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Mechanisms of Obesity-induced Gastrointestinal Neoplasia

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Abstract

Obesity is among the fastest growing diseases worldwide; treatment is inadequate and associated disorders, including gastrointestinal cancers, have high morbidity and mortality. An increased understanding of the mechanisms of obesity-induced carcinogenesis is required to develop methods to prevent or treat these cancers. We review the mechanisms of obesity-associated colorectal, esophageal, gastric, and pancreatic cancers and potential treatment strategies.

Keywords

obesity; colorectal cancer; esophageal cancer; gastric cancer; pancreatic cancer; gastrointestinal cancer; mechanisms

Introduction

The World Health Organization defines obesity as “abnormal or excessive fat accumulation to the extent that health is impaired.[1]” Obesity is the fastest growing lethal disease in the Western and developing worlds. People do not die from obesity itself but from its complications, which shorten life span.[2] Up to 20% of all cancers can be attributed to obesity.[3, 4] Since there are few effective therapies for obesity beside bariatric surgery, it is appropriate to define preventive measures for obesity-associated cancer. Obesity and

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increased waist circumference increase the risk of gastrointestinal (GI) cancers, which include colon, esophageal, gastric, and pancreatic cancers (Figure 1). We review possible mechanisms for the association between obesity and GI cancer initiation and progression, based on human and preclinical studies.

A single mechanism is unlikely to be responsible for all obesity-associated tumors. Mechanisms that contribute to the multiple complications of obesity are likely to include the insulin and insulin-like growth factor (IGF) signaling pathways, adipokines, inflammation and immune responses, and the GI microbiota. However, different tissues have different mechanisms of obesity-associated carcinogenesis. Obesity is associated with the metabolic syndrome, which comprises insulin resistance, altered lipid levels, and increased blood pressure. Metabolic syndrome is more strongly associated with GI cancers than is obesity.

However, not all obese individuals, even those with severe disease, develop these complications,[5] so it is important to identify those at risk. Increasing our understanding of the mechanisms for obesity complications should lead to the discovery of biomarkers of risk. Furthermore, obese patients also have a poor prognosis when diagnosed with GI cancers.[6]

Insulin and IGF1 Signaling

Insulin is a mitogenic hormone believed to affect cancer development. Since the discovery of insulin, researchers have proposed associations between type 2 diabetes and cancer, despite equivocal and controversial evidence.[7, 8] Clarification of this association requires separation of the effects of concurrent hyperinsulinemia, hyperglycemia, their shared risk factors, and the IGF1 signaling pathway.

Obese patients frequently have hyperinsulinemia, independently of type 2 diabetes, presumably based on their increased need for energy regulation of metabolic processes.[9] Insulin is anabolic in muscle, adipose tissue, and liver, to increase tissue mass, augment glucose uptake, and synthesize nutrients respectively. These anabolic effects are not directly related to carcinogenesis. Insulin-deficient diabetic animals are protected from cancer formation but this has not been reported in humans.[10] Insulin-sensitive tissues such as liver, adipose tissue, and muscle infrequently develop malignancies, suggesting that insulin regulation of metabolic processes might protect against carcinogenesis.[11] Hyperglycemia also can increase the availability of nutrients to cancer cells, which metabolize glucose via the Warburg effect, in which cancer cells produce energy via a high rate of glycolysis, followed by lactic acid fermentation in the cytosol, rather than by a comparatively low rate of glycolysis, followed by oxidation of pyruvate in mitochondria.[12, 13] Furthermore, diabetes and cancer are common diseases that develop in adults and share risk factors, including inactivity and an unhealthy diet.[14] Epidemiology studies have clearly associated type 2 diabetes with GI cancers. The molecular basis for this association is unclear, but could involve IGF1 signaling, which is mitogenic under conditions of hyperglycemia and/or hyperinsulinemia, independently of the metabolic features of type 2 diabetes.

IGF1 and GI Cancers—IGF1 production by the liver is stimulated by pituitary growth hormone, in response to hypothalamic integration of nutrient balance during periods of growth. IGF1 stimulates cell division and inhibits apoptosis and could therefore contribute to cancer development and metastasis.[15] Excess production of IGF1 in patients with acromegaly increases their incidence to aggressive colon cancer,[16] whereas individuals with IGF1 deficiency (Laron syndrome) are protected from cancer development.[17, 18] Obese patients have been reported with higher circulating levels of IGF1 than non-obese individuals, in the presence of hyperinsulinemia.[19]

Human liver produces multiple isoforms of IGF; IGF1 is the most highly abundant isoform in circulation. IGF1 is transported in blood via IGF binding proteins (IGFBPs), predominantly bound by IGFBP3 in humans. The IGFs bind IGF receptors (IGFRs) and the insulin receptor (IR) as well as alternatively spliced combinations of their respective subunits. For the purposes of this review we shall focus on IGF1 action on IGF1R

IGF1R expression and activity vary among human tissues. The GI expresses IGF1R, and this expression is altered in the mucosa and submucosa of involved intestinal areas of patients with Crohn's disease.[20] In the gut, IGF1 appears to modulate nutrient uptake through endocrine and neural pathways.[21] The remarkable ability of the intestine to regenerate enterocytes depends on IGF1 and other signals.

IGF1R expression varies among tumor cells, and can have paracrine and autocrine effects that promote tumorigenesis and metastasis.[22] IGF1 signals via its receptor to insulin receptor substrate 1, phosphatidylinositol 3-kinase (PI3K), AKT, and mammalian target of rapamycin (mTOR) to stimulate cell proliferation.[23] These shared features of IGF1 and insulin signaling provide evidence for conservation of proliferation signaling pathways in response to nutrient excess. Divergent effects of insulin and IGF1 signaling result from heterogeneity in IGFR expression during development (prenatal vs postnatal) and in different tissues.[24] In insulin-sensitive tissues, IGF1 signals through the Ras–mitogen activated kinase-like protein (MAPK) pathway to stimulate proliferation, rather than inducing FOXO1 transcriptional activity, which regulates metabolism.[23, 24] Continuous exposure of cells to IGF1 could promote tumorigenesis through the Ras–MAPK pathway.[25, 26]

The cellular actions of IGF1 can be inhibited by hormones such as somatostatin, by scavenging circulating IGF1 or blocking IGF1R. Monoclonal antibodies against IGF1 have been shown to inhibit colorectal cancer (CRC) stem cells in mice.[27] Studies are underway to test the effects of monoclonal antibodies that block circulating IGF1 or IGF1R in patients with cancer and high serum levels of IGF.

