REVIEWS: CURRENT TOPICS

Obesity and colorectal cancer: epidemiology, mechanisms and candidate genes

Marc J. Gunter*, Michael F. Leitzmann
Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD 20852, USA

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Abstract

There is increasing evidence that dysregulation of energy homeostasis is associated with colorectal carcinogenesis. Epidemiological data have consistently demonstrated a positive relation between increased body size and colorectal malignancy, whereas mechanistic studies have sought to uncover obesity-related carcinogenic pathways. The phenomenon of “insulin resistance” or the impaired ability to normalize plasma glucose levels has formed the core of these pathways, but other mechanisms have also been advanced. Obesity-induced insulin resistance leads to elevated levels of plasma insulin, glucose and fatty acids. Exposure of the colonocyte to heightened concentrations of insulin may induce a mitogenic effect within these cells, whereas exposure to glucose and fatty acids may induce metabolic perturbations, alterations in cell signaling pathways and oxidative stress. The importance of chronic inflammation in the pathogenesis of obesity has recently been highlighted and may represent an additional mechanism linking increased adiposity to colorectal carcinogenesis. This review provides an overview of the epidemiology of body size and colorectal neoplasia and outlines current knowledge of putative mechanisms advanced to explain this relation.

Family-based studies have shown that the propensity to become obese is heritable, but this is only manifest in conditions of excess energy intake over expenditure. Inheritance of a genetic profile that predisposes to increased body size may also be predictive of colorectal cancer. Genomewide scans, linkage studies and candidate gene investigations have highlighted more than 400 chromosomal regions that may harbor variants that predispose to increased body size. The genetics underlying the pathogenesis of obesity are likely to be complex, but variants in a range of different genes have already been associated with increased body size and insulin resistance. These include genes encoding elements of insulin signaling, adipocyte metabolism and differentiation, and regulation of energy expenditure. A number of investigators have begun to study genetic variants within these pathways in relation to colorectal neoplasia, but at present data remain limited to a handful of studies. These pathways will be discussed with particular reference to genetic polymorphisms that have been associated with obesity and insulin resistance.

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1. Introduction

Obesity is a result of positive “energy balance” and prevails in conditions of energy excess. As a consequence of major economic, social and technological changes, many populations find themselves in environments characterized by abundant calorie-rich food and low physical activity requirements. As a result, obesity is rapidly approaching epidemic proportions in many parts of the world and has become a major public health concern. At present, more than 1 billion people are overweight, whereas more than 300 million people worldwide can be classified as obese [with body mass index (BMI) of 30 kg/m² or higher] [1]. Over the past 40 years, the prevalence of obesity in the United States has increased from around 13% to 30% [2]. Two thirds of the American population is overweight, and this trend is mirrored in most other western populations. A

Abbreviations: ATP, adenosine triphosphate; BMI, body mass index; HbA1c, glycated hemoglobin; IGF, insulin-like growth factor; IL-6, interleukin 6; SNP, single nucleotide polymorphism; TNF-α, tumor necrosis factor α; T2DM, diabetes mellitus Type 2; VNTR, variable number of tandem repeats.

* Corresponding reviewer. Tel.: +1 301 451 9581; fax: +1 301 496 6829. E-mail address: gunterm@mail.nih.gov (M.J. Gunter).
global comparison reveals the highest obesity rates in the United States, Europe and the Middle East and the lowest in sub-Saharan Africa and East Asia [3]. Mounting epidemiological evidence suggests that obesity is associated with cancer, particularly cancer of the colorectum. Indeed, consensus panels have cited convincing evidence for obesity as a cause of colorectal cancer [4]. In parallel to the geographic variation seen in obesity rates worldwide, colorectal cancer incidence is highest in affluent industrialized countries such as the United States, Australia and Western Europe and lowest in India and sub-Saharan Africa [5]. In concordance with ecological data that have demonstrated rapid increases in colorectal cancer in populations with positive energy balance (Fig. 1), experimental data have indicated that energy intake contributes to colorectal cancer etiology. Data from animal models suggests that overnutrition augments colorectal carcinogenesis, whereas caloric restriction reduces colorectal tumor incidence [6,7].

