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Obesity-associated cancer risk: The role of intestinal microbiota in in the etiology of the host pro-inflammatory state

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Abstract

Obesity increases the risks of many cancers. One important mechanism behind this association is the obesity-associated pro-inflammatory state. Although the composition of the intestinal microbiome undoubtedly can contribute to the pro-inflammatory state, perhaps the most important aspect of host-microbiome interactions is host exposure to components of intestinal bacteria that stimulate the inflammatory reactions. Systemic exposures to intestinal bacteria can be modulated by dietary factors by altering both the composition of the intestinal microbiota as well as absorption of bacterial products from the intestinal lumen. In particular, high fat and high energy diets have been shown to facilitate absorption of bacterial lipopolysaccharide (LPS) from intestinal bacteria. Biomarkers of bacterial exposures that have been measured in blood include LPS-binding protein, sCD14, fatty acids characteristic of intestinal bacteria and immunoglobulins specific for bacterial LPS and flagellin. The optimal strategies to reduce these pro-inflammatory exposures, whether by altering diet composition, avoiding a positive energy balance or reducing adipose stores, likely differ in each individual. Biomarkers that assess systemic bacterial exposures therefore should be useful to optimize and personalize preventive approaches for individuals and groups with specific characteristics, and to gain insight into the possible mechanisms involved with different preventive approaches.

Keywords

Cancer; obesity; microbiome; inflammation; biomarkers

PRO-INFLAMMATORY PATHWAYS ASSOCIATED WITH OBESITY INCREASE RISK OF CANCER

Obesity is one of the factors that increase the risk of many cancers. The data is especially compelling for cancers of the endometrium, kidney, colorectum, esophagus, pancreas and

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postmenopausal breast cancer (1). More recently, gall bladder, liver, thyroid and ovarian cancers have been identified to be among those cancers strongly affected by obesity (2, 3). Obesity-related cancer risks do vary by factors such as ethnicity, sex and menopausal status, but nonetheless substantial increases in risk have been observed with body mass index (BMI) increases above the normal weight range (2). For colorectal cancer, risk increases with obesity in a dose-dependent fashion, with a risk that is elevated by 32–41% in obese versus normal weight individuals (4, 5).

Several mechanistic pathways are identified to be operative in this link between obesity and cancer. These include hormonal alterations (e.g. leptin, estrogen), induction of insulin-signaling pathways and activation of pro-inflammatory pathways (6). More and more research is turning to the role of activated pro-inflammatory pathways in mediating obesity-associated risks of not only cardiovascular diseases and diabetes, but also of cancer. Indeed, experimental data supports the role of inflammation in the development of many cancers (7). Although immune surveillance does have a role in eliminating tumor cells, chronic, low-level activation of immune pathways also can alter the homeostatic state to stimulate tumor growth.

Cytokines, acute phase proteins and cancer risk

Excess body fat accumulation results in polarization of immune cells, resulting in generation of pro-inflammatory cytokines and chemokines (8). This activated immune state has been characterized by presence of “classically activated”, termed M1, macrophage-secreted factors, increased pro-inflammatory T-helper cell type 1 (Th1) cytokines, and decreased Th2, immune-regulatory cytokines (9–13). Among the many functions of cytokines, they signal production of acute-phase proteins secreted by the liver during injury or infection, including C-reactive protein (CRP), serum amyloid SAA. Interestingly, one of the functions of CRP is to bind to components of microorganisms to assist in their removal by immune cells (14, 15).

Elevated serum CRP is associated with elevated risks of several cancers, including that of the colon and breast (16–19). In the prospective European Prospective Investigation Into Cancer (EPIC) study, elevated CRP was associated with elevated risk of colorectal cancer (20). A pro-inflammatory state also plays an important role in survival from cancer, and an elevated pro-inflammatory state is a risk factor for breast cancer recurrence and survival (21–29). In a meta-analysis of ten studies, relatively high levels of CRP were associated with reduced overall survival, disease free survival and breast cancer specific survival (23). CRP also was predictive of cancer survival when measured at diagnosis or 2–3 years post diagnosis (21, 25, 28). Unlike CRP, cytokines such as IL-6 have not been as consistently associated with cancer risk (18, 19, 30, 31).

Eicosanoids and cancer risk

In addition to cytokines, eicosanoid production may be of interest as a more rapidly-responsive biomarker of the pro-inflammatory state of tissues since cytokines can take weeks to be fully manifest via induction of T cells (10). Eicosanoids are bioactive molecules formed from the metabolism of arachidonic acid. Eicosanoid formation is inextricably linked

with activation and de-activation of immune cells. For example, inhibition of cyclooxygenases that produce eicosanoids using indomethacin decreased the pro-inflammatory cytokines interferon γ and tumor necrosis factor α , and increased the immuno-regulatory cytokine interleukin (IL) 10 (32).

One of the most widely studied eicosanoids with regard to carcinogenic processes is prostaglandin E₂ (PGE₂). Increased PGE₂ concentrations have been linked with increased risk of many cancers, including that of the colon, breast and skin (33–35). Eicosanoids, and especially PGE₂, have critical roles in the initiation and progression of cancer (36–38). Eicosanoids can also indirectly affect cancer growth. For example, PGE₂ induces aromatase expression, which is relevant to survival from postmenopausal breast cancer (39), in addition to the more direct effects of PGE₂ on driving breast cancer growth and metastases (33, 40, 41). Eicosanoids can be measured in tissues, but in epidemiological studies stable metabolites have more often been measured in urine. Increased concentration of the prostaglandin E₂ (PGE₂) metabolite in urine was positively predictive of increased breast cancer risk and of breast cancer metastases (42–45). Non-steroidal anti-inflammatory agents, that inhibit cyclooxygenases and PGE₂ formation, decreased breast cancer recurrence in overweight and obese women (46).

In the colon, pro-inflammatory changes characterized by increased colonic production of PGE₂ also have been shown to increase risk of cancer (47–49). PGE₂ has an important repair role for resolving frank inflammatory conditions such as colitis, but in normal tissue, low-level, chronic elevated PGE₂ promotes carcinogenic processes (50, 51). PGE₂ mediates colonic crypt cellular expansion that can subsequently result in adenoma formation (52–56).

Data in human colon tissue is more sparse than in animal models, but one study of subjects with a history of polyps showed that PGE₂ in the rectal mucosa was significantly increased with increasing BMI (57). In another study, expression of cyclooxygenase-2, and inducible form of the enzyme, was higher in the colonic mucosa adjacent to tumor of obese versus normal weight subjects (58).

Beneficial effects of weight loss on reversing obesity-associated inflammation

This obesity-associated, pro-inflammatory state likely is sensitive to the energy balance that drives metabolic processes towards either lipid synthesis or lipid oxidation. This could be one reason why pro-inflammatory states are not always associated with obesity; conversely, a pro-inflammatory state can occur in lean individuals (59, 60). A modest weight loss, in which case many obese individuals will remain in the obese state, appears sufficient for reducing inflammation. A weight loss of at least 5–10% of initial weight has been shown to be clinically significant and effective for eliciting beneficial effects on circulating adipokines and cytokines (61–63). Furthermore, 10% weight loss (of baseline weight) reduced cytokine concentrations 25–57% and down-regulated proteins involved in PGE₂ synthesis in rectal biopsies from 10 obese women (64).

The trajectory of weight change may therefore be important in governing the inflammatory state. Weight loss decreases systemic inflammation, and multiple studies have shown that serum CRP is linearly associated with weight change (61, 65, 66). In rodent models of

cancer, diet-induced obesity increased and calorie restriction decreased colon tumorigenesis with analogous effects on systemic inflammation (67).

Perspective on the etiology of the obesity-associated pro-inflammatory state

In summary, the relationships between weight change, obesity and pro-inflammatory states are well described in the literature, but little is known about the etiology of the pro-inflammatory changes. One important factor may be increased systemic exposure to intestinal bacteria stemming from either the nature of the obesity-associated microbiome and/or to increased intestinal permeability. Biomarkers of bacterial exposure would be useful in gauging to what extent the intestinal microbiome plays in the obesity-associated pro-inflammatory state. If weight loss and/or avoiding a positive energy balance decreases bacterial exposures, this has implications not only for risk of colorectal cancers but also for risk of other cancers that are affected by obesity.

OBESITY INCREASES SYSTEMIC EXPOSURES TO INTESTINAL BACTERIA

Role of intestinal microbial composition

A number of studies have evaluated the effects of obesity on the composition of the intestinal microbiota. These studies have failed to reach a consensus on the effects that obesity has on the intestinal microbiome. An initial observation that obesity affects the relative abundance of Firmicutes (Gram-positive) and Bacteroidetes (Gram-negative) taxa has not been replicated, but many of these studies were limited in sample size and often failed to separate the effects of obesity and diet composition (68–83). For example, taxa in the *Bacteroidetes* phylum utilize fiber for growth and therefore would be expected to be decreased with high fat, low fiber diets (84, 85).

A re-analysis of data across published studies indicates that the relative abundance at the phylum level of Firmicutes and Bacteroidetes is more highly dependent on the study methodology rather than on true differences by the presence of obesity (86). A recent study found that the ratio of Firmicutes to Bacteroidetes was elevated in obese persons with metabolic syndrome relative to those without metabolic syndrome, suggesting that it may be important to look beyond BMI values (87). There has also been variability in findings of obesity-associated differences between animal models, and between humans and mice (81, 88, 89).

Lipopolysaccharide exposures

Although the composition of the intestinal microbiome is undoubtedly important, perhaps the most important aspect of host-microbiome interactions is host exposure to bacterial components that stimulate the immune system. Many components of bacteria are potentially immunogenic and this has been known for quite some time (90). Newer findings indicate that metabolites of bacteria should be considered. For example, microbial vitamin B metabolites are immunogenic (91).