Ligand-targeting agents, such as octreotide, have been limited by the large reservoir of circulating IGF1 bound to IGFBP3 and other proteins.[28] The antibody CP-751781, which blocks IGF1R, was tested in a phase 1 dose-escalation study of 6 patients with colorectal cancer with acceptable tolerability, expected side effects of hyperglycemia and preliminary evidence of efficacy at the highest dose of 20 mg/kg.[29, 30] Subsequent studies showed modest success in patients with non-small cell lung cancers that express IGF1.[31]

Adipokines—Adipose tissues synthesize and secrete many polypeptide growth factors and cytokines known as adipokines. Adipokines are produced mainly by white adipose tissue preadipocytes and mature adipocytes. Numerous adipokines have been reported to alter metabolic cellular function in rodents and humans.[32] Altered of leptin and adiponectin have been associated with GI cancers; changes have also been reported in levels of resistin, although these findings are unconvincing.[33]

Leptin is a 16-KDa non-glycosylated protein encoded by *LEP;* it was originally described as a regulator of energy balance via the hypothalamus.[34] Leptin is secreted by adipocytes, in proportion to white adipose tissue mass; more is produced by subcutaneous than visceral tissue.[35] Concentrations of circulating leptin, bound to plasma proteins, vary from 5 to 10 ng/ml in normal-weight individuals, and also vary with obesity and pregnancy.[36]

Factors that alter leptin production and action include insulin, estrogen, and inflammatory mediators such as IL1B, IL6, and TNFα.[37] Lipopolysaccharides (LPS) (membrane components of gram-negative bacteria) also increase leptin expression in white adipose

tissue.[38] Agents that block the β3 adrenergic receptor, free fatty acids, growth hormone, and peroxisome proliferator-activated receptor (PPAR) agonists reduce leptin secretion. Leptin binds to transmembrane receptors on stomach and colon cancer cells, resulting in activation of the JAK–STAT, MAPK, PI3K–AKT, insulin receptor substrate, and mTOR signaling pathways.[39]

Many GI tissues, cancer cell lines, and immune cells express a functional leptin receptor (LEPR or OB-R).[40] Some tumors even express leptin and its receptor, to allow for autocrine signaling.[41] Leptin stimulates cellular proliferation, migration, and invasion of tumor cells and inhibits apoptosis. Leptin also increases cytokine release from macrophages and increases insulin resistance.[42] Leptin produced by adipose tissue can affect adjacent tumors.[43] Leptin is involved in angiogenesis and can activate aromatase in adipose tissue.[44] Furthermore, since leptin inhibits the activity of T regulatory (Treg) cells, it can regulate immune surveillance of GI cancers.[45] Clearly, leptin's diverse biologic functions make it a good candidate for a mediator of cancer development and progression.

Adiponectin is a 30 kDa polypeptide with a C-terminal globular domain similar to TNFα. Circulating concentrations of adiponectin are 3–30ng/ml. Adiponectin occurs as a monomer that can form low- and high-molecular weight multimeric oligomers with biologic activities.[46] Multiple circulating active forms of this hormone complicate analysis of adiponectin concentrations in obesity. These forms show an integrated pulsatile diurnal rhythm which is paralleled by leptin-binding protein concentrations.[47] Adiponectin is expressed in differentiated adipocytes, at higher concentrations in subcutaneous than visceral adipose tissue, and in an inverse association with total body fat mass.[48] Transcription of *ADIPOQ* and secretion of the protein are stimulated by IGF1 and PPARγ agonists, and inhibited by TNFα, IL6, or glucocorticoids.[49, 50]

Adiponectin interacts with its receptors 1 and 2 to increase insulin sensitivity.[51] Adiponectin also has anti-proliferative and angiogenic effects.[52] Many cancers express adiponectin receptors, including gastric, colon, and pancreatic tumors.[40, 53, 54] In rodents, adiponectin prevents NFκB-dependent expression of the inflammatory cytokines TNFα, interferon-γ, and IL6.[55] Adiponectin inhibits IL6 and increases IL10 and TIMP1 activity mediated by the AMPK pathway.[56] Overall, the actions of adiponectin and leptin on cell functions tend to balance each other out.[57]

The anti-inflammatory effects of adiponectin are supported by an observed inverse correlation between plasma levels of adiponectin and c-reactive protein in obese diabetic and non-diabetic individuals.[46] Adiponectin also blocks LPS-stimulated production of TNFα by macrophage, inhibits toll-like receptor-mediated activation of NFκB,[58] and increases M2-type macrophage, while reducing markers of M1 types.[59] Since chronic inflammation promotes carcinogenesis in many GI organs, these anti-inflammatory effects of adiponectin may be important in limiting cancer risk.

Sex Hormones—Epidemiologic studies suggest differences in complications from obesity in men vs women, potentially due to altered distribution of adipose tissue mass between the sexes, which determines differences in plasma levels of sex hormones (Figure 1). For example, the increased incidence of post-menopausal breast cancer in obese women (compared with non-obese women) could be explained in part by their higher circulating levels of estrogen. This results from greater aromatization of androgenic precursors to estradiol via increased adipose tissue activity of cytochrome P450 aromatase.[60] Men have a higher incidence of CRC than women of the same age; post-menopausal estrogen replacement therapy reduces the incidence of CRC—particularly of estrogen receptor 3 tumors.[61, 62]

Genetic Factors—Sixty five to 80% of the variation in body mass index (BMI) is determined by genetic factors.[63] Gene polymorphisms that affect insulin signaling have been associated with body size.[64] Potential genetic factors predisposing to obesity also may enhance some cancers.[65] Genome-wide association studies have described altered "macrophage-enriched metabolic network genes", [66, 67] and have explored mutual candidate genes in selected areas of the genome. To our knowledge, genome-wide epigenetic studies have not revealed changes pertinent to mechanisms of neoplasia involved in obesity. The most powerfully associated single-nucleotide polymorphism associated with increased body mass is the fat mass and obesity-related (FTO) gene, which may function through nutrient sensing but with no relation to GI cancers.[68]

Inflammation—Inflammatory responses may be beneficial, limited with minimal impact, or pathologic with dysregulated immune function. Obesity is associated with chronic low-grade inflammation (also called meta-inflammation), characterized by abnormal cytokine production, immune activation, and increased inflammatory signaling. This chronic inflammation is more pronounced in the visceral than subcutaneous fat compartments. In obese individuals, adipocytes, preadipocytes, and surrounding stromal macrophages release inflammatory cytokines and chemokines, including IL17, IL22, TNFα, IL6, and the chemoattractant MCP-1 (Figure 2).[69] These factors have a role in cancer.[70] Although the NLRP-inflammosome is involved in obesity and cancer in rodents, it might not be in humans.[71] It is not clear these immune and inflammatory proteins act on GI tissues through the circulation. Increased levels of leukocyte calprotectin in the feces of obese otherwise healthy individuals indicate the presence of low-grade intestinal inflammation.[72] Reduced levels of IL8, TNFα, MCP1, and T-cell infiltration were observed in colonic biopsies of obese patients after weight loss.[73]

In obese patients, chronic inflammation appears in the GI tract, liver (steatohepatitis), vasculature, and pancreas.[74] Obesity increases the size of adipocytes, leading to their necrosis and subsequent accumulation of activated macrophages that appear, histologically, as crown-like structures.[75] These secrete inflammatory mediators, including IL6, MCP1, and TNFα, which have been implicated in development of insulin resistance.[76, 77] This inflammation is accompanied by upregulation of the anti-inflammatory factors IL10, IL4, and TGFβ. Adipose tissue in obese patients has a restricted T-cell receptor repertoire, containing fewer Treg cells than adipose tissue in lean individuals.[78] The altered activity of Treg cells might increase inflammation in the adipose tissue to promote carcinogenesis.