In recent years, several hypotheses have emerged to explain this relationship. The notion of “insulin resistance” or the impaired ability to normalize plasma glucose levels has formed the core of these hypotheses, but other related mechanisms have also been advanced (Fig. 2). As we move forward into an era of greater understanding of the human genome, there is a strong impetus to identify susceptibility genes for body size. Family-based studies suggest that the heritability of body size is substantial: up to 80% of the variability in BMI can be accounted for by genetic factors [8]. The identification of genetic variants that confer susceptibility to obesity may not only enhance knowledge of the biology that underlies its development, but may also lead to the discovery of genes that predispose to colorectal malignancy in the general population. This review will focus on the putative mechanisms that link increased body size to colorectal cancer. In addition, the paper will provide an overview of candidate genes for obesity and colorectal neoplasia.

2. Epidemiological studies of body size and colorectal cancer

Cohort and case-control studies have consistently demonstrated a positive relation between body size and colorectal cancer. A report published in 2002 by IARC evaluated all available studies on obesity and colorectal cancer risk and found elevated risks in men and women with risks being stronger for men than women [4]. Of the eight case-control studies on BMI and colorectal cancer published to date, all reported relative risks greater than one for overweight (BMI >25 kg/m²) or obese individuals (BMI >30 kg/m²) compared with normal weight individuals (BMI 18.5–25 kg/m²) apart from one study that found an inverse association between BMI and colorectal cancer risk among females [9–15] and one that reported no association [16]. Similarly, for the 10 prospective cohort investigations, all reported a positive association between BMI and colorectal cancer, with relative risks in the range of 1.2 to 3.4 [17–26]. In general, the association has proven stronger for cancer of the colon than the rectum and for the distal than the proximal colon. Body size also seems to influence early stages of colorectal carcinogenesis: BMI has been associated with colorectal adenoma and, in particular, large adenomas of the distal colorectum in seven epidemiological studies [16,27–32].

There is evidence to suggest that abdominal or visceral adiposity is a risk factor for colorectal cancer independent of BMI. Indeed, waist to hip ratio (WHR) or waist circumference appear to be superior indicators of obesity than BMI, particularly in older individuals. One recent study conducted among men reported a 2.1-fold increased risk of colon cancer for men comparing a high WHR to those with a low WHR, whereas a high BMI (>29.2 kg/m²) conferred a 1.7-fold increased risk of colon cancer compared to a BMI <24.8 kg/m² [33]. Following adjustment for BMI, a large prospective study found a twofold elevated risk for colorectal cancer among men and women.
with a waist size greater than 99.1 cm compared to a waist size less than 83.8 cm [26].

3. Macronutrient intake, physical activity and colorectal cancer

The maintenance of a healthy body weight is determined by the ratio of energy intake to energy expenditure. An excess of energy input over energy output results in positive energy balance and leads to weight gain. Disturbance of energy balance leads to various metabolic perturbations, which may be related to colorectal carcinogenesis. Energy is consumed primarily in the form of macronutrients such as carbohydrates, protein and fat, which are ultimately converted into glucose molecules that enter oxidative metabolic pathways. The energy released during this process is coupled to the synthesis of adenosine triphosphate (ATP) — the universal currency of energy expenditure. High intake of energy has been associated, albeit inconsistently, with colorectal cancer risk in several epidemiological studies. In general, case-control studies have reported a positive association between energy intake and colorectal cancer risk, whereas cohort studies have been null [16,18,34,35]. In addition, a number of studies have investigated the relation between intake of the main sources of energy, such as carbohydrate and fat, and colorectal cancer risk. Dietary glycemic load, a quantitative measure of the glycemic effect of food, has been positively associated with colorectal cancer risk in several cohort and case-control studies [35–38]. The positive relationship observed between dietary fat and colorectal carcinogenesis in animal studies has failed to be substantiated by epidemiological investigations [39]. Excess energy intake can be compensated for by an increase in physical activity in order to maintain energy balance. Indeed, an inverse relationship between physical activity and colorectal cancer risk has been consistently demonstrated [40].

4. Biological mechanisms linking body size to colorectal cancer

4.1. Insulin resistance

The term insulin resistance refers to a state of cellular unresponsiveness to the effects of insulin with higher levels of insulin required to normalize plasma glucose. Insulin resistance is believed to underlie a cluster of metabolic perturbations, including elevated levels of blood triglycerides and glucose, low levels of high-density lipoprotein cholesterol and high blood pressure. It was noted some years ago that many of the risk factors for becoming insulin resistant coincide with those for colorectal cancer, particularly high BMI, a sedentary lifestyle, a diet rich in energy, red meat and saturated fat, and low in fiber and fruits and vegetables. Concurrent with this, there is observational and experimental evidence for a direct link between insulin resistance and colorectal neoplasia.