Both Gram negative and Gram positive bacteria can induce an immune response, but the immunological response is greater with Gram negative bacteria (92). The cell wall of Gram

negative bacteria contains lipopolysaccharide (LPS) that is an endotoxin. LPS absorption from the gastrointestinal tract likely is a critical etiological agent in obesity-associated inflammation and has been studied more extensively than other bacterial antigens (93–96). Endotoxin has been detected in human serum and is associated with metabolic syndrome (97). The inflammatory response to LPS includes production of cytokines and chemokines, and this is likely mediated by production of eicosanoids such as prostaglandin E₂ (98, 99).

Of relevance to colon cancer, LPS promotes colon cancer cell invasion into the extracellular matrix through the TLR4 pathway (100). This response in the colon appears to be mediated via initial interaction of LPS with soluble CD14 and LPS binding protein (LBP) that concentrate LPS at the cell surface. LPS exposure also induces production of LBP (101). This is followed by activation of toll-like receptor 4, TLR4 (102, 103). Both TLR4 and CD14 are needed for initiating the inflammatory response to LPS since knockout of either gene in mice resulted in resistance to the adverse effects of a high fat diet on induction of obesity and inflammation (104, 105). Effectors of TLR4 activation are MyD88 and subsequently NF κ B, which is a key signaling molecule for the inflammatory response and cytokine production (100, 106–110). The LPS/TLR4/NF κ B pathway has been suggested to be a target for colon cancer prevention because of the central role of NF κ B in cell proliferation, transformation and tumor progression (107–109).

Flagellin absorption

As compared with LPS, there is much less known about the relationships of obesity with exposures to flagellin, another marker of bacterial exposures. Flagellin in serum was identified to be elevated in patients with Crohn's disease (111). Bacterial flagellin is a structural protein in flagellated bacteria, which include both Gram negative and Gram positive species. Flagellin is recognized by both TLR-5 and the NLRC4 inflammasome, which subsequently activate NF- κ B and caspase-1, respectively, to result in production of inflammatory cytokines (112, 113).

DIET MODULATES ABSORPTION OF BACTERIAL COMPONENTS

Dietary factors potentially could alter both the composition of the intestinal microbiota as well as absorption of bacterial products from the intestinal lumen. Ingested foods can directly alter the intestinal environment not only in the small intestine but also in the colon where the majority of intestinal microbiota reside. Undigested fiber that reaches the colon can be digested, in part, by colonic bacteria to produce short-chain fatty acids, which have beneficial effects on colon health (114). In addition, although most nutrients are absorbed in the small intestine, some fat does reach the colon. About 5% of dietary fats are excreted in feces, and increased dietary saturated fat or dietary fiber increases fat excretion (115, 116). Colon does have nutrient absorptive capacity (117, 118), and it is possible that diet affects absorption of bacterial products in the colon as well as in the small intestine.

High fat, high energy diets

High fat and high energy diets facilitate absorption of bacterial LPS from intestinal bacteria (93–96, 119, 120). A high fat diet results in increased intestinal permeability and decreased

antimicrobial peptides in the protective mucin layer (121). Studies have been conflicting as to whether or not high fat diets favor growth of Gram negative bacteria (121, 122). Interestingly, even a single high-fat meal increases postprandial endotoxemia (119, 123, 124). It is often difficult to separate the effects of a high fat diet from the effects of obesity discussed previously since energy dense diets tend to result in a positive energy balance and weight gain. Accordingly, it is not clear if increased LPS levels are due to a high fat diet *per se* or to a positive energy balance that results in weight gain. In one study of healthy men, circulating LPS was increased with increased dietary energy, but not independently with other macronutrients (93). Interestingly, there is rodent data that males may be more susceptible to the pro-inflammatory effects of a high fat diet than females (125).

Once exposure to LPS occurs, this can exacerbate the effects of an obesogenic diet. A low dose of LPS in animals can mimic the effects of a high fat diet on inducing obesity (104). The microflora also can alter energy harvest from the intestinal contents to help propagate the obese state (75, 126, 127). This makes the relationship between the microbiome and obesity bidirectional.

Types of dietary fat

In addition to the obesogenic effects of a high-fat diet, specific types of dietary fat can have disparate effects on exposure to intestinal bacteria. In mice, a high-fat saturated fat diet, but not a high omega-6 fatty acid diet, increased colonic permeability and mesenteric fat inflammation (128). The high saturated-fat diet was associated with decreased hydrogen-sulfide producing bacteria, and a large portion of the variability in intestinal variability could be accounted for by hydrogen-sulfide producing bacteria (128). Fish oil reduced the inflammation elicited by the high saturated fat diet (128). Fish oils have also been shown to counteract the dysbiotic effects of high omega-6 fatty acid diets under normal conditions, but in the case of frank sepsis fish oils impair the detoxification of LPS (129).

Production of cytokines and chemokines stimulated by bacterial exposures also is magnified by saturated fatty acids, and each fatty acid appears to affect distinct mechanisms (130). Further, LPS exposure induced cyclooxygenases and production of PGE2 both in vitro and in vivo (131, 132). Conversely, high fiber diets are expected to reduce LPS exposures via alteration of microbial composition, improvement in the mucosal barrier function through facilitating tight junction assembly and reduction in epithelial permeability through production of short chain fatty acids (133–136). Likewise, dietary antioxidants can counteract the adverse effects of LPS exposure in colon smooth muscle cells (137).

Dietary patterns

The interactions of obesity and certain types of dietary patterns are known to increase inflammation. Many studies have suggested that a Western diet (high n6 fats, low plant foods, low fiber) is pro-inflammatory and conversely that a Mediterranean diet (high MUFA, high n3/n6 ratios, high fruit, vegetables and whole grains) has anti-inflammatory effects (138). Importantly, a Mediterranean diet also appears to prevent weight gain (139, 140). In our studies, a Mediterranean diet accompanied by a very small weight loss resulted in reduced serum CRP (141). Whether or not this is mediated by changes in the microbiome is

not known. More information on the role of diet composition with and without weight loss would be especially important for long term recommendations since a negative energy balance cannot be sustained indefinitely.

MUCIN PRODUCTION CAN MODULATE EPITHELIAL EXPOSURES TO INTESTINAL BACTERIA

In most studies, microbiota are typically quantified in excreted stool, or in the ceca of rodents. The microbiota, however, differ along the length of the intestine (142, 143). The taxa present in the lumen also may differ from those adhering to the mucin layer. Mucin in the intestine provides an epithelial barrier, but it is also a niche for bacterial growth (144, 145).

The bacterial species present in the mucin layer lining the luminal epithelium differ from those in the stool and were suggested to be present in horizontal layers (146). Other studies have suggested that species such as *Bacteroides thetaiotaomicron* can shift from degrading dietary fiber in the lumen to degrading mucin when dietary fiber is low (147–150). A higher prevalence of oxygen-tolerant species (vs. strict anaerobes) has been noted in the intestinal mucosa versus that in the lumen (151, 152). Finally, colonic mucin does appear to change in malignancy (153), but changes in mucin also may precede malignancy. In mice, a defective intestinal barrier function facilitates absorption of bacterial products, triggering an inflammatory environment that promotes colon tumors (154).

The amount of mucin produced can be greater in obese than lean subjects but the balance of mucin production to mucin degradation is what ultimately determines the integrity of the intestinal barrier. Receptors for the obesity associated hormone leptin are present in the colon, and activation of this receptor increases mucin and cytokine production (155–158). Pro-inflammatory stimuli such as cytokines also increase mucin production initially, likely as a defense mechanism (155, 159–162). Expression of mucin-encoding genes increases early in infection (163). This then would provide a niche for growth of mucin-degrading microbiota near the luminal, epithelial surface (144, 164), and eventually might lead to depleted mucin and an impaired mucosal barrier.

Interestingly, secretion of mucus is the initial colonic response to both low-level LPS and increased leptin, an obesity-associated hormone (155–158, 165–167). Increased mucin in turn should favor growth of mucin-degrading microbiota in close proximity to the epithelial cells. Elevated LPS in obesity therefore is not necessarily due to a compromised mucin layer such as that seen in frank inflammation, and it provocatively may result from increased mucin production and/or changes in the microbiota within the mucin. Notably, the mucin contains peptides such as resistin like molecule- β (RELM β) that can further stimulate the pro-inflammatory response in response to the presence of bacteria (168–172).

Although some Gram negative Enterobacteriaceae have been found to be increased in obesity, one Gram-negative species that is a mucin-degrading bacterium in the human colon, *Akkermansia muciniphila*, is decreased in obesity (173, 174). *Akkermansia* appears to normalize changes in the mucin glycoproteins as well as in antimicrobial peptides that are

altered by a high fat diet (174). *Akkermansia* also was shown to induce expression of regulatory (Th2-like) immune cells (175). In a small study of 16 adults, the relative abundance of *Akkermansia* was increased in individuals with successful weight loss and weight loss maintenance over two years (87). It should be noted, however, that although the beneficial effects of *Akkermansia* appear consistent, the studies generally have been small and require confirmation.

BIOMARKERS OF SYSTEMIC BACTERIAL EXPOSURES

LBP and sCD14

There is direct evidence of systemic exposures to intestinal bacteria from animal models. For example, bacteria trans-located into mesenteric fat as determined by presence of the 16S bacterial gene, and this correlated positively with changes in intestinal permeability (128). In order to identify factors that affect systemic exposures to intestinal bacteria in clinical trials, biomarkers of exposures are needed.