If inflammation is an important determinant for obesity–associated cancer, could reducing inflammation lower cancer risk? Inflammation might be reduced by weight loss,[79, 80] exercise, drugs, or diets designed to reduce inflammation—such as those high in omega-3 fatty acids[81]. Reducing adipose tissue inflammation reduces insulin resistance and could alter adipokine concentrations or the intestinal microbiota in obese individuals, but no study has examined such effects on GI carcinogenesis.

It is important to recognize that not all obese individuals have these inflammatory complications, and to ask whether macrophage activation is an initiator or effector of adipose inflammation. Some individuals appear to have metabolically benign obesity,[82] assisted by a protective effect of abdominal superficial fat.[83] Whether such individuals are relatively protected from GI cancers is unknown.

Endotoxemia—Endotoxemia is an important component of obesity-associated inflammation, resulting in uptake across the intestinal epithelium of LPS. In humans a high-fat diet increases, whereas a prudent low-fat diet reduces, endotoxemia.[84] Endotoxemia can result from increased intestinal permeability, increased levels of LPS-containing bacteria in

the intestine, or both. Researchers have not clearly determined the mechanisms of endotoxemia in obese individuals, and it is not clear whether endotoxemia affects GI carcinogenesis.

Intestinal Microbiota—High-fat diets do not lead to obesity or insulin resistance in germ-free mice, whereas transfer of fecal contents from obese to germ-free mice increased their fat cell mass, indicating a role for the intestinal microbiota in obesity.[85] Furthermore, transfer of microbiota from human twins, discordant for obesity, to mice altered metabolism in the mice.[86] The intestinal microbiota might contribute to obesity via its capacity to increase caloric salvage of indigestible dietary polysaccharides, or by regulating intestinal genes that increase fat storage in adipose tissues.[87] A high-fat diet might also induce GI inflammation[88]—partially through induction of toll-like receptor 4,[89] accompanied by LPS uptake and endotoxemia,[90] which could contribute to obesity-associated GI carcinogenesis.

Although the fecal microbiota can differ between obese and lean individuals,[91, 92] the changes are inconsistent. The abundance of bacteroides species and the ratio of bacteroides to firmacutes are reduced with weight loss[93] and bariatric surgery[94] in obese subjects, but this observation has been inconsistent.[95] Local host factors are important, because experimentally induced GI inflammation can alter gut microbiota.[96] Bacterial transformation of bile acids in the colonic lumen could act on mucosal epithelia and host metabolism. It is not clear if these changes can be used in strategies to prevent or treat CRC.

Overall, human studies have not clarified the role of microbiota in the development or maintenance of obesity. Transfer of fecal microbiota from non-diabetic subjects into the small intestine of diabetics induced a small but significant change in insulin resistance, indicating that the microbiota might be manipulated to treat diabetes.[97] Fecal transplantation is frequently used to treat patients with chronic relapsing *C difficile* infection.[98] The composition of the intestinal microbiota affects tissues other than the small and large intestine, and could be involved in development of esophageal, gastric, and even pancreatic neoplasms.

CRC

Approximately 1.2 million new cases of CRC are diagnosed annually worldwide, with almost 600,000 deaths.[99] CRC has the highest incidence and mortality among GI cancers. Epidemiologic studies have correlated obesity with CRC. A meta-analysis showed that in men, an increase of 5kg/m^2 in BMI confers a relative risk (RR) of 1.24 for colon cancer.[3] However, in women, the relationship between BMI and cancer risk is complicated by difference in fat distribution. A pooled analysis associated waist circumference and waist—hip ratio with sex-related differences in risk of colon cancer.[100] There is a statistically significant difference in the effects of waist circumference on cancer risk (stronger association for men than women), but not for waist-hip-ratio. In men, BMI > 35 increases the risk of dying from hepato-digestive cancers. However, the effects of obesity on the early stages of colon carcinogenesis require clarification. In animal models of colon cancer, obesity and energy restriction affect development of aberrant crypt foci (ACF).[101] The mechanisms that mediate the association between obesity and colorectal cancer are complex and are likely to involve insulin and IGF signaling, adipokines, and inflammation (Figure 3).

Insulin and IGF Signaling—IGFRs are expressed in the mucosal and muscular layers of the normal colon, and are important for colonocyte metabolism. Insulin stimulates proliferation of cultured colonocytes and CRC cells directly, by binding IGFR to activate signaling via the MAPK pathway, or indirectly, by increasing concentrations of IGF1.[25, 102, 103]

Colon cancer cells overexpress IGFIR[104]; binding of IGF1 to its receptor inhibits apoptosis, increases proliferation, and contributes to the development, progression, and metastatic potential of CRC.[26, 105-107]

In $Apc^{Min/+}$ mice, IGF1 showed a stage-specific effect on colorectal carcinogenesis, increasing proliferation in preneoplastic, but not in normal epithelial cells.[108] Increased plasma levels of IGF1 and hyperinsulinemia appeared also to induce development of dysplastic ACF.[109]

Adipokines—Leptin stimulates the proliferation, migration, and invasion of tumor cells. The proliferative and survival effects of leptin are mediated by the Ob-R–signal transducer and activator of transcription 3 (STAT3) pathway in colon cancers in mice.[110] Moreover, leptin can stimulate invasive activity of cell lines derived from colonic adenomas, increasing their metastatic potential.[111] Leptin induces production of inflammatory cytokines by colonocytes.[112-114]

Most data from humans on the effects of leptin relate to CRC risk and prognosis, but epidemiologic data are unconvincing. Leptin concentrations were associated with increased risk of CRC in men but not women in 2 nested control studies.[115, 116] However, leptin levels were associated with increased risk in women in other studies,[117, 118] although these did not account for lifestyle factors, body fat distribution, and metabolic markers. A European Prospective Investigation into Cancer and nutrition (EPIC) cohort nested case-control study found no relation between leptin concentrations and CRC risk, but a strong inverse relationship between soluble leptin receptor (OB-R) concentrations and colon cancer in men.[119] A study from the Middle East reported higher levels of OB-R in adenomas and carcinomas than healthy colon tissues, which surprisingly were associated with increased survival.[120] Another study correlated high circulating levels of soluble OB-R with advanced-stage colon cancer, indicating an effect on cancer progression.[121] In contrast, in a recent large nested case-control study, plasma level of OB-R was not associated with overall risk of CRC.[122] Overall, serum levels of leptin have not been associated with progression-free survival of patients with CRC. Most of these studies appeared to be limited in design and small patient numbers; data associating colonic adenoma incidence and leptin concentrations were weak.[123]