Observational studies have focused on several distinct markers of insulin resistance and their association with colorectal neoplasia. The occurrence of diabetes mellitus Type 2 (T2DM), a disease that arises when insulin resistance coincides with impaired pancreatic insulin secretion, has been positively associated with colorectal cancer. Type 2 diabetics have up to a threefold increased risk of colorectal cancer compared with nondiabetics [41], and colon cancer patients exhibit glucose intolerance and insulin resistance [42]. Furthermore, serum levels of C-peptide (the cleaved product of proinsulin and marker of insulin secretion), glycated hemoglobin and glucose have all been positively associated with colorectal neoplasia [43–47]. In addition, plasma levels of insulin-like growth factor I (IGF-I), the bioactivity of which may be enhanced by increased insulin levels, have been positively associated with colon cancer [48]. Several metabolic consequences of the insulin-resistant state, including hyperinsulinemia, hyperglycemia, hypertriglyceridemia and increased plasma levels of non-esterified fatty acids (NEFAs), have been positively associated with colorectal cancer among fasting subjects in prospective studies [49,50].

At least three mechanisms exist through which insulin resistance potentially causes colorectal cancer. The elevated concentrations of plasma insulin, triglycerides, NEFA and glucose associated with insulin resistance lead to increased insulin exposure of nonclassical insulin target tissues that express insulin receptors, such as the colon. This can potentially have a number of consequences. First, insulin is known to have growth as well as metabolic effects, and data from a variety of sources suggest that insulin is functionally involved in colorectal carcinogenesis [51–53]. Specifically, insulin stimulates proliferation and reduces apoptosis in colorectal cancer cell lines [54,55], and it promotes colorectal tumor growth in animal models [56–58]. Upon binding to its receptor, insulin initiates a signal transduction cascade, which results in not only translocation of the GLUT4 receptor to the cell surface (thereby facilitating glucose uptake), but also increased proliferation and decreased apoptosis via the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI-3K) pathways, respectively [59]. Because the colon does not represent a classical insulin-target tissue, the colonocyte may lack a specific mechanism through which the mitogenic actions of insulin are regulated, as is the case in classical insulin target tissues such as skeletal muscle, adipose tissue and liver. Thus, elevated insulin signaling in the colonocyte may engender an enhanced proliferative state with tumorigenic consequences.

Second, in conjunction with the metabolic effects of insulin, the increased concentrations of available energy substrates such as glucose, triglycerides and NEFA may provide increased energy for transformed colonocytes as well as induce changes in cell signaling pathways. Elevated intracellular levels of triglycerides and their metabolites such as diaclyglycerol may activate the protein kinase-C and
MAPK pathways with potentially mitogenic and carcinogenic effects [60]. Triglycerides and other fat metabolites are known to affect the activity of peroxisome proliferator-activated receptors (PPARs), a class of transcription factors that play key roles in lipid, glucose and energy homeostasis and in adipocyte differentiation regulation. Peroxisome proliferator-activated receptors have antiproliferative, proapoptotic and anti-inflammatory effects [61]. Peroxisome proliferator-activated receptor gamma (PPAR-γ) is expressed in colonic tissue and inhibits the growth and increases the differentiation of colonic tumors [62]. In addition, PPAR-γ plays a key role in insulin sensitization, and several functional variants of PPARG have been associated with T2DM [63].

Increased energy availability may also contribute to colon carcinogenesis by stimulating reactive oxygen species synthesis. An intracellular lipolytic environment rich in oxidizable substrates may result in the generation of lipid oxidation products, depleted levels of antioxidants and an overall environment of oxidative stress [64]. Hyperglycemia may also increase oxidative stress [65]. In support of this, DNA damage is known to be higher in diabetic individuals compared with healthy subjects [66].