LPS is unfortunately difficult to measure in biological samples. The limulus amebocyte lysate (LAL) reactivity assay can be used to measure bacterial LPS, but this assay has been fraught with technical problems when applied to analyses of serum or plasma due to interfering compounds (176, 177). Many studies have therefore quantified LPS-binding protein (LBP). LBP is synthesized not only by the liver but also by adipose and intestinal epithelial cells, and in the intestinal cells LBP production is induced by cytokines (178, 179). Thus LBP represents both LPS load and obesity-related changes in the intestinal barrier and pro-inflammatory pathways.

LBP is the major LPS transporter in blood, and sCD14 serves to buffer the effects of LPS. In the colon, LBP and sCD14 function to concentrate LPS at the membrane toll-like receptor 4 (TLR4). LBP or the LBP/sCD14 ratio therefore has been used as a more reliable marker of LPS exposure in blood than the LAL assay, and this also has advantages over measuring LPS directly due to the short half-life of LPS (180–184). Most studies have utilized measures of LBP alone. LBP binds constituents of both Gram positive and Gram negative bacteria, making it a more general marker of bacterial exposures than the LPS that stems only from Gram negative bacteria (183).

LBP is increased in infection (185), but more subtle inflammatory states such as obesity also increase LBP. Glucose and saturated fatty acids can acutely increase plasma LBP, showing a dietary relationship (123, 180). Elevated LBP is tightly associated with obesity (178, 181, 186). In a Mediterranean dietary intervention, serum LBP was affected by obesity and modest weight loss, but not by 6 months of dietary change per se (187). The interpretation of LBP concentrations, however, can be a complicated and caution is advisable. LBP has a role in detoxifying LPS via an HDL-mediated pathway, and LBP has been shown to protect animals from septic shock (188, 189).

Fatty acids unique to bacteria

Bacteria contain fatty acids with odd numbers of carbon chains, branched chains and hydroxyl groups (190–192). These can be measured at low levels by gas chromatography

with mass spectral detection. Accordingly, presence of bacterial 3-hydroxy fatty acids in environmental samples has been useful as an indication of endotoxin contamination (193). Quantitation of these fatty acids in serum would represent total bacterial exposures while the LAL reactivity assay represents only free LPS that is dissociated from the bacterial cell wall (194). A principal advantage of measuring bacterial fatty acids in serum is that this likely is more quantitative than the LAL assay or measures of antibodies to bacterial products.

The most conserved portion of LPS from Gram negative bacteria is lipid A. The lipid A fatty acids do differ by bacterial species, but 3-hydroxy fatty acids are widely distributed in Gram negative bacteria (195, 196). For example, 3-hydroxy 16:0, 3-hydroxy 14:0 and 3-hydroxy i17:0 (15-methyl hexadecanoic acid) are common in several species of *Bacteroides fragilis* (191, 192). *B. fragilis* associates with the colonic mucin, which would facilitate absorption, and has been implicated in risk of colon cancer (197–199). Of relevance to their use as biomarkers of bacterial exposures, blood measures of bacterial fatty acids have been shown to reflect the microbes present in the intestinal tract (200).

Quantitation of 3-hydroxy fatty acids also has been useful in clinical studies of infection: bronchial lavage fluid of patients with lung diseases (201); salivary 3-hydroxy fatty acids in periodontitis (202); and serum 3-hydroxy fatty acids in cardiac patients with endotoxemia (203). Importantly, the 3-hydroxy fatty acids in LPS appear to be active in stimulating the immune system (204, 205).

Unlike the 3-hydroxy fatty acids, branched chain (iso-methyl) fatty acids, namely 13-methylmyristic acid (i15:0), 14-methylpentadecanoic acid (i16:0), and 15-methylpalmitic acid (i17:0), are common in both Gram negative and Gram positive bacteria (192). In addition to commensal bacteria, another source of iso-methyl fatty acids is endogenous synthesis in the skin, but this does not appear to be operative in other organs (206). Branched chain bacterial fatty acids also are known to be present in the meat and milk of ruminants: beef and dairy constitutes the majority of U.S. intakes of iso-methyl bacterial fatty acids (207). This raises the interesting possibility that iso-methyl bacterial fatty acids could be markers of both intestinal permeability and meat intake, while 3-hydroxy fatty acids are more specific for bacterial LPS.

Antibodies to LPS and flagellin

Flagellins are antigens present on the surface of flagellated bacteria, and flagellins are a major antigenic target of the immune system. Enzyme-linked immunoassays have been developed to quantify specific serum IgG and IgA that are formed in response to flagellin exposures (208, 209). For example, serum flagellin, LPS, or both were detected in most patients with short bowel syndrome, but not in normal control sera, using an ELISA for immunoglobulins specific for flagellin and LPS (210). In patients with colon adenomas, IgA antibodies to bacterial LPS from *Escherichia coli* and flagellin from *Salmonella typhimurium* were both increased by obesity, and antibody concentrations were higher in men than women (211).

EVIDENCE THAT SYSTEMIC EXPOSURES TO INTESTINAL BACTERIA INCREASE CANCER RISK

One large study evaluated systemic exposures to intestinal bacteria and colon cancer risk. In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, systemic exposures to LPS from *Escherichia coli* and flagellin from *Salmonella typhimurium*, were assessed in prospectively-collected serum using quantitation of immunoglobulins against those antigens (212). There were positive associations of these specific immunoglobulin biomarkers with risk of colorectal cancer in men, but not in women, pointing to sex-based differences in the immune response and/or in the nature of the microbiota (212). The associations in men between immunoglobulins and cancer risk were stronger in those subjects with either obesity, higher CRP concentrations or higher alcohol intakes (212). In another study using the same biomarkers of bacterial exposures, men were identified to have higher intestinal permeability and concentrations of bacterial immunoglobulin biomarkers than women, and in both sexes higher CRP and higher BMI was associated with higher biomarker concentrations (211). In two population-based case-control studies, higher serum antibodies to flagellin were associated with increased colorectal cancer risk (213).

Data is sparse for biomarkers of bacterial exposures in the risks of other cancers, although one might expect that similar pro-inflammatory responses elicited by chronic, low-level exposures to bacteria would increase risks of other cancer as well. In the liver, endotoxin exposure was shown to prevent apoptosis and promote tumorigenesis in rodents (214). In infection-associated cancers the association of cancer and inflammation is more obvious, although it is less likely to be modulated by obesity. The microbiome has a major role in liver cirrhosis and hepatocellular carcinoma (215). Increases in markers of microbial translocation likewise increased risk of AIDS-related lymphoma (216).

SUMMARY AND OUTLOOK

Both diet and the physiological changes resulting from obesity can work together to increase absorption of bacterial products from the intestine. Biomarkers of bacterial exposures have been detected in the blood. These exposures in turn result in a pro-inflammatory response that is evident systemically (Figure 1). The optimal strategy to reduce the pro-inflammatory stimuli, whether by diet composition, attaining energy balance or reducing adipose stores, however, may differ in each individual. Biomarkers that assess pro-inflammatory exposures therefore should be useful tools to optimize and personalize preventive approaches for individuals and groups with specific characteristics, and to gain insight into the possible mechanisms involved with different preventive approaches designed to reduce the inflammatory state.

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Abbreviations

BMI	Body mass index
CRP	C-reactive protein
LAL	limulus amebocyte lysate
LPS	lipopolysaccharide
LBP	lipopolysaccharide binding protein
PGE₂	prostaglandin E ₂
Th1	T-helper cell type 1

References

1. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. Washington, D.C.: American Institute for Cancer Research; 2007.
2. Wang J, Yang DL, Chen ZZ, Gou BF. Associations of body mass index with cancer incidence among populations, genders, and menopausal status: A systematic review and meta-analysis. *Cancer Epidemiol.* 2016; 42:1–8. [PubMed: 26946037]
3. Anderson AS, Key TJ, Norat T, et al. European Code against Cancer 4th Edition: Obesity, body fatness and cancer. *Cancer Epidemiol.* 2015; 39(Suppl 1):S34–45. [PubMed: 26205840]
4. Ning Y, Wang L, Giovannucci EL. A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies. *Obes Rev.* 2010; 11(1):19–30. [PubMed: 19538439]
5. Okabayashi K, Ashrafian H, Hasegawa H, et al. Body mass index category as a risk factor for colorectal adenomas: a systematic review and meta-analysis. *Am J Gastroenterol.* 2012; 107(8): 1175–85. [PubMed: 22733302]
6. Byers T, Sedjo RL. Body fatness as a cause of cancer: epidemiologic clues to biologic mechanisms. *Endocr Relat Cancer.* 2015; 22(3):R125–34. [PubMed: 25870250]
7. Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J Clin Invest.* 2007; 117(5):1175–83. [PubMed: 17476347]
8. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *J Clin Invest.* 2011; 121(6):2111–7. [PubMed: 21633179]
9. Fenton JI, Nunez NP, Yakar S, et al. Diet-induced adiposity alters the serum profile of inflammation in C57BL/6N mice as measured by antibody array. *Diabetes Obes Metab.* 2009; 11(4):343–54. [PubMed: 19267713]
10. Strissel KJ, DeFuria J, Shaul ME, et al. T-cell recruitment and Th1 polarization in adipose tissue during diet-induced obesity in C57BL/6 mice. *Obesity (Silver Spring).* 2010; 18(10):1918–25. [PubMed: 20111012]
11. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology.* 2007; 132(6):2169–80. [PubMed: 17498510]
12. Ferrante AW Jr. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. *J Intern Med.* 2007; 262(4):408–14. [PubMed: 17875176]
13. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest.* 2007; 117(1):175–84. [PubMed: 17200717]
14. Jain S, Gautam V, Naseem S. Acute-phase proteins: As diagnostic tool. *J Pharm Bioallied Sci.* 2011; 3(1):118–27. [PubMed: 21430962]
15. Volanakis JE. Complement activation by C-reactive protein complexes. *Ann N Y Acad Sci.* 1982; 389:235–50. [PubMed: 7046577]