Adiponectin–/– mice fed high-fat diets gained more weight and developed larger orthotopic colon tumors than control mice; subsequent administration of adiponectin reduced colon tumor growth.[124] In mice, lower levels of adiponectin and adiponectin receptor 1 expression were associated with a higher incidence of polyps under high-fat diet.[125] Furthermore, plasma levels of adiponectin were inversely related to numbers of preneoplastic ACF in patients,[109] whereas low levels of adiponectin were frequently observed in obese individuals and those with type 2 diabetes.[126] These lower levels are an independent risk reduction factor for the development of several tumors including colon cancer. A large prospective nested case–control study found an inverse association between plasma level of adiponectin and risk for CRC in men but not women.[122] These findings were confirmed by a meta-analysis showing a 2% decreased risk of colorectal neoplasms for each 1 μg/ml increment in adiponectin level, only in men.[127]

Different molecular weight adiponectins could have varying effects on development of colorectal neoplasia in obese individuals. In the EPIC cohort, a nested case-control study found that high-molecular weight adiponectin was not associated with increased CRC risk whereas non-nigh molecular weight adiponectin was inversely associated with CRC, even after adjusting for BMI and waist circumference.[128] The mechanisms for these contrasting

observations remain to be explained. Adiponectin polymorphisms have not clearly been related to colorectal neoplasia.

Inflammatory Factors

Studies addressing a direct relation between circulating inflammatory markers and CRC showed equivocal results. Patients with colorectal adenomas or CRC have increased levels of IL6 levels and may parallel tumor size.[129, 130] IL6-deficient mice develop smaller size and numbers of colonic adenomas following administration of azoxymethane and dextran sodium sulphate.[131] Furthermore, in the same model, a weekly dose of a neutralizing antibody against the IL6 receptor reduced average tumor numbers and size compared to control mice.[132]

In a study of a large cohort of CRC patients matched with healthy controls, Chan et al. associated increased risk of CRC with baseline plasma level soluble tumor necrosis factor receptor-2 (sTNFR2, a surrogate marker for TNFα), but not levels of IL6 nor c-reactive protein.[133] Interestingly, sTNFR2 is associated with increased insulin resistance, and in this study it was also related to increased BMI. Consumption of anti-inflammatory agents (aspirin and non-steroidal anti-inflammatory drugs) reduced risk of CRC among women with higher baseline levels of sTNFR-2.[133]

The inflammatory leukotriene D4 (LTD4) has also been proposed to be involved in development of CRC. LTD4 stimulates proliferation and reduces apoptosis in several non-transformed intestinal epithelial cell lines.[134, 135] Higher BMI is accompanied by higher levels of prostaglandin, whereas physical activity lowers the levels.[136]

Obesity and Molecular Pathways—Type II diabetes and obesity are influenced by genetic and functional variations in the WNT signaling pathway, important for energy metabolism.[137] Altered WNT signaling, mutations in RAS and RAF, DNA epigenetic changes and loss of function of p53 are all involved in development of CRC. Among other things, p53 and p21 regulate cell metabolism and energy balance. Loss of p53 function is a late event in carcinogenesis, leading to abnormalities in the regulation of cell energy and metabolism, including mTOR signaling.[138]

An analysis of 2 large databases (the Nurses' Health Study and the Health Professionals Follow-up Study) showed that tumors with 50% or more cells that stained positive for nuclear p53 were associated with significantly shorter cancer-specific survival in non-obese patients (BMIs<30), but were not associated with longer survival of patients with BMIs>30.[139] Obesity was significantly associated with increased mortality among patients with tumor cells that were negative for nuclear p53. The authors of this study subsequently associated loss of p21 from tumor cells with increased cancer-specific mortality among patients under 60 y of age.[140] In patients with BMIs>30, p21 expression reduced survival, as observed for p53. These findings associate p53 and p21 regulation with cancer cell metabolism and obesity.

Loss of 18q frequently occurs during late stages colorectal carcinogenesis; it is inversely associated with MSI and CpG island methylation. Data from 532 CRC samples without high MSI independently associated loss of 18q with BMIs>30.[141]

Furthermore, higher BMIs and physical inactivity were associated only with CRCs that were negative for β-catenin activation.[142] However, activation of β-catenin significantly increased cancer-specific and overall survival only in patients with BMIs ≥ 30. Physical activity after a diagnosis of CRC correlated with increased cancer-specific survival of patients with tumors that were negative for β-catenin activation.[143] The progression of colorectal tumors that are

negative for β-catenin activation appears to be dependent on the patient's energy balance after diagnosis is made. Tumors with active β-catenin may progress regardless of metabolic status—β-catenin might affect influence cell sensitivity to obesity, as well as to physical activity, during colon carcinogenesis. It is important to note that obesity-associated molecular changes in the colon could determine outcomes of patients with cancer, and be used to direct therapy. Finally, a recent increase in BMI (by 5 kg/m^2 increments) was associated with microsatellite stable and MSI-low, but not with MSI-high tumors.

Diet—The Western diet and life style are risk factors for CRC, although there is no direct proof for this association. Case-control studies have generally associated energy intake with colorectal cancer risk whereas cohort studies have not.[144, 145] Dietary glycemic load and CRC risk have been positively associated in cohort and case-control studies,[146] but the relationship between dietary fat and CRC have not been substantiated by epidemiology studies.[147] In obese individuals, hyperlipidermia could feed tumor anabolism. If obesity increases the risk for cancers of the GI tract, along with morbidity and mortality after diagnosis, what do we know about the effect of weight loss or other interventions on these complications?

In human weight loss studies, intentional weight loss must be distinguished from antecedent weight loss produced by the cancer itself. The IOWA Health Study showed that intentional weight loss greater than 20 lbs in women followed for 7 y reduced total cancers by 11%, breast cancer by 19%, CRC by 9%, and all obesity-related cancers by 14%.[148] Another study also showed that recent weight loss reduced CRC incidence.[149] Fiber intake is negatively related to CRC incidence, but the effects on weight loss are controversial.[150]

Studies of obese patients who underwent bariatric surgery have reported reductions in cancer incidence.[151, 152] Among patients followed for more than 10 y, the incidence of breast cancer was reduced by 45%, but bariatric surgery had no effect on overall cancer development,[153, 154] and surprisingly, increased the incidence of CRC.[155] This increase might result from the increased concentrations of colonic bile acids or fatty acids in these patients.

Esophageal Cancer

Esophageal cancer is the eighth most common cancer and is the sixth most common cause of cancer death. [156] Incidences of esophageal squamous cell carcinoma (ESC) and adenocarcinoma (EAC) vary among countries. Though ESC is predominant worldwide, the incidence of EAC has been increasing—particularly in western countries, accounting for 50% of esophageal cancers.[157] This likely is due in part due to increasing BMIs.

Many studies have identified obesity as a risk factor for EAC in men and women.[158] A meta-analysis of prospective observational studies identified a RR of 1.52 and 1.51 per 5Kg/m^2 increase in BMI in men and women, respectively.[3] (Figure 1) The prospective NIH-AARP Diet and Health Study found EAC risk was highest for those with BMIs > 35 kg/m^2.[159]

Obesity and Progression to EAC—Obese individuals have a higher prevalence of gastroesophgeal reflux disease, which can lead to Barrett's esophagus (BE) and intestinal metaplasia, which are precursors to EAC.[160-162] A meta-analysis showed significant and dose-dependent associations between obesity and gastroesophgeal reflux disease, with RRs increasing from 1.43 to 1.94 for BMIs 25–30 kg/m^2.[163] Abdominal obesity is also a risk factor for BE (adjusted RR, 2.9);[164] levels of risk are similar to those of increasing BMI.[165, 166]

It is unclear what stage of EAC development adiposity affects (Figure 4). The most recent data indicate that obesity early in life increases risk for EAC. In the Factors Influencing the Barrett's/Adenocarcinoma Relationship (FINBAR) population-based case-control study, EAC occurred more commonly among subjects who were overweight or obese 5 y before diagnosis.[167] Similarly, in a hospital-based, case-control study, EAC cases were more likely to have been overweight (BMI > 25) at age 20 or 10 y before diagnosis, indicating an effect of early-life obesity.[168]

The Seattle BE Project associated increasing waist to hip ratio with risk of abnormal esophageal histology, aneuploidy, increase in the percentage of cells with 4N DNA content, and other genetic defects (loss of heterozygosity at 9p and 17p), which occur in premalignant lesions.[169] Other markers of malignancy include DNA methylation, oxidative DNA damage, telomere length, and altered levels of specific microRNAs—these require further investigation. [170-173]

Preliminary data from human studies have associated EAC progression with changes in the miRNA profile in the affected epithelium.[174] There are few data on the contribution of epigenetic alterations to the metaplasia–dysplasia–EAC pathway. The biologic and diagnostic implications of epigenetic changes and altered metabolism remain to be explored and may provide novel targets for the prevention and treatment of BE and EAC.

Insulin and IGF1 Signaling—Adipose tissue is metabolically active, secreting numerous biologically active products [175-177] that promote inflammation and insulin resistance. [178, 179] Insulin and IGF signaling have been shown to promote BE and EAC [180, 181] Gene expression analyses of EAC samples from viscerally obese subjects with increased total and free levels of IGF1 showed an association between obesity and increased tumor expression of IGF1R. Patients whose tumors did not express IGF1R survived longer than patients with IGF1R-positive tumors. However, in a longitudinal study of patients with BE, concentrations of IGF1 and IGFBP3 were not associated with EAC risk.[182] Aneuploidy was 3-fold greater among participants with higher levels of IGFBP3, indicating that IGF signaling could mediate the association between obesity and EAC.

Adipokines—Serum levels adiponectin levels are low in patients with EAC (but not ESC), and decrease significantly with tumor progression and metastasis.[183-185] Recently, using data from the Seattle BE Study, Duggan et. al[185] found that among patients with BE, levels of adiponectin had a nonlinear inverse association with risk of developing EAC. Other studies have also demonstrated how adiponectin may influence the development of EAC, although more data are needed to validate these findings.[186-188] Further translational research is needed to determine how to increase adiponectin signaling, such as by upregulating adiponectin receptors, providing adiponectin receptor agonists, or administering human recombinant adiponectin.[189]

Leptin could also have a role in BE and EAC development[190, 191]—it stimulates cell proliferation and inhibits apoptosis in EAC cell lines.[188, 192, 193] Increased leptin levels have been significantly associated with risk of progression from BE to EAC.[185] The relationship between leptin and EAC warrants further study. Leptin receptor signaling might be inhibited with epidermal growth factor receptor or extracellular signal-regulated kinase inhibitors.[188]

Obesity and Development of EAC—The homeobox transcription factors CDX1 and CDX2 are determinants of cell fate that are required for GI tract development. CDX1 and 2 are not normally expressed in the adult esophagus; their overexpression in mice promoted intestinal metaplasia.[194] Variants at the CDX2 binding site of *VDR*, which encodes the human vitamin D receptor, have been associated with obesity and fat mass.[195] Altered

activities of CDX1 and 2 have been shown to promote the epithelial to mesenchymal transition in GI cancer cells. This process can be mediated by epidermal growth factor, fibroblast growth factors, and transforming growth factors; levels of these factors are increased in obese individuals. Retinoic acid regulates an intracellular network of signaling pathways that lead to expression of CDX1 and 2, which also is modulated by thyroxine and its receptors. The thyroxine signaling mechanisms are linked to activation of farnesoid X nuclear receptor (FXR) and the G protein-coupled bile acid receptor 1 (GPBAR1 or TGR5).[196] TGR5 is expressed in colon and activated by bile acids, diet, and microbiome-derived ligands, which release incretins with multiple effects on systemic cellular processes. Obese mice have been reported to have altered Tgr5 signaling; [197] studies are needed in humans. The TGF5 pathway could provide a link between the intestinal microbiome and EAC in obesity.

Intestinal Microbiota—The intestinal microbiota has been linked to activation of the inflammasome and inflammation in the intestinal epithelia. Inflammasomes help regulate aerobic glycolysis, which is involved in cell transformation, via the Warburg effect.[198] It is not clear how obesity might alter the esophageal microbiome. Microbiota that colonize the esophagus are predominantly composed of *Streptococcus* species, but may be altered in esophagitis and BE patients to move gram-negative anaerobes and microaerophile.[199] An altered esophageal microbiome might be involved in genesis of EAC after *Helicobacter pylori* eradication or in obese individuals, but further studies are needed.

Gastric Adenocarcinoma (GCA)

Gastric cancer ranks fourth in incidence and second in cancer-related death.[156] About 90% of gastric cancers are GCAs, which are further categorized as distal or non-cardia GCAs and proximal or cardia-GCAs. Although the incidence of non-cardia GCA has decreased, that of cardia-GCA has increased. Like EAC, this is in part due to increasing BMIs and obesity.[158, 159, 200] In a population-based cohort study, Chow et. al found a 2-fold increase for development of cardia-GCA with increased BMI. Additional studies showed that obesity increased the incidence of cardia-GCA.[201] A meta-analysis of 4 cohort studies found no association between non-cardia GCA and obesity.[202] Subgroup analysis also showed no differences for total GCA between obese and normal weight patients, after adjusting for sex, but did find a 1.5-fold increase in cardia-GCA among obese individuals.

Insulin and IGF1 Signaling—It is unclear how obesity might increase risk for EAC or GCA. The diseases share proposed mechanisms.[203] Healthy gastric mucosa, hyperplastic polyps, intraepithelial neoplasia, and adenocarcinomas all express IGF1;[204] levels increase progressively from benign proliferating lesions to cancer, indicating its role in tumor progression. Another study reported an increasing percentage of IGF1R-positive cells from healthy stomach, to hyperplastic tissue adjacent to carcinomas, to cancer.[205] This study also associated IGF1R expression with metastasis and invasion. Low levels of *IGF1R* mRNA were associated with increased rate of overall survival in patients with GCA.[206] Strategies to block IGF1R might therefore be developed to treat GCA.

Adipokines—Three small case-controlled studies reported varying levels of adiponectin in patients with GCA.[54, 207, 208] One found lower plasma levels of adiponectin in patients with GCA than controls, but the relationship between BMI and adiponectin was stronger in controls than in patients. Another study made similar findings, but found a strong correlation between BMI and leptin in controls and patients. A small cohort study found no correlation between plasma level of adiponectin and BMI, but did associate level of adiponectin with tumor grade, so this protein might reduce GCA progression.

GCAs express levels of leptin and its receptor, especially during invasion.[209-213] One study reported higher concentrations of leptin in patients with intestinal metaplasia. Another associated higher levels of leptin with stage and histologic features of GCA, Borrmann classification, metastasis to lymph nodes, and poor outcome. It is unclear if leptin activation of JAK–STAT signaling directly promotes or facilitates pathogenesis.

Inflammatory Factors—Obesity-induced inflammation is believed to promote development of GCA, via TNFα, IL6, and MCP1. In vitro and in vivo studies have shown that TNFα, IL6, IL17, and MCP1 stimulate proliferation and inhibit apoptosis of human gastric cancer cell lines.[214, 215] Strategies to target these pathways could reduce GCA growth and invasion.

Pancreatic Adenocarcinoma (PAC)

Pancreatic cancer is the thirteenth most-common cancer and the eighth-leading cause of cancer-related death.[156] The most common and deadly form of pancreatic cancer is pancreatic adenocarcinoma (PAC), which accounts for more than 90% of cases. Based on data from 23 cohort and 13 case-controlled studies, The Word Cancer Research Fund Panel concluded that there is “convincing increased risk” of PAC related to body adiposity and a “probable increased risk” with abdominal adiposity.[216] A large meta-analysis found RRs of 1.07 and 1.12 for PAC per 5 kg/m^2 increase in BMI in men and women, respectively.[3] This was also observed in a pooled analysis of 7 prospective cohorts, with a RR of 1.06 for every $5kg/m^2$ increment of BMI.[217]

BMI has been associated with risk of PAC, age at onset, and overall survival. A case-control study reported an increased risk for PAC, and an earlier age of onset, among individuals who were overweight or obese in early adulthood (ORs, 1.67–2.58).[218] Overweight or obese older patients with PAC were less likely to survive by an average of 4.5 months, with a RRs of 1.26 and 1.86, respectively.

Insulin and IGF1 Signaling—Several prospective studies associated increased circulating levels of glucose, insulin, and plasma C-peptide with increased risk for PAC.[219-222] Epidemiology studies found no significant associations between circulating IGF1 or its binding proteins with PAC, but other studies associated lower levels of IGFBP1 with increased risk for PAC.[223-225] A case–control study found that subjects in the lowest quartile of plasma IGFBP1 level had an odds ratio for PAC of 2.07, compared to the 3 highest quartiles; the effects of low plasma IGFBP1 became progressively stronger with time. IGF1 and IGF1R are highly expressed in pancreatic cell lines; IGF1 signaling promotes their proliferation, invasion, expression of angiogenic factors, and reduces apoptosis.[226-229]

Adipokines—There have been few studies of leptin and adiponectin levels in PAC patients. In obese rats injected with human PAC cells, no associations were made between leptin levels and cell proliferation or tumor progression. However, these processes did have an inverse relationship with adiponectin level. Other studies produced contradictory data. Most patients with PAC patients have lost weight by the time they receive their diagnosis, which could lower levels of leptin and increase levels of adiponectin; circulating adiponectin has been inversely associated with tumor progression. [53, 230-232] Future studies should clarify the relationships among adipokine levels, obesity, and PAC. It will be interesting to investigate the effects of metformin on the AMP-activated protein kinase pathway, via adiponectin receptors 1 and 2.[189]

Genetic associations between obesity and PAC—Genetic factors that contribute to obesity might also increase susceptibility to PAC. A genome-wide association study identified *NR5A2* as a susceptibility gene for PAC.[233] In a case-control study, carries of a specific NR5A2 variant had a lower risk of PAC compared to carries of a common allele, regardless of BMI or diabetes.[234, 235] The association between PAC and polymorphisms in *PPARG* is controversial.

CONCLUSIONS

Our understanding of how obesity contributes to the pathogenesis and development of GI cancers is increasing; greater insight into the molecular mechanisms might lead to identification of new therapeutic targets. Given the lack of current effective therapies for weight control or reduction beyond bariatric surgery, research and clinical efforts will focus on the connections between increase in adipose cell mass and GI carcinogenesis. Further studies of the hormonal, inflammatory, genetic, and dietary factors that contribute to development and progression of GI cancers will help us understand the role of obesity in these processes.

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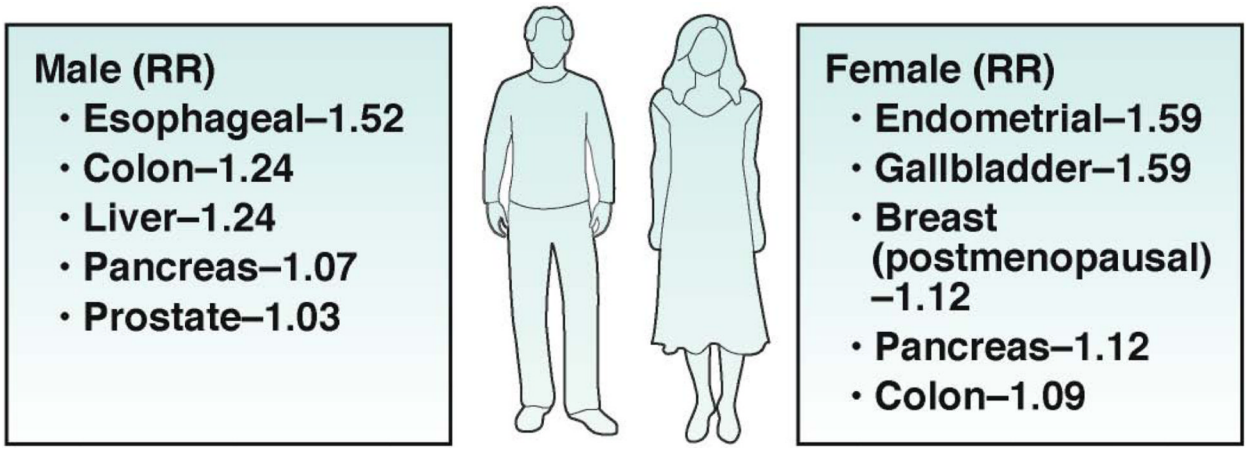

Figure 1. Relative Risks of GI Cancers in Obese Men and Women

Obesity confers increased risk of several malignancies. Reductions in obesity rates should result in decreased cancer incidence and potentially mortality. In men, obesity-associated cancers include esophageal, colon, liver, pancreas and prostate. In women, obesity-associated cancers include endometrial, gallbladder, breast (postmenopausal women), pancreas and colon. Data presented as relative risk per 5 kg/m^2 higher BMI. Adapted from [3].

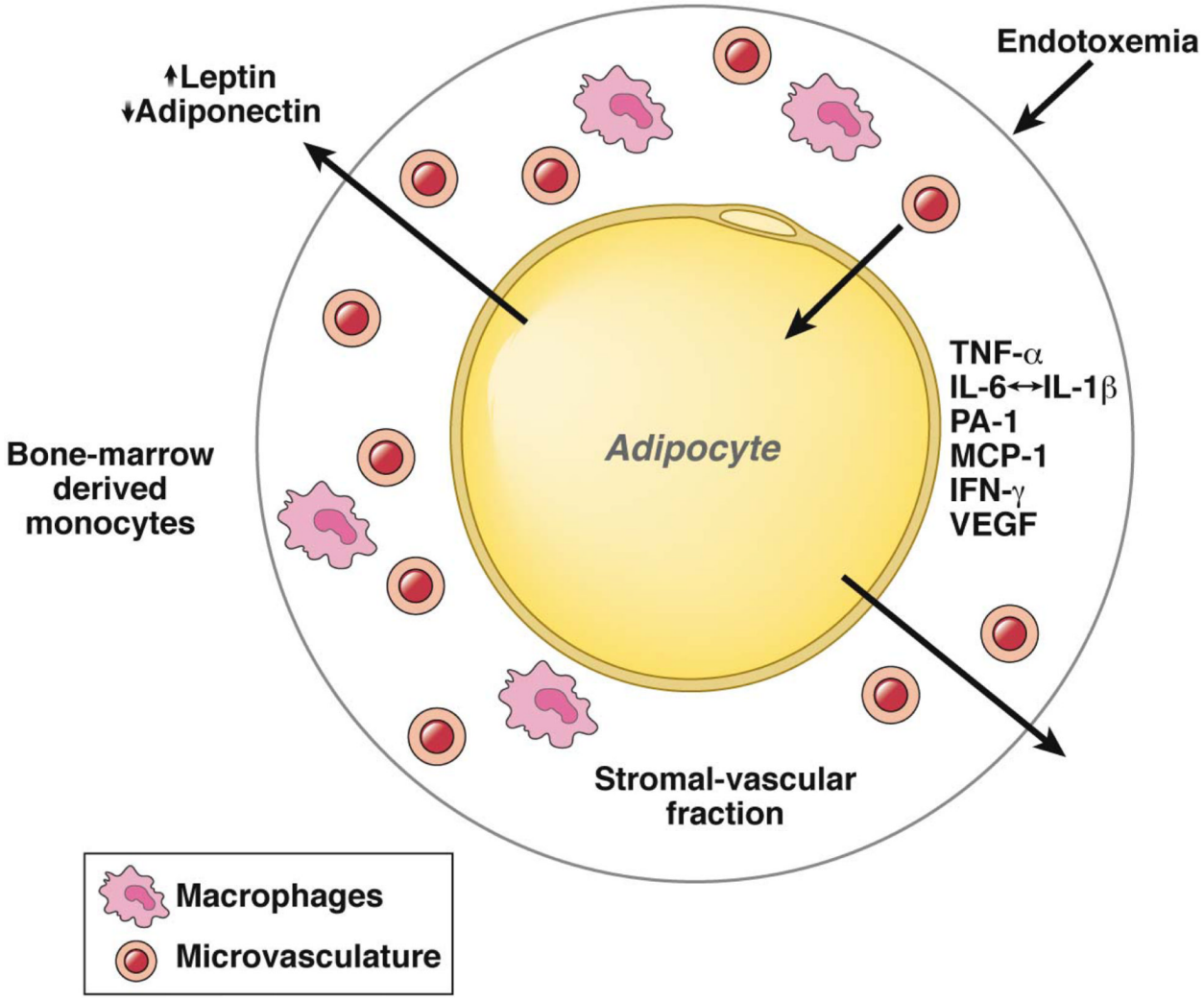

Figure 2. Inflammation and Adipocytes

Interactions among circulating and local factors contribute to obesity-associated inflammation. Adipocytes are cells specialized for storage of nutrients in the form of triglyceride and cholesterol. Leptin and adiponectin are examples of adipokines produced in response to adipocyte size and overall energy balance. After reaching an undefined trigger (adipocyte size, hypoxia, insulin resistance), immune cells, including macrophages, are recruited to adipocytes. This activates an inflammatory signaling response that leads to secretion of TNFα, IL6, PA1, MCP1, IFNγ and VEGF. Resulting chronic inflammation leads to insulin resistance, cardiovascular disease, and different cancers.

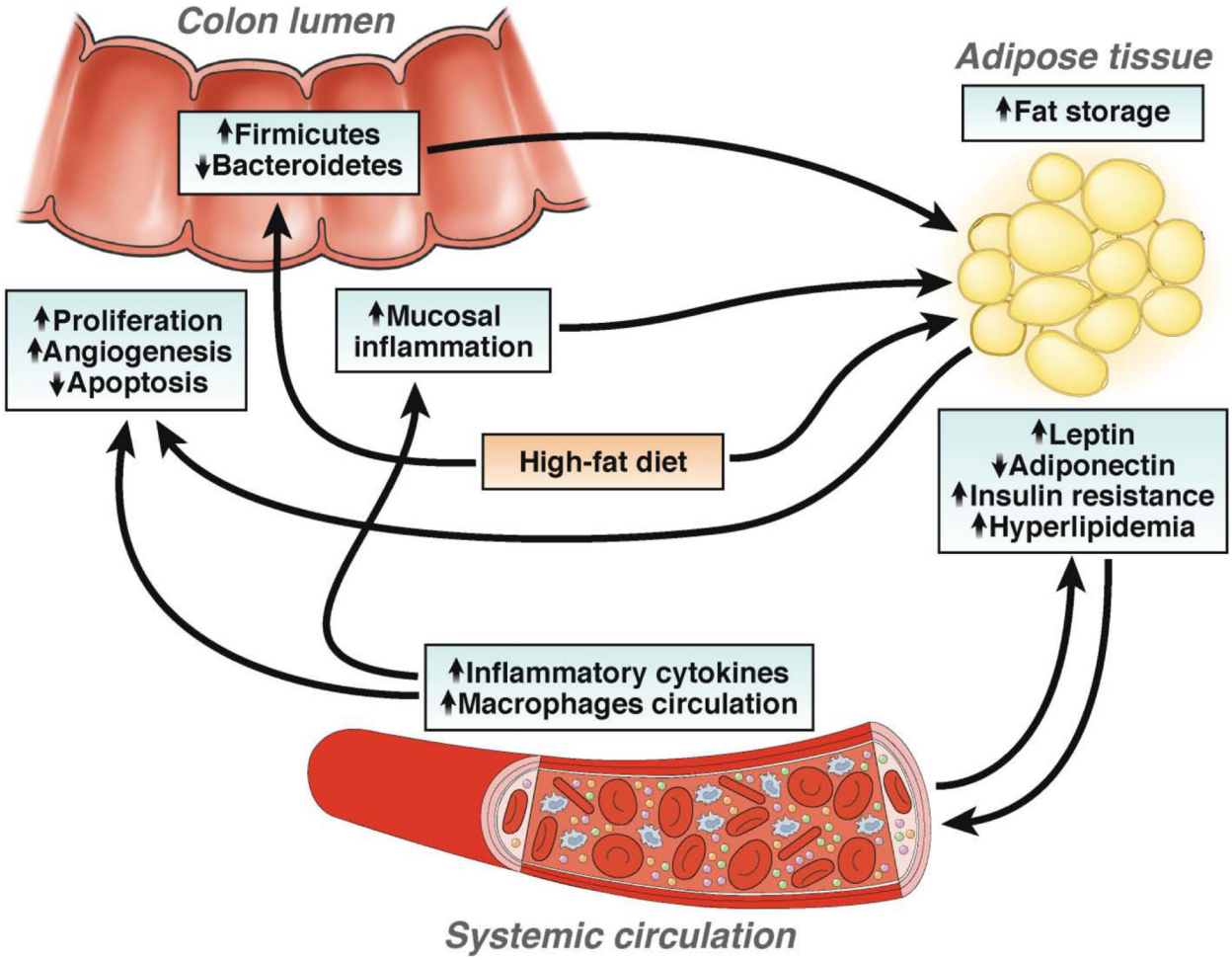

Figure 3. Obesity-induced Factors Contribute to Colorectal Carcinogenesis Mechanisms by which obesity could contribute to development of CRC

Western-style diets lead to increased adiposity and changes in the microbiota, to adapt to the increased energy supply. Adipokines such as leptin and adiponectin could allow for establishment of a tumor microenvironment. In obese individuals, hyperlipidemia and insulin resistance lead to low-grade systemic inflammation, which promotes tumor cell proliferation and angiogenesis and reduces apoptosis. These mechanisms are likely to vary among individuals and little is known about their interactions.

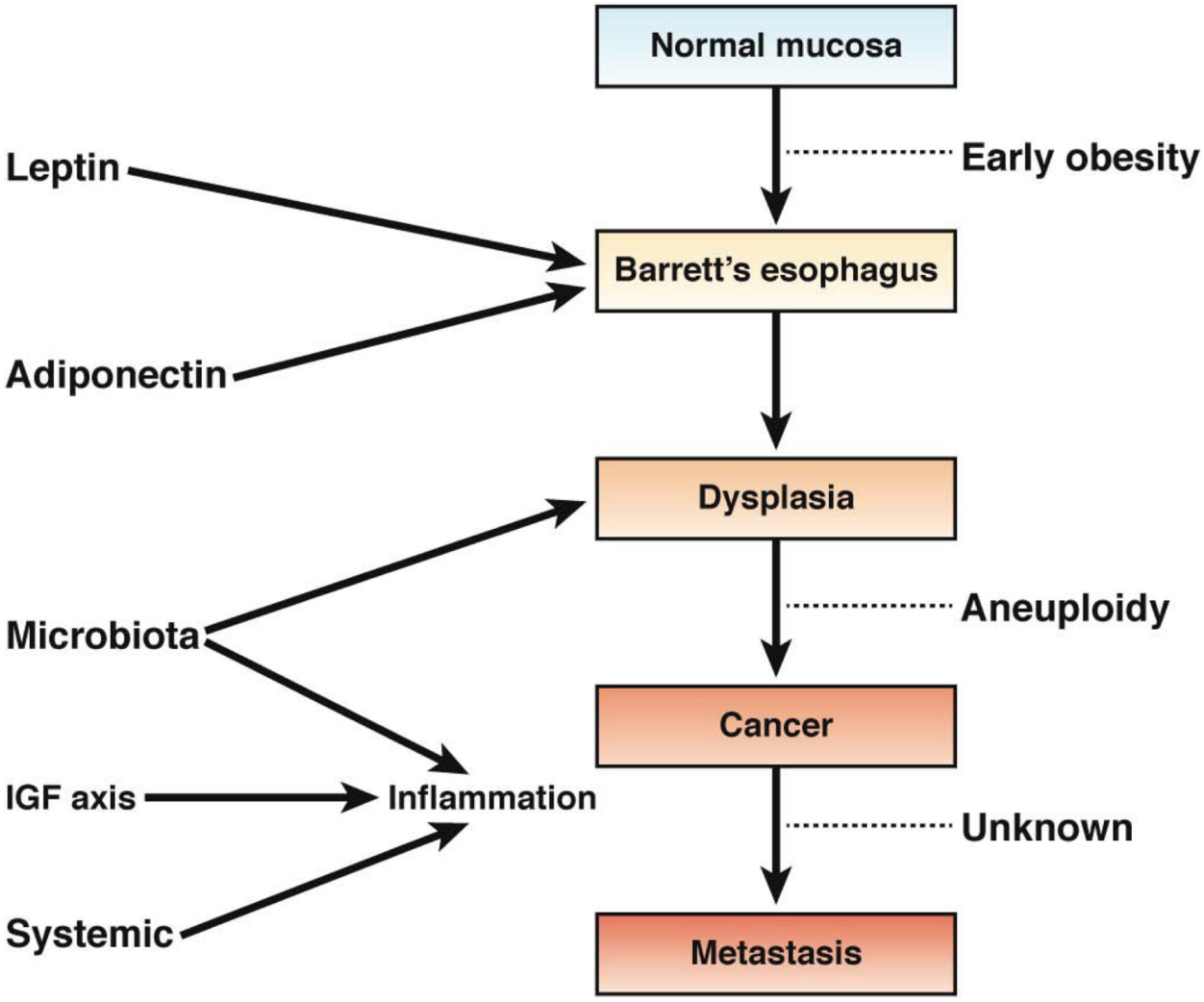

Figure 4. Obesity and Esophageal Cancer Mechanisms by which obesity could contribute to carcinogenesis in the esophagus

In early stages of obesity, leptin and adiponectin contribute to the frequency and development of BE. The transition from benign metaplasia to dysplasia is thought to be partially mediated by changes in the microbiota, in addition to an acid environment. Development of aneuploidy and subsequent cancer have been associated with chronic low-grade inflammation and altered levels of IGF1. It is not clear whether obesity contributes to metastasis of esophageal cancer.