Third, insulin resistance causes alterations in the IGF system with concomitant effects on cellular growth pathways. Insulin and IGF are representative of energy availability and stimulate anabolic pathways, leading to cell growth and differentiation. In the hyperinsulinemic state, IGF-binding protein (IGFBP) levels decrease, whereas free IGF-1 levels rise [67]. The colon expresses IGF receptors, and following activation by IGF binding, colonocyte apoptosis is inhibited and cell cycle progression ensues. Elevated levels of IGF may therefore provide a selective growth stimulus, causing clonal expansion of epithelial cells with abnormal growth regulation. High circulating levels of IGF-1 have been positively associated with colorectal cancer risk, whereas high IGFBP-3 levels are associated with reduced risk [48,53]. Furthermore, sufferers of acromegaly, a condition characterized by overproduction of IGF and growth hormone (GH), have increased risk of developing colorectal cancer [68]. Obesity has also been associated with perturbations in the bioavailability of plasma androgens and estrogens mediated by several mechanisms. In response to insulin resistance, enhanced IGF-1 activity in the liver inhibits hepatic sex hormone binding globulin synthesis leading to increasing levels of circulating sex hormones such as estrogen and testosterone. In addition, insulin and IGF-1 stimulate sex hormone synthesis by the gonads and adrenal glands [69]. Observed gender differences in the relation of body size and colon cancer may be explained, in part, by alterations in sex hormone levels.

4.2. Chronic inflammation

Obesity is associated with a state of chronic inflammation, induced perhaps by excessive production of storage lipids and high circulating levels of glucose, both of which create a proinflammatory oxidative environment [70,71]. The relation between obesity and inflammation was demonstrated by the finding that adipocytes constitutively express the proinflammatory cytokine tumor necrosis factor α (TNF-α), and that TNF-α expression in adipocytes of obese rodents is markedly increased [72]. This finding was subsequently replicated in humans, and it has since been shown that BMI and plasma TNF-α, C-reactive protein (CRP) and interleukin 6 (IL-6) levels are highly correlated [73].

Traditionally, adipose tissue had been thought of as an inert storage repository for fat and triglycerides. The notion of the adipocyte as a more active entity emerged from the discovery of “adipokines” such as leptin, resistin, adiponectin, adipsin, visfatin, IL-6 and TNF-α, which are produced by adipocytes and function to regulate adipocyte homeostasis and metabolism. Under conditions of increasing adiposity, macrophages are known to accumulate in white adipose tissue, possibly in response to increasing levels of chemotactic signals from the adipocyte. This leads to the secretion of a range of proinflammatory peptides from adipocytes and macrophages. Compared to lean people, adipose tissue of the obese expresses higher quantities of proinflammatory molecules such as TNF-α, IL-6, inducible nitric oxide synthase, CRP and monocyte chemotactic protein-1.

There is emerging evidence that chronic inflammation is causally associated with colorectal neoplasia. Among patients with idiopathic inflammatory bowel disease, colorectal cancer incidence rates increase progressively over time, reaching 19% after 30 years of disease [74]. Conversely, habitual use of nonsteroidal anti-inflammatory drugs confers a 40–50% reduction in disease risk [75]. Furthermore, data suggest that elevated levels of CRP predict colorectal cancer incidence [76,77], though not all studies have demonstrated a positive relation [78]. It should be noted, however, that the elevated levels of serum inflammatory markers observed in some of these studies may also be due to the presence of a subclinical tumor. In addition to observational data, there is direct evidence to suggest that inflammation in the colon leads to DNA damage and the promotion of carcinogenesis [79,80]. Because obesity and chronic inflammation are related to colorectal cancer and obesity engenders a proinflammatory state, one may hypothesize that inflammation lies on the causal pathway linking obesity to colorectal cancer.

In addition to this direct relationship, chronic inflammation induced by obesity may also be related to colorectal neoplasia via an insulin resistance mechanism. There is a growing body of evidence that describes a correlative and causative relationship between inflammation and insulin resistance [81]. Serum levels of CRP and c-peptide, insulin, glucose and glycated hemoglobin are positively correlated [82], whereas high levels of IL-6 and CRP predict T2DM incidence [83]. Tumor necrosis factor-α promotes insulin
resistance in a number of insulin-responsive tissues, and animal models have demonstrated that obese TNF-α/C0 mice are protected from obesity-induced insulin resistance [72,84]. Mechanistic work has shown that TNF-α lies at the core of the association between obesity and insulin resistance. Phosphorylation of tyrosine residues of insulin receptor substrate 1 (IRS-1) upon activation of the insulin receptor is a critical step in insulin signaling. It had been noted that this phosphorylation step is reduced in obesity, and it has since been demonstrated that TNF-α inhibits tyrosine phosphorylation, effectively blunting insulin signaling and engendering an insulin-resistant state [85,86]. In addition, TNF-α induces sustained suppressor of cytokine-signaling protein 3 synthesis. Suppressor of cytokine-signaling protein 3 inhibits insulin signaling by reducing IRS-1 phosphorylation and inhibiting its association with PI-3K [87]. Tumor necrosis factor α and IL-6 have also been shown to stimulate lipolysis in adipocytes, leading to hypertriglyceridemia [88]. Intracellular fatty acids can inhibit IRS-Tyr phosphorylation, thereby blunting the insulin signal [89]. Increasing adiposity leads to enhanced synthesis of proinflammatory cytokines, such as TNF-α, which attenuate insulin signaling and cause insulin resistance.

5. Candidate genes for increased body size

The tendency to become overweight or obese is clearly heritable, as evidenced by family, twin and adoption studies [90]. The penetrance of genetic variants that predispose to weight gain is only evident under favorable environmental conditions. These conditions of abundant calorie-rich food and a sedentary lifestyle are what many human beings currently experience at this time. Humans evolved in an environment where food was often scarce; hence, a phenotype that favored adiposity and the tendency to retain energy as fat was selected for. It has been posited that this “thrifty genotype” hypothesis, that is, the inheritance of alleles that provided increased energy storage in the past, is now deleterious to health. Carriage of a particular set of genetic variants, which lead to increased energy storage and obesity, may also predispose to colorectal cancer.

A large number of candidate genes exist, which potentially influence energy balance and may therefore mediate the relation between obesity and colorectal cancer. To date, candidate gene searches, linkage studies and genomewide scans have identified more than 400 chromosomal regions that have been associated with obesity, and it is generally believed that a combination of genetic variants, each exerting modest effects, underlies the obesity phenotype. These genes may be classified according to the pathways upon which they act. The following sections outline a selection of these genes and pathways with particular reference to common variants identified in those genes that are associated with obesity and insulin resistance (see also Table 1).

5.1. Genes involved in insulin signaling

Insulin action is the result of a complex series of signaling events. The engagement of insulin with its receptor activates the insulin receptor tyrosine kinase domain, which leads to phosphorylation of tyrosine residues on the IRS molecules. Binding of the activated IRSs to downstream target molecules, such as PI-3K, leads to stimulation of several signal transduction pathways. These pathways, such as translocation of glucose transporters to the cell membrane and activation of pro-proliferative and anti-apoptotic pathways,
mediate the cellular effects of insulin. Common variants in genes of the insulin-signaling cascade may contribute to insulin resistance susceptibility. Much of the knowledge that exists on common variants of insulin-signaling genes and insulin resistance and obesity originates from the search to identify susceptibility alleles for T2DM.

Variants of the insulin gene (INS) have been associated with birth weight, BMI and WHI [91]. A variable number of tandem repeats (VNTR) polymorphism, which is in linkage disequilibrium with a translation initiation codon, has been associated with levels of mRNA transcripts, lower prevalence of T2DM and higher concentrations of insulin in obese children [92].

The insulin receptor (INSR) is a strong candidate gene for insulin resistance, considering its important functional role and the high frequency of INSR mutations in conditions of severe insulin resistance. Despite this, there is very little evidence to implicate common variants of INSR in T2DM. The Val1985Met polymorphism has been associated with T2DM in two Dutch populations, but prevalence of the variant allele is low and is unlikely to contribute significantly to insulin resistance in the general population [93]. INSR is a very large gene, encompassing 80 kb of DNA and the existence of variants within the noncoding regions, which may contribute to insulin resistance cannot be ruled out.

The IRS genes are among the best characterized of the insulin-signaling cascade. The IRS1 gene has been intensively studied as a candidate gene for insulin resistance and T2DM. A number of nonsynonymous amino acid changes have been identified in IRS-1 with varying functional consequences. The Gly972Arg substitution lies adjacent to two tyrosine phosphorylation sites that bind the p85 subunit of PI-3K. Functional studies have demonstrated that the Arg972 variant confers a 40% reduction in IRS-1 associated PI-3K activity and a 25–40% decrease in binding of the p85 subunit to IRS-1 [94,95]. Despite extensive investigation in several populations, the Gly972Arg polymorphism does not appear to be strongly associated with T2DM. This polymorphