone H2A-H2B dimers, around which approximately 146 bp of DNA is wrapped (37). The function of histones can be regulated by post-translational modifications, which regulates the DNA binding properties of histones and the recruitment of effector proteins. More than 60 different histone modifications combine to create a variety of functional contexts capable of orchestrating complex processes such as gene transcription, DNA repair, DNA replication and splicing (38). Histone acetylation, particularly the acetylation of lysine 9 on histone H3 (H3K9ac), as well as the trimethylation of lysine 4 on histone H3 (H3K4me3) at promoter regions, is associated with gene expression. However, modifications such as H3K9me3 and H3K27me3 are associated with gene silencing. The precise positioning of nucleosomes is also important in the regulation of gene expression and nucleosome occlusion of gene promoters or enhancers is associated with the transcriptional silencing of genes (38,39). Another layer of epigenetic regulation is the higher-order structure of chromatin in the nucleus which, broadly speaking, is organised into transcriptionally active regions towards the centre of the nucleus and transcriptionally repressed regions at the periphery. Finally, non-coding RNAs such as micro RNAs (miRNAs) and long non-coding RNAs (lncRNAs) can play an important role in directing epigenetic changes and dictating gene expression levels (40).

DNA in the promoter regions of expressed genes is usually unmethylated and associated with active histone marks such as H3K9ac and H3K4me3. In cancer, critical genes can become silenced and this is associated with promoter DNA hypermethylation, the repressive marks H3K9me3 and H3K27me3, and nucleosome occlusion of the transcription start site.

Microbial-induced epigenetic changes

Pathogenic bacterial infections, as well as commensal bacteria, can affect the epigenomes of host cells (41) including changes in histone modifications and DNA methylation. Bacteria may cause changes to the host epigenome by producing epigenetically active metabolites or by activating cell signalling pathways that lead to epigenetic modulation of gene expression. In this review, the term epigenetically active metabolite describes a bacterial-derived chemical capable of causing changes to chromatin modifications. The gut microbiota produces large amounts of epigenetically active metabolites such as folate and short chain fatty acids such as butyrate and acetate. Folate is essential for DNA methylation and acts as a methyl donor for the regeneration of the intracellular methyl substrate *S*-adenosyl methionine (SAM). SAM is used as a substrate of the DNA methyltransferase 1, 3A and 3B enzymes (DNMT1, DNMT3A and DNMT3B, respectively) and by various histone methyltransferases. Daily diet is the primary source of folate in humans, however folate-synthesising gut bacteria such as *Bifidobacterium* spp. also contribute to adequate folate supply (8). Deficiency of folate may contribute to colonic DNA hypomethylation and increased colorectal cancer risk (42). In cells, folate exists as functionally distinct coenzyme species that are required for DNA methylation (5-methyltetrahydrofolate) or DNA synthesis (5-formyltetrahydrofolate and 5,10-methenyltetrahydrofolate) (43). A recent study of global methylation in normal colorectal mucosa from colorectal cancer patients and healthy individuals

demonstrated that the relative abundance of these different folate species determines methylation levels rather than total folate levels (43). Therefore, it will be important to determine whether dysbiosis is also associated with changes to the relative levels of these folate species in cells of the colorectal mucosa. Butyrate, a potent inhibitor of histone deacetylases (HDACs), is produced following the fermentation of undigested dietary carbohydrates and proteins, primarily by Gram-positive *firmicutes* (44). Butyrate is known to cause hyperacetylation of histones and changes to the expression of critical cell cycle regulatory genes such as cyclin D3 (*CCND3*) and cyclin-dependent kinase inhibitor 1A (*CDKN1A*, also known as p21/CIP1) in intestinal cells (45). Therefore, the relative abundance of *Bifidobactierum* and *firmicutes* in the gut can alter the levels of these metabolites, which may in turn affect the epigenome (8).

Epigenetic changes can be associated with some pathogenic bacterial infections. An example is *Helicobacter pylori* (*H. pylori*) infection of the stomach, which can lead to gastritis (inflammation of the gastric mucosa), gastric ulcers and in some cases gastric cancer (46). A study of gastric biopsy samples collected from patients infected with *H. pylori* showed that chronic gastritis was associated with promoter hypermethylation of the DNA repair gene O^6-methylguanine-DNA methyltransferase (*MGMT*) (47). Interestingly, the *CagA*-positive strain of *H. pylori*, which induces a more pronounced inflammatory response in the gastric mucosa (48), was associated with the highest frequency of *MGMT* hypermethylation (47). Furthermore, eradication of *H. pylori* infection in these patients resulted in reduced *MGMT* methylation (47). Others have reported hypermethylation at several other gene promoters in gastric mucosa biopsies from *H. pylori* infected patients including E-cadherin (*CDH1*) (49) and MutL homolog 1 (*MLH1*) (50). *H. pylori*-associated gastritis thus serves to reiterate the interplay between the gut microbiota, inflammation and epigenetic alterations. However, methylation changes are not restricted to pathogenic bacterial infections. In head and neck squamous cell carcinoma (HNSCC) patients, specific micorobial profiles (increased *Enterobacteriaceae* and *Tenericutes*) of the oral mucosa were associated with hypermethylation of the promoter regions of the *MDR1*, *IL-8*, *RARB* and *TGFBR2* genes and worse regional nodal metastasis (51).

Commensal and pathogenic bacteria can also regulate the epigenome of host cells through activation of particular signalling pathways. For example, colonisation of rats with the commensal gut microbe *Bacteroides vulgatus* was found to induce phosphorylation and nuclear translocation of RelA (a component of the NF-κB complex) in intestinal epithelial cells. This led to RelA recruitment to the *IL-6* gene promoter, increased H3K9ac, increased phosphorylation of serine 10 on histone H3 and increased *IL-6* expression (52). Infection with the bacterium *Listeria monocytogenes* (*L. monocytogenes*) causes H3K18 deacetylation at the promoters of many genes including *SMAD1*, *IRF2*, *SMARCA2* and the chemokine *CXCL12*, which are important in the regulation of the host immune response (53). Deacetylation of these promoters was dependent on translocation of the host deacetylase sirtuin 2 (SIRT2) to the nucleus as well as InlB present on the surface of *L. monocytogenes*, which the bacterium uses to gain entry into the cell following the binding of c-Met on the host cell surface (53). Therefore, *L. monocytogenes* epigenetically regulates critical genes to gain transcriptional control of host cells, thereby facilitating infection by dampening the host immune response. Finally, bacterial factors such as LPS induce expression of *IL-12* in macrophages and this is dependent on the eviction of a nucleosome immediately upstream of the *IL-12* transcription start site (54,55). This involves activation of the p38α MAPK pathway in a toll-like receptor 4 (TLR4)-dependent manner, followed by phosphoacetylation of histone H3 (H3S10K14) at the *IL-12* promoter. This chromatin remodelling was essential for the binding of NF-κB to the *IL-12* promoter (56).

Conclusions and clinical implications for obesity-related gastrointestinal cancer

This review summarises some of the important factors involved in the pathogenesis of obesity-related gastrointestinal cancer and describes key roles for chronic inflammation and dysbiosis. As discussed above, dysbiosis is a potential source of microbial-induced epigenetic change. It can therefore be hypothesised that microbial-induced epigenetic changes to host cells is involved in the pathogenesis of these diseases.

Dietary changes can alter the species composition of gut microbiota in both the short-term and long-term. Therefore therapeutic interventions aimed at modulating the composition of the gut microbiota, such as the use of prebiotics and probiotics, may be an important treatment strategy for re-establishing a balanced gut microbiota (57). As mentioned previously, another approach for modifying gut microbiota is FMT, which involves the transplantation

of faecal matter from a healthy individual into the gastrointestinal tract of another person. FMT is an effective treatment for recurrent *Clostridium difficile* infection and has shown promise in the treatment of IBD and obesity (58).

Identification of the microbial profiles important in the pathogenesis of obesity and cancer could potentially offer an effective marker for the early detection or prediction of these diseases, as well as the opportunity for early therapeutic intervention. However, it will be important to define which microbes and metabolites are beneficial to health, or conversely, those that are associated with disease. At present it is still unclear whether the bacterial species associated with CRC may also be associated with obesity. Further research into the mechanisms by which changes in gut microbiota contribute to diseases such as obesity and cancer will also be necessary. In particular, it will be important to determine what effects obesity or cancer-related dysbiosis has on the spectrum of microbial metabolites and whether these alter the epigenomes of host cells. It is also unclear whether obesity-related CRC is associated with a distinct epigenetic profile and this would be an interesting avenue of further research.

In summary, the gut microbiota plays an important role in health and there is evidence that dysbiosis plays a causative role in the development of several diseases. This review presents the view that the gut microbiota is at the centre of a web of interactions between inflammation, cancer and epigenomic changes. Therefore, dysbiosis may contribute to the pathogenesis of obesity-related CRC by promoting epigenetic changes to host cells. This may involve changes to the spectrum of microbial metabolites, some of which have been shown to regulate epigenetic modifications, or by the activation of host cell signalling pathways involved in inflammation and immune response.

Acknowledgements

Thanks to Neil Youngson, Robert Rapkins, Vibha Patil and Peter Zarzour for critical review of the manuscript and helpful discussions. LBH is funded by a Cancer Institute New South Wales Fellowship.
Disclosure: The author declares no conflict of interest.

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Cite this article as: Hesson LB. Gut microbiota and obesity-related gastrointestinal cancer: a focus on epigenetics. Transl Gastrointest Cancer 2013;2(4):204-210. doi: 10.3978/j.issn.2224-4778.2013.10.03