16. Chan DS, Bandera EV, Greenwood DC, Norat T. Circulating C-Reactive Protein and Breast Cancer Risk-Systematic Literature Review and Meta-analysis of Prospective Cohort Studies. *Cancer Epidemiol Biomarkers Prev.* 2015; 24(10):1439–49. [PubMed: 26224798]
17. Tsilidis KK, Branchini C, Guallar E, et al. C-reactive protein and colorectal cancer risk: a systematic review of prospective studies. *Int J Cancer.* 2008; 123(5):1133–40. [PubMed: 18528865]
18. Zhou B, Shu B, Yang J, et al. C-reactive protein, interleukin-6 and the risk of colorectal cancer: a meta-analysis. *Cancer Causes Control.* 2014; 25(10):1397–405. [PubMed: 25053407]
19. Gunter MJ, Wang T, Cushman M, et al. Circulating Adipokines and Inflammatory Markers and Postmenopausal Breast Cancer Risk. *J Natl Cancer Inst.* 2015; 107(9):pii: djv169.
20. Nimptsch K, Aleksandrova K, Boeing H, et al. Association of CRP genetic variants with blood concentrations of C-reactive protein and colorectal cancer risk. *Int J Cancer.* 2015; 136(5):1181–92. [PubMed: 25043606]
21. Pierce BL, Ballard-Barbash R, Bernstein L, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol.* 2009; 27(21):3437–44. [PubMed: 19470939]
22. Allin KH, Bojesen SE, Nordestgaard BG. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. *J Clin Oncol.* 2009; 27(13):2217–24. [PubMed: 19289618]
23. Han Y, Mao F, Wu Y, et al. Prognostic role of C-reactive protein in breast cancer: a systematic review and meta-analysis. *Int J Biol Markers.* 2011; 26(4):209–15. [PubMed: 22139643]
24. Liu S, Ginestier C, Ou SJ, et al. Breast cancer stem cells are regulated by mesenchymal stem cells through cytokine networks. *Cancer Res.* 2011; 71(2):614–24. [PubMed: 21224357]
25. Allin KH, Nordestgaard BG, Flyger H, Bojesen SE. Elevated pre-treatment levels of plasma C-reactive protein are associated with poor prognosis after breast cancer: a cohort study. *Breast Cancer Res.* 2011; 13(3):R55. [PubMed: 21639875]
26. Soria G, Ofri-Shahak M, Haas I, et al. Inflammatory mediators in breast cancer: coordinated expression of TNFalpha & IL-1beta with CCL2 & CCL5 and effects on epithelial-to-mesenchymal transition. *BMC Cancer.* 2011; 11:130. [PubMed: 21486440]
27. Sicking I, Edlund K, Wesbuer E, et al. Prognostic influence of pre-operative C-reactive protein in node-negative breast cancer patients. *PLoS One.* 2014; 9(10):e111306. [PubMed: 25340395]
28. Villasenor A, Flatt SW, Marinac C, et al. Postdiagnosis C-reactive protein and breast cancer survivorship: findings from the WHEL study. *Cancer Epidemiol Biomarkers Prev.* 2014; 23(1):189–99. [PubMed: 24220913]
29. Alkhateeb AA, Leitzel K, Ali SM, et al. Elevation in inflammatory serum biomarkers predicts response to trastuzumab-containing therapy. *PLoS One.* 2012; 7(12):e51379. [PubMed: 23300545]
30. Jin WJ, Xu JM, Xu WL, Gu DH, Li PW. Diagnostic value of interleukin-8 in colorectal cancer: a case-control study and meta-analysis. *World J Gastroenterol.* 2014; 20(43):16334–42. [PubMed: 25473192]
31. Joshi RK, Lee SA. Obesity related adipokines and colorectal cancer: a review and meta-analysis. *Asian Pac J Cancer Prev.* 2014; 15(1):397–405. [PubMed: 24528064]
32. Feitoza CQ, Semedo P, Goncalves GM, et al. Modulation of inflammatory response by selective inhibition of cyclooxygenase-1 and cyclooxygenase-2 in acute kidney injury. *Inflamm Res.* 2010; 59(3):167–75. [PubMed: 19711010]
33. Reader J, Holt D, Fulton A. Prostaglandin E2 EP receptors as therapeutic targets in breast cancer. *Cancer Metastasis Rev.* 2011; 30(3–4):449–63. [PubMed: 22002714]
34. Rundhaug JE, Simper MS, Surh I, Fischer SM. The role of the EP receptors for prostaglandin E2 in skin and skin cancer. *Cancer Metastasis Rev.* 2011; 30(3–4):465–80. [PubMed: 22012553]
35. Wang D, Dubois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. *Oncogene.* 2010; 29(6):781–8. [PubMed: 19946329]
36. Harvey AE, Lashinger LM, Hursting SD. The growing challenge of obesity and cancer: an inflammatory issue. *Ann N Y Acad Sci.* 2011; 1229:45–52. [PubMed: 21793838]
37. Wang D, Dubois RN. Eicosanoids and cancer. *Nat Rev Cancer.* 2010; 10(3):181–93. [PubMed: 20168319]

38. Chen EP, Smyth EM. COX-2 and PGE2-dependent immunomodulation in breast cancer. *Prostaglandins Other Lipid Mediat.* 2011; 96(1–4):14–20. [PubMed: 21907301]
39. Wang X, Docanto MM, Sasano H, et al. Prostaglandin E2 inhibits p53 in human breast adipose stromal cells: a novel mechanism for the regulation of aromatase in obesity and breast cancer. *Cancer Res.* 2015; 75(4):645–55. [PubMed: 25634217]
40. Li S, Xu X, Jiang M, et al. Lipopolysaccharide induces inflammation and facilitates lung metastasis in a breast cancer model via the prostaglandin E2-EP2 pathway. *Mol Med Rep.* 2015; 11(6):4454–62. [PubMed: 25625500]
41. Vona-Davis L, Rose DP. The obesity-inflammation-eicosanoid axis in breast cancer. *J Mammary Gland Biol Neoplasia.* 2013; 18(3–4):291–307. [PubMed: 24170420]
42. Cui Y, Shu XO, Gao YT, et al. Urinary prostaglandin E2 metabolite and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2014; 23(12):2866–73. [PubMed: 25214156]
43. Kim S, Taylor JA, Milne GL, Sandler DP. Association between urinary prostaglandin E2 metabolite and breast cancer risk: a prospective, case-cohort study of postmenopausal women. *Cancer Prev Res (Phila).* 2013; 6(6):511–8. [PubMed: 23636050]
44. Morris PG, Zhou XK, Milne GL, et al. Increased levels of urinary PGE-M, a biomarker of inflammation, occur in association with obesity, aging, and lung metastases in patients with breast cancer. *Cancer Prev Res (Phila).* 2013; 6(5):428–36. [PubMed: 23531446]
45. Wang D, DuBois RN. Urinary PGE-M: a promising cancer biomarker. *Cancer Prev Res (Phila).* 2013; 6(6):507–10. [PubMed: 23636051]
46. Bowers LW, Maximo IX, Brenner AJ, et al. NSAID use reduces breast cancer recurrence in overweight and obese women: role of prostaglandin-aromatase interactions. *Cancer Res.* 2014; 74(16):4446–57. [PubMed: 25125682]
47. Yehuda-Shnaidman E, Schwartz B. Mechanisms linking obesity, inflammation and altered metabolism to colon carcinogenesis. *Obes Rev.* 2012; 13(12):1083–95. [PubMed: 22937964]
48. Grivennikov SI. Inflammation and colorectal cancer: colitis-associated neoplasia. *Semin Immunopathol.* 2013; 35(2):229–44. [PubMed: 23161445]
49. Vendramini-Costa DB, Carvalho JE. Molecular link mechanisms between inflammation and cancer. *Curr Pharm Des.* 2012; 18(26):3831–52. [PubMed: 22632748]
50. Duffin R, O'Connor RA, Crittenden S, et al. Prostaglandin E(2) constrains systemic inflammation through an innate lymphoid cell-IL-22 axis. *Science.* 2016; 351(6279):1333–8. [PubMed: 26989254]
51. Montrose DC, Nakanishi M, Murphy RC, et al. The role of PGE2 in intestinal inflammation and tumorigenesis. *Prostaglandins Other Lipid Mediat.* 2015:116–117. 26–36.
52. Sonoshita M, Takaku K, Oshima M, Sugihara K-i, Taketo MM. Cyclooxygenase-2 Expression in Fibroblasts and Endothelial Cells of Intestinal Polyps. *Cancer Research.* 2002; 62:6846–9. [PubMed: 12460897]
53. Takeda H, Sonoshita M, Oshima H, et al. Cooperation of Cyclooxygenase 1 and Cyclooxygenase 2 in Intestinal Polyposis. *Cancer Research.* 2003; 63:4872–7. [PubMed: 12941808]
54. Kargman SL, O'Neil GP, Vickers PJ, et al. Expression of prostaglandin G/H synthase-1 and -2 protein in human colon cancer. *Cancer Research.* 1995; 55(12):2556–9. [PubMed: 7780968]
55. Eberhart CE, Coffey RJ, Radhika A, et al. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. *Gastroenterology.* 1994; 107(4):1183–01188. [PubMed: 7926468]
56. Sano H, Kawahito Y, Wilder RL. Expression of cyclooxygenase-1 and -2 in human colorectal cancer. *Cancer REsearch.* 1995; 55(17):3785–9. [PubMed: 7641194]
57. Martinez ME, Heddens D, Earnest DL, et al. Physical activity, body mass index, and prostaglandin E2 levels in rectal mucosa. *J Natl Cancer Inst.* 1999; 91(11):950–3. [PubMed: 10359547]
58. Delage B, Rullier A, Capdepon M, Rullier E, Cassand P. The effect of body weight on altered expression of nuclear receptors and cyclooxygenase-2 in human colorectal cancers. *Nutr J.* 2007; 6:20. [PubMed: 17767717]
59. Lee SH, Han K, Yang HK, et al. A novel criterion for identifying metabolically obese but normal weight individuals using the product of triglycerides and glucose. *Nutr Diabetes.* 2015; 5:e149. [PubMed: 25915739]

60. Gomez-Ambrosi J, Catalan V, Rodriguez A, et al. Increased cardiometabolic risk factors and inflammation in adipose tissue in obese subjects classified as metabolically healthy. *Diabetes Care*. 2014; 37(10):2813–21. [PubMed: 25011950]
61. Varady KA, Tussing L, Bhutani S, Braunschweig CL. Degree of weight loss required to improve adipokine concentrations and decrease fat cell size in severely obese women. *Metabolism*. 2009; 58(8):1096–101. [PubMed: 19477470]
62. Klempel MC, Varady KA. Reliability of leptin, but not adiponectin, as a biomarker for diet-induced weight loss in humans. *Nutr Rev*. 2011; 69(3):145–54. [PubMed: 21348878]
63. Madsen EL, Rissanen A, Bruun JM, et al. Weight loss larger than 10% is needed for general improvement of levels of circulating adiponectin and markers of inflammation in obese subjects: a 3-year weight loss study. *Eur J Endocrinol*. 2008; 158(2):179–87. [PubMed: 18230824]
64. Pendyala S, Neff LM, Suarez-Farinas M, Holt PR. Diet-induced weight loss reduces colorectal inflammation: implications for colorectal carcinogenesis. *Am J Clin Nutr*. 2011; 93(2):234–42. [PubMed: 21147860]
65. Selvin E, Paynter NP, Erlinger TP. The effect of weight loss on C-reactive protein: a systematic review. *Arch Intern Med*. 2007; 167(1):31–9. [PubMed: 17210875]
66. Hermisdorff HH, Zulet MA, Abete I, Martinez JA. Discriminated benefits of a Mediterranean dietary pattern within a hypocaloric diet program on plasma RBP4 concentrations and other inflammatory markers in obese subjects. *Endocrine*. 2009; 36(3):445–51. [PubMed: 19816812]
67. Olivo-Marston SE, Hursting SD, Perkins SN, et al. Effects of Calorie Restriction and Diet-Induced Obesity on Murine Colon Carcinogenesis, Growth and Inflammatory Factors, and MicroRNA Expression. *PLoS One*. 2014; 9(4):e94765. [PubMed: 24732966]
68. Ley RE, Backhed F, Turnbaugh P, et al. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A*. 2005; 102(31):11070–5. [PubMed: 16033867]
69. Nadal I, Santacruz A, Marcos A, et al. Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. *Int J Obes (Lond)*. 2009; 33(7):758–67. [PubMed: 19050675]
70. Santacruz A, Marcos A, Warnberg J, et al. Interplay between weight loss and gut microbiota composition in overweight adolescents. *Obesity (Silver Spring)*. 2009; 17(10):1906–15. [PubMed: 19390523]
71. Furet JP, Kong LC, Tap J, et al. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. *Diabetes*. 2010; 59(12):3049–57. [PubMed: 20876719]
72. Ravussin E, Redman LM. Adiposity and comorbidities: favorable impact of caloric restriction. *Nestle Nutr Workshop Ser Pediatr Program*. 2009; 63:135–47.
73. Fleissner CK, Huebel N, Abd El-Bary MM, et al. Absence of intestinal microbiota does not protect mice from diet-induced obesity. *Br J Nutr*. 2010; 104(6):919–29. [PubMed: 20441670]
74. Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome. *Nature*. 2011; 473(7346):174–80. [PubMed: 21508958]
75. Jumpertz R, Le DS, Turnbaugh PJ, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am J Clin Nutr*. 2011; 94(1):58–65. [PubMed: 21543530]
76. Zhang H, DiBaise JK, Zuccolo A, et al. Human gut microbiota in obesity and after gastric bypass. *Proc Natl Acad Sci U S A*. 2009; 106(7):2365–70. [PubMed: 19164560]
77. Momozawa Y, Deffontaine V, Louis E, Medrano JF. Characterization of bacteria in biopsies of colon and stools by high throughput sequencing of the V2 region of bacterial 16S rRNA gene in human. *PLoS One*. 2011; 6(2):e16952. [PubMed: 21347324]
78. Mozes S, Bujnakova D, Sefcikova Z, Kmet V. Intestinal microflora and obesity in rats. *Folia Microbiol (Praha)*. 2008; 53(3):225–8. [PubMed: 18661297]
79. Murphy EF, Cotter PD, Healy S, et al. Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models. *Gut*. 2010; 59(12):1635–42. [PubMed: 20926643]
80. Faith JJ, Guruge JL, Charbonneau M, et al. The long-term stability of the human gut microbiota. *Science*. 2013; 341(6141):1237439. [PubMed: 23828941]

81. Walker AW, Parkhill J. Microbiology. Fighting obesity with bacteria. *Science*. 2013; 341(6150): 1069–70. [PubMed: 24009379]
82. Hamilton MK, Boudry G, Lemay DG, Raybould HE. Changes in Intestinal Barrier Function and Gut Microbiota in High-Fat Diet Fed Rats Are Dynamic and Region-Dependent. *Am J Physiol Gastrointest Liver Physiol*. 2015 ajpgi 00029 2015.
83. Blaut M. Gut microbiota and energy balance: role in obesity. *Proc Nutr Soc*. 2014;1–8.
84. Salyers AA, Palmer JK, Wilkins TD. Degradation of polysaccharides by intestinal bacterial enzymes. *Am J Clin Nutr*. 1978; 31(10 Suppl):S128–S30. [PubMed: 707363]
85. Martens EC, Lowe EC, Chiang H, et al. Recognition and degradation of plant cell wall polysaccharides by two human gut symbionts. *PLoS Biol*. 2011; 9(12):e1001221. [PubMed: 22205877]
86. Finucane MM, Sharpton TJ, Laurent TJ, Pollard KS. A taxonomic signature of obesity in the microbiome? Getting to the guts of the matter. *PLoS One*. 2014; 9(1):e84689. [PubMed: 24416266]
87. Louis S, Tappu RM, Damms-Machado A, Huson DH, Bischoff SC. Characterization of the Gut Microbial Community of Obese Patients Following a Weight-Loss Intervention Using Whole Metagenome Shotgun Sequencing. *PLoS One*. 2016; 11(2):e0149564. [PubMed: 26919743]
88. Knoch B, Barnett MP, McNabb WC, et al. Dietary arachidonic acid-mediated effects on colon inflammation using transcriptome analysis. *Mol Nutr Food Res*. 2010; 54(Suppl 1):S62–74. [PubMed: 20440721]
89. Greiner T, Backhed F. Effects of the gut microbiota on obesity and glucose homeostasis. *Trends Endocrinol Metab*. 2011; 22(4):117–23. [PubMed: 21353592]
90. Lambris JD, Ricklin D, Geisbrecht BV. Complement evasion by human pathogens. *Nat Rev Microbiol*. 2008; 6(2):132–42. [PubMed: 18197169]
91. Birkinshaw RW, Kjer-Nielsen L, Eckle SB, McCluskey J, Rossjohn J. MAITs, MR1 and vitamin B metabolites. *Curr Opin Immunol*. 2014; 26:7–13. [PubMed: 24556396]
92. Abe R, Oda S, Sadahiro T, et al. Gram-negative bacteremia induces greater magnitude of inflammatory response than Gram-positive bacteremia. *Crit Care*. 2010; 14(2):R27. [PubMed: 20202204]
93. Amar J, Burcelin R, Ruidavets JB, et al. Energy intake is associated with endotoxemia in apparently healthy men. *Am J Clin Nutr*. 2008; 87(5):1219–23. [PubMed: 18469242]
94. Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des*. 2009; 15(13):1546–58. [PubMed: 19442172]
95. Laugerette F, Vors C, Peretti N, Michalski MC. Complex links between dietary lipids, endogenous endotoxins and metabolic inflammation. *Biochimie*. 2011; 93(1):39–45. [PubMed: 20433893]
96. Lajunen T, Vikatmaa P, Bloigu A, et al. Chlamydial LPS and high-sensitivity CRP levels in serum are associated with an elevated body mass index in patients with cardiovascular disease. *Innate Immun*. 2008; 14(6):375–82. [PubMed: 19039061]
97. Lassenius MI, Pietilainen KH, Kaartinen K, et al. Bacterial endotoxin activity in human serum is associated with dyslipidemia, insulin resistance, obesity, and chronic inflammation. *Diabetes Care*. 2011; 34(8):1809–15. [PubMed: 21636801]
98. Uematsu S, Matsumoto M, Takeda K, Akira S. Lipopolysaccharide-dependent prostaglandin E(2) production is regulated by the glutathione-dependent prostaglandin E(2) synthase gene induced by the Toll-like receptor 4/MyD88/NF-IL6 pathway. *J Immunol*. 2002; 168(11):5811–6. [PubMed: 12023384]
99. Blatteis CM, Li S, Li Z, Feleder C, Perlik V. Cytokines, PGE2 and endotoxin fever: a reassessment. *Prostaglandins Other Lipid Mediat*. 2005; 76(1–4):1–18. [PubMed: 15967158]
100. Killeen SD, Wang JH, Andrews EJ, Redmond HP. Bacterial endotoxin enhances colorectal cancer cell adhesion and invasion through TLR-4 and NF-kappaB-dependent activation of the urokinase plasminogen activator system. *Br J Cancer*. 2009; 100(10):1589–602. [PubMed: 19436306]
101. Xiao S, Fei N, Pang X, et al. A gut microbiota-targeted dietary intervention for amelioration of chronic inflammation underlying metabolic syndrome. *FEMS Microbiol Ecol*. 2014; 87(2):357–67. [PubMed: 24117923]

102. Kobayashi M, Saitoh S, Tanimura N, et al. Regulatory roles for MD-2 and TLR4 in ligand-induced receptor clustering. *J Immunol.* 2006; 176(10):6211–8. [PubMed: 16670331]
103. Godowski PJ. A smooth operator for LPS responses. *Nat Immunol.* 2005; 6(6):544–6. [PubMed: 15908933]
104. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes.* 2007; 56(7):1761–72. [PubMed: 17456850]
105. Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Loss of function mutation in toll-like receptor-4 does not offer protection against obesity and insulin resistance induced by a diet high in trans fat in mice. *J Inflamm (Lond).* 2011; 8(1):2. [PubMed: 21314942]
106. Reigstad CS, Lunden GO, Felin J, Backhed F. Regulation of serum amyloid A3 (SAA3) in mouse colonic epithelium and adipose tissue by the intestinal microbiota. *PLoS One.* 2009; 4(6):e5842. [PubMed: 19513118]
107. Carothers AM, Davids JS, Damas BC, Bertagnolli MM. Persistent cyclooxygenase-2 inhibition downregulates NF- κ B, resulting in chronic intestinal inflammation in the min/+ mouse model of colon tumorigenesis. *Cancer Res.* 2010; 70(11):4433–42. [PubMed: 20484034]
108. Liu L, Li YH, Niu YB, et al. An apple oligogalactan prevents against inflammation and carcinogenesis by targeting LPS/TLR4/NF- κ B pathway in a mouse model of colitis-associated colon cancer. *Carcinogenesis.* 2010; 31(10):1822–32. [PubMed: 20400476]
109. Murillo G, Nagpal V, Tiwari N, Benya RV, Mehta RG. Actions of vitamin D are mediated by the TLR4 pathway in inflammation-induced colon cancer. *J Steroid Biochem Mol Biol.* 2010; 121(1–2):403–7. [PubMed: 20214986]
110. Rakoff-Nahoum S, Medzhitov R. Toll-like receptors and cancer. *Nat Rev Cancer.* 2009; 9(1):57–63. [PubMed: 19052556]
111. Sitaraman SV, Klapproth JM, Moore DA 3rd, et al. Elevated flagellin-specific immunoglobulins in Crohn's disease. *Am J Physiol Gastrointest Liver Physiol.* 2005; 288(2):G403–6. [PubMed: 15388489]
112. Hayashi F, Smith KD, Ozinsky A, et al. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. *Nature.* 2001; 410(6832):1099–103. [PubMed: 11323673]
113. Steiner TS. How flagellin and toll-like receptor 5 contribute to enteric infection. *Infect Immun.* 2007; 75(2):545–52. [PubMed: 17118981]
114. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. *J Clin Gastroenterol.* 2006; 40(3):235–43. [PubMed: 16633129]
115. Soerensen KV, Thorning TK, Astrup A, Kristensen M, Lorenzen JK. Effect of dairy calcium from cheese and milk on fecal fat excretion, blood lipids, and appetite in young men. *Am J Clin Nutr.* 2014; 99(5):984–91. [PubMed: 24622806]
116. Ijiri D, Nojima T, Kawaguchi M, et al. Effects of feeding outer bran fraction of rice on lipid accumulation and fecal excretion in rats. *Biosci Biotechnol Biochem.* 2015; 79(8):1337–41. [PubMed: 25867004]
117. Rossi L, Kadamba P, Hugosson C, et al. Pediatric short bowel syndrome: adaptation after massive small bowel resection. *J Pediatr Gastroenterol Nutr.* 2007; 45(2):213–21. [PubMed: 17667718]
118. Snipes RL. Limited fat absorption in the large intestine of mice. A morphological study. *Acta Anat (Basel).* 1977; 99(4):435–9. [PubMed: 899707]
119. Erridge C, Attina T, Spickett CM, Webb DJ. A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. *Am J Clin Nutr.* 2007; 86(5):1286–92. [PubMed: 17991637]
120. Moreira AP, Texeira TF, Ferreira AB, Peluzio Mdo C, Alfenas Rde C. Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. *Br J Nutr.* 2012; 108(5):801–9. [PubMed: 22717075]
121. Everard A, Lazarevic V, Gaia N, et al. Microbiome of prebiotic-treated mice reveals novel targets involved in host response during obesity. *ISME J.* 2014 advance online publication, 3 April 2014: ismej.2014.45.
122. Nicholson JK, Holmes E, Kinross J, et al. Host-gut microbiota metabolic interactions. *Science.* 2012; 336(6086):1262–7. [PubMed: 22674330]

123. Deopurkar R, Ghanim H, Friedman J, et al. Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 and suppressor of cytokine signaling-3. *Diabetes Care*. 2010; 33(5):991–7. [PubMed: 20067961]
124. Ghanim H, Abuaysheh S, Sia CL, et al. Increase in plasma endotoxin concentrations and the expression of Toll-like receptors and suppressor of cytokine signaling-3 in mononuclear cells after a high-fat, high-carbohydrate meal: implications for insulin resistance. *Diabetes Care*. 2009; 32(12):2281–7. [PubMed: 19755625]
125. Morselli E, Frank AP, Palmer BF, et al. A sexually dimorphic hypothalamic response to chronic high-fat diet consumption. *Int J Obes (Lond)*. 2016; 40(2):206–9. [PubMed: 26073655]
126. Turnbaugh PJ, Ridaura VK, Faith JJ, et al. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci Transl Med*. 2009; 1(6):6ra14.
127. De Bandt J-P, Waligora-Dupriet A-J, Butel M-J. Intestinal microbiota in inflammation and insulin resistance: relevance to humans. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2011; 14(4):334–40. [PubMed: 21587065]
128. Lam YY, Ha CW, Hoffmann JM, et al. Effects of dietary fat profile on gut permeability and microbiota and their relationships with metabolic changes in mice. *Obesity (Silver Spring)*. 2015; 23(7):1429–39. [PubMed: 26053244]
129. Ghosh S, DeCoffe D, Brown K, et al. Fish oil attenuates omega-6 polyunsaturated fatty acid-induced dysbiosis and infectious colitis but impairs LPS dephosphorylation activity causing sepsis. *PLoS One*. 2013; 8(2):e55468. [PubMed: 23405155]
130. de Lima-Salgado TM, Alba-Loureiro TC, do Nascimento CS, Nunes MT, Curi R. Molecular mechanisms by which saturated fatty acids modulate TNF-alpha expression in mouse macrophage lineage. *Cell Biochem Biophys*. 2011; 59(2):89–97. [PubMed: 20809180]
131. Walton KL, Holt L, Sartor RB. Lipopolysaccharide activates innate immune responses in murine intestinal myofibroblasts through multiple signaling pathways. *Am J Physiol Gastrointest Liver Physiol*. 2009; 296(3):G601–11. [PubMed: 19136385]
132. Plummer SM, Hill KA, Festing MF, et al. Clinical development of leukocyte cyclooxygenase 2 activity as a systemic biomarker for cancer chemopreventive agents. *Cancer Epidemiol Biomarkers Prev*. 2001; 10(12):1295–9. [PubMed: 11751448]
133. Abnous K, Brooks SP, Kwan J, et al. Diets enriched in oat bran or wheat bran temporally and differentially alter the composition of the fecal community of rats. *J Nutr*. 2009; 139(11):2024–31. [PubMed: 19776187]
134. Hamer HM, Jonkers DM, Bast A, et al. Butyrate modulates oxidative stress in the colonic mucosa of healthy humans. *Clin Nutr*. 2009; 28(1):88–93. [PubMed: 19108937]
135. Peng L, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *J Nutr*. 2009; 139(9):1619–25. [PubMed: 19625695]
136. Suzuki T, Yoshida S, Hara H. Physiological concentrations of short-chain fatty acids immediately suppress colonic epithelial permeability. *Br J Nutr*. 2008; 100(2):297–305. [PubMed: 18346306]
137. Matarrese P, Petitta C, Scirocco A, et al. Antioxidants counteract lipopolysaccharide-triggered alterations of human colonic smooth muscle cells. *Free Radic Biol Med*. 2012; 53(11):2102–11. [PubMed: 23044262]
138. Pauwels EK. The protective effect of the Mediterranean diet: focus on cancer and cardiovascular risk. *Med Princ Pract*. 2011; 20(2):103–11. [PubMed: 21252562]
139. Romaguera D, Norat T, Vergnaud AC, et al. Mediterranean dietary patterns and prospective weight change in participants of the EPIC-PANACEA project. *Am J Clin Nutr*. 2010; 92(4):912–21. [PubMed: 20810975]
140. Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D. Mediterranean diet and weight loss: meta-analysis of randomized controlled trials. *Metab Syndr Relat Disord*. 2011; 9(1):1–12. [PubMed: 20973675]
141. Sidahmed E, Cornellier ML, Ren J, et al. Development of exchange lists for Mediterranean and Healthy Eating diets: implementation in an intervention trial. *J Hum Nutr Diet*. 2014; 27(5):413–25. [PubMed: 24112099]

142. Hu S, Wang Y, Lichtenstein L, et al. Regional differences in colonic mucosa-associated microbiota determine the physiological expression of host heat shock proteins. *Am J Physiol Gastrointest Liver Physiol*. 2010; 299(6):G1266–75. [PubMed: 20864653]
143. Booiijink CC, El-Aidy S, Rajilic-Stojanovic M, et al. High temporal and inter-individual variation detected in the human ileal microbiota. *Environ Microbiol*. 2010; 12(12):3213–27. [PubMed: 20626454]
144. Derrien M, Vaughan EE, Plugge CM, de Vos WM. *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *Int J Syst Evol Microbiol*. 2004; 54(Pt 5):1469–76. [PubMed: 15388697]
145. De Lisle RC, Roach E, Jansson K. Effects of laxative and N-acetylcysteine on mucus accumulation, bacterial load, transit, and inflammation in the cystic fibrosis mouse small intestine. *Am J Physiol Gastrointest Liver Physiol*. 2007; 293(3):G577–84. [PubMed: 17615175]
146. Gosiewski T, Strus M, Fyderek K, et al. Horizontal Distribution of the fecal microbiota in adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2012; 54(1):20–27. [PubMed: 21788912]
147. Sonnenburg JL, Xu J, Leip DD, et al. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. *Science*. 2005; 307(5717):1955–9. [PubMed: 15790854]
148. Koropatkin NM, Cameron EA, Martens EC. How glycan metabolism shapes the human gut microbiota. *Nat Rev Microbiol*. 2012; 10(5):323–35. [PubMed: 22491358]
149. Marcobal A, Barboza M, Sonnenburg ED, et al. Bacteroides in the infant gut consume milk oligosaccharides via mucus-utilization pathways. *Cell Host Microbe*. 2011; 10(5):507–14. [PubMed: 22036470]
150. Pudlo NA, Urs K, Kumar SS, et al. Symbiotic Human Gut Bacteria with Variable Metabolic Priorities for Host Mucosal Glycans. *MBio*. 2015; 6(6):e01282–15. [PubMed: 26556271]
151. Yasuda K, Oh K, Ren B, et al. Biogeography of the intestinal mucosal and luminal microbiome in the rhesus macaque. *Cell Host Microbe*. 2015; 17(3):385–91. [PubMed: 25732063]
152. Albenberg L, Esipova TV, Judge CP, et al. Correlation between intraluminal oxygen gradient and radial partitioning of intestinal microbiota. *Gastroenterology*. 2014; 147(5):1055–63 e8. [PubMed: 25046162]
153. Boland CR, Montgomery CK, Kim YS. A cancer-associated mucin alteration in benign colonic polyps. *Gastroenterology*. 1982; 82(4):664–72. [PubMed: 6800870]
154. Grivennikov SI, Karin M. Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. *Ann Rheum Dis*. 2011; 70(Suppl 1):i104–8. [PubMed: 21339211]
155. Smirnova MG, Guo L, Birchall JP, Pearson JP. LPS up-regulates mucin and cytokine mRNA expression and stimulates mucin and cytokine secretion in goblet cells. *Cell Immunol*. 2003; 221(1):42–9. [PubMed: 12742381]
156. Plaisancie P, Ducroc R, El Homs M, et al. Luminal leptin activates mucin-secreting goblet cells in the large bowel. *Am J Physiol Gastrointest Liver Physiol*. 2006; 290(4):G805–12. [PubMed: 16455789]
157. Smirnova MG, Kiselev SL, Birchall JP, Pearson JP. Up-regulation of mucin secretion in HT29-MTX cells by the pro-inflammatory cytokines tumor necrosis factor- α and interleukin-6. *Eur Cytokine Netw*. 2001; 12(1):119–25. [PubMed: 11282555]
158. El Homs M, Ducroc R, Claustre J, et al. Leptin modulates the expression of secreted and membrane-associated mucins in colonic epithelial cells by targeting PKC, PI3K, and MAPK pathways. *Am J Physiol Gastrointest Liver Physiol*. 2007; 293(1):G365–73. [PubMed: 17495032]
159. Jarry A, Vallette G, Branka JE, Labois C. Direct secretory effect of interleukin-1 via type I receptors in human colonic mucous epithelial cells (HT29-C1.16E). *Gut*. 1996; 38(2):240–2. [PubMed: 8801204]
160. Enss ML, Cornberg M, Wagner S, et al. Proinflammatory cytokines trigger MUC gene expression and mucin release in the intestinal cancer cell line LS180. *Inflamm Res*. 2000; 49(4):162–9. [PubMed: 10858016]

161. Krimi RB, Kotelevets L, Dubuquoy L, et al. Resistin-like molecule beta regulates intestinal mucous secretion and curtails TNBS-induced colitis in mice. *Inflamm Bowel Dis*. 2008; 14(7): 931–41. [PubMed: 18300276]
162. Rescigno M. The intestinal epithelial barrier in the control of homeostasis and immunity. *Trends Immunol*. 2011; 32(6):256–64. [PubMed: 21565554]
163. Gustafsson JK, Navabi N, Rodriguez-Pineiro AM, et al. Dynamic changes in mucus thickness and ion secretion during *Citrobacter rodentium* infection and clearance. *PLoS One*. 2013; 8(12):e84430. [PubMed: 24386378]
164. Macfarlane S, Woodmansey EJ, Macfarlane GT. Colonization of mucin by human intestinal bacteria and establishment of biofilm communities in a two-stage continuous culture system. *Appl Environ Microbiol*. 2005; 71(11):7483–92. [PubMed: 16269790]
165. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, et al. High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology*. 2009; 137(5):1716–24. e1–2. [PubMed: 19706296]
166. Steppan CM, Brown EJ, Wright CM, et al. A family of tissue-specific resistin-like molecules. *Proc Natl Acad Sci U S A*. 2001; 98(2):502–6. [PubMed: 11209052]
167. Yamauchi J, Kawai Y, Yamada M, et al. Altered expression of goblet cell- and mucin glycosylation-related genes in the intestinal epithelium during infection with the nematode *Nippostrongylus brasiliensis* in rat. *APMIS*. 2006; 114(4):270–8. [PubMed: 16689826]
168. Asano T, Sakosda H, Fujishiro M, et al. Physiological Significance of Resistin and Resistin-Like Molecules in the Inflammatory Process and Insulin Resistance. *Current Diabetes Reviews*. 2006; 2:449–54. [PubMed: 18220647]
169. Barnes SL, Vidrich A, Wang ML, et al. Resistin-like molecule beta (RELM beta/FIZZ2) is highly expressed in the ileum of SAMP1/YitFc mice and is associated with initiation of ileitis. *Journal of Immunology*. 2007; 179(10):7012–20.
170. Hogan SP, Seidu L, Blanchard C, et al. Resistin-like molecule beta regulates innate colonic function: Barrier integrity and inflammation susceptibility. *Journal of Allergy and Clinical Immunology*. 2006; 118(1):257–68. [PubMed: 16815164]
171. Renigunta A, Hild C, Rose F, et al. Human RELM beta is a mitogenic factor in lung cells and induced in hypoxia. *FEBS letters*. 2006; 580(3):900–3. [PubMed: 16427636]
172. Endo H, Hosono K, Fujisawa T, et al. Involvement of JNK pathway in the promotion of the early stage of colorectal carcinogenesis under high-fat dietary conditions. *Gut*. 2009; 58(12):1637–43. [PubMed: 19570763]
173. Everard A, Belzer C, Geurts L, et al. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A*. 2013; 110(22):9066–71. [PubMed: 23671105]
174. Underwood MA. Intestinal dysbiosis: Novel mechanisms by which gut microbes trigger and prevent disease. *Prev Med*. 2014; 65C:133–7.
175. Shin NR, Lee JC, Lee HY, et al. An increase in the *Akkermansia* spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut*. 2014; 63(5): 727–35. [PubMed: 23804561]
176. Cohen J. The detection and interpretation of endotoxaemia. *Intensive Care Med*. 2000; 26(Suppl 1):S51–6. [PubMed: 10786959]
177. Novitsky TJ. Limitations of the *Limulus* amoebocyte lysate test in demonstrating circulating lipopolysaccharides. *Ann N Y Acad Sci*. 1998; 851:416–21. [PubMed: 9668634]
178. Moreno-Navarrete JM, Escote X, Ortega F, et al. A role for adipocyte-derived lipopolysaccharide-binding protein in inflammation- and obesity-associated adipose tissue dysfunction. *Diabetologia*. 2013; 56(11):2524–37. [PubMed: 23963324]
179. Vreugdenhil AC, Dentener MA, Snoek AM, Greve JW, Buurman WA. Lipopolysaccharide binding protein and serum amyloid A secretion by human intestinal epithelial cells during the acute phase response. *J Immunol*. 1999; 163(5):2792–8. [PubMed: 10453023]
180. Laugerette F, Furet JP, Debarb C, et al. Oil composition of high-fat diet affects metabolic inflammation differently in connection with endotoxin receptors in mice. *Am J Physiol Endocrinol Metab*. 2012; 302(3):E374–86. [PubMed: 22094473]

181. Sun L, Yu Z, Ye X, et al. A marker of endotoxemia is associated with obesity and related metabolic disorders in apparently healthy Chinese. *Diabetes Care*. 2010; 33(9):1925–32. [PubMed: 20530747]
182. Elsing C, Ernst S, Kayali N, Stremmel W, Harenberg S. Lipopolysaccharide binding protein, interleukin-6 and C-reactive protein in acute gastrointestinal infections: value as biomarkers to reduce unnecessary antibiotic therapy. *Infection*. 2011; 39(4):327–31. [PubMed: 21523403]
183. Schumann RR. Old and new findings on lipopolysaccharide-binding protein: a soluble pattern-recognition molecule. *Biochem Soc Trans*. 2011; 39(4):989–93. [PubMed: 21787335]
184. Laugerette F, Alligier M, Bastard JP, et al. Overfeeding increases postprandial endotoxemia in men: Inflammatory outcome may depend on LPS transporters LBP and sCD14. *Mol Nutr Food Res*. 2014; 58(7):1513–8. [PubMed: 24687809]
185. Garcia de Guadiana-Romualdo L, Espanol-Morales I, Cerezuela-Fuentes P, et al. Value of lipopolysaccharide binding protein as diagnostic marker of infection in adult cancer patients with febrile neutropenia: comparison with C-reactive protein, procalcitonin, and interleukin 6. *Support Care Cancer*. 2015; 23(7):2175–82. [PubMed: 25564222]
186. Gonzalez-Quintela A, Alonso M, Campos J, et al. Determinants of serum concentrations of lipopolysaccharide-binding protein (LBP) in the adult population: the role of obesity. *PLoS One*. 2013; 8(1):e54600. [PubMed: 23349936]
187. Umoh FI, Kato I, Ren J, et al. Markers of systemic exposures to products of intestinal bacteria in a dietary intervention study. *Eur J Nutr*. 2016; 55(2):793–8. [PubMed: 25903259]
188. Lamping N, Dettmer R, Schroder NW, et al. LPS-binding protein protects mice from septic shock caused by LPS or gram-negative bacteria. *J Clin Invest*. 1998; 101(10):2065–71. [PubMed: 9593762]
189. Vreugdenhil AC, Rousseau CH, Hartung T, et al. Lipopolysaccharide (LPS)-binding protein mediates LPS detoxification by chylomicrons. *J Immunol*. 2003; 170(3):1399–405. [PubMed: 12538700]
190. Moss CW, Daneshvar MI. Identification of some uncommon monounsaturated fatty acids of bacteria. *J Clin Microbiol*. 1992; 30(9):2511–2. [PubMed: 1401029]
191. Wollenweber HW, Rietschel ET, Hofstad T, Weintraub A, Lindberg AA. Nature, type of linkage, quantity, and absolute configuration of (3-hydroxy) fatty acids in lipopolysaccharides from *Bacteroides fragilis* NCTC 9343 and related strains. *J Bacteriol*. 1980; 144(3):898–903. [PubMed: 7440508]
192. Brondz I, Olsen I, Haapasalo M, Van Winkelhoff AJ. Multivariate analyses of fatty acid data from whole-cell methanolysates of *Prevotella*, *Bacteroides* and *Porphyromonas* spp. *J Gen Microbiol*. 1991; 137(6):1445–52. [PubMed: 1919518]
193. Leppanen HK, Taubel M, Roponen M, et al. Determinants, reproducibility, and seasonal variation of bacterial cell wall components and viable counts in house dust. *Indoor Air*. 2015; 25(3):260–72. [PubMed: 24992650]
194. Sonesson A, Larsson L, Schutz A, Hagmar L, Hallberg T. Comparison of the limulus amebocyte lysate test and gas chromatography-mass spectrometry for measuring lipopolysaccharides (endotoxins) in airborne dust from poultry-processing industries. *Appl Environ Microbiol*. 1990; 56(5):1271–8. [PubMed: 2187411]
195. Szponar B, Krasnik L, Hryniewiecki T, Gamian A, Larsson L. Distribution of 3-hydroxy fatty acids in tissues after intraperitoneal injection of endotoxin. *Clinical chemistry*. 2003; 49(7):1149–53. [PubMed: 12816912]
196. Binding N, Jaschinski S, Werlich S, Bletz S, Witting U. Quantification of bacterial lipopolysaccharides (endotoxin) by GC-MS determination of 3-hydroxy fatty acids. *J Environ Monit*. 2004; 6(1):65–70. [PubMed: 14737472]
197. Huang JY, Lee SM, Mazmanian SK. The human commensal *Bacteroides fragilis* binds intestinal mucin. *Anaerobe*. 2011; 17(4):137–41. [PubMed: 21664470]
198. Wu S, Rhee KJ, Albesiano E, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. *Nat Med*. 2009; 15(9):1016–22. [PubMed: 19701202]

199. Toprak NU, Yagci A, Gulluoglu BM, et al. A possible role of *Bacteroides fragilis* enterotoxin in the aetiology of colorectal cancer. *Clin Microbiol Infect*. 2006; 12(8):782–6. [PubMed: 16842574]
200. Osipov GA, Verkhovtseva NV. Study of human microecology by mass spectrometry of microbial markers. *Beneficial Microbes*. 2011; 2(1):63–78. [PubMed: 21831791]
201. Szponar B, Larsson L, Domagala-Kulawik J. Endotoxin markers in bronchoalveolar lavage fluid of patients with interstitial lung diseases. *Multidiscip Respir Med*. 2012; 7(1):54. [PubMed: 23259971]
202. Ferrando R, Szponar B, Sanchez A, Larsson L, Valero-Guillen PL. 3-Hydroxy fatty acids in saliva as diagnostic markers in chronic periodontitis. *J Microbiol Methods*. 2005; 62(3):285–91. [PubMed: 15941605]
203. Krasnik L, Szponar B, Walczak M, Larsson L, Gamian A. Routine clinical laboratory tests correspond to increased serum levels of 3-hydroxy fatty acids, markers of endotoxins, in cardiosurgery patients. *Arch Immunol Ther Exp (Warsz)*. 2006; 54(1):55–60. [PubMed: 16642258]
204. Chen YS, Lin HH, Liu PJ, et al. Use of 3-hydroxy fatty acid concentrations in a murine air pouch infection model as a surrogate marker for LPS activity: a feasibility study using environmental *Burkholderia cenocepacia* isolates. *J Microbiol Methods*. 2011; 87(3):368–74. [PubMed: 22008505]
205. de Bont N, Netea MG, Rovers C, et al. LPS-induced release of IL-1 beta, IL-1Ra, IL-6, and TNF-alpha in whole blood from patients with familial hypercholesterolemia: no effect of cholesterol-lowering treatment. *J Interferon Cytokine Res*. 2006; 26(2):101–7. [PubMed: 16487030]
206. Oku H, Onotogi M, Nagata J, Wada K, Chinen I. Selective use of L-valine and L-isoleucine for the biosynthesis of branched-chain fatty acids in rat skin. *Biosci Biotechnol Biochem*. 1995; 59(5):891–5. [PubMed: 7787304]
207. Ran-Ressler RR, Bae S, Lawrence P, Wang DH, Brenna JT. Branched-chain fatty acid content of foods and estimated intake in the USA. *Br J Nutr*. 2014; 112(4):565–72. [PubMed: 24830474]
208. Lopez-Yglesias AH, Zhao X, Quarles EK, et al. Flagellin induces antibody responses through a TLR5- and inflammasome-independent pathway. *J Immunol*. 2014; 192(4):1587–96. [PubMed: 24442437]
209. Lodes MJ, Cong Y, Elson CO, et al. Bacterial flagellin is a dominant antigen in Crohns disease. *J Clin Invest*. 2004; 113(9):1296–306. [PubMed: 15124021]
210. Ziegler TR, Luo M, Estivariz CF, et al. Detectable serum flagellin and lipopolysaccharide and upregulated anti-flagellin and lipopolysaccharide immunoglobulins in human short bowel syndrome. *Am J Physiol Regul Integr Comp Physiol*. 2008; 294(2):R402–10. [PubMed: 18003793]
211. Yang B, Bostick RM, Tran HQ, et al. Circulating Biomarkers of Gut Barrier Function: Correlates and Nonresponse to Calcium Supplementation among Colon Adenoma Patients. *Cancer Epidemiol Biomarkers Prev*. 2016; 25(2):318–26. [PubMed: 26677212]
212. Kong SY, Tran HQ, Gewirtz AT, et al. Serum Endotoxins and Flagellin and Risk of Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort. *Cancer Epidemiol Biomarkers Prev*. 2016; 25(2):291–301. [PubMed: 26823475]
213. Kato I, Boleij A, Kortman GA, et al. Partial associations of dietary iron, smoking and intestinal bacteria with colorectal cancer risk. *Nutr Cancer*. 2013; 65(2):169–77. [PubMed: 23441604]
214. Yu LX, Yan HX, Liu Q, et al. Endotoxin accumulation prevents carcinogen-induced apoptosis and promotes liver tumorigenesis in rodents. *Hepatology*. 2010; 52(4):1322–33. [PubMed: 20803560]
215. Roderburg C, Luedde T. The role of the gut microbiome in the development and progression of liver cirrhosis and hepatocellular carcinoma. *Gut Microbes*. 2014; 5(4):441–5. [PubMed: 25006881]
216. Marks MA, Rabkin CS, Engels EA, et al. Markers of microbial translocation and risk of AIDS-related lymphoma. *AIDS*. 2013; 27(3):469–74. [PubMed: 23169327]

FIGURE 1.

Overview of processes contributing to pro-inflammatory states and increased cancer risk. Western diets low in plant-based foods and high in saturated fats favor excess energy intakes and obesity. This results in increased absorption of bacterial products that contribute to a chronic, pro-inflammatory state that in turn increases risks of cancer, cardiovascular diseases and diabetes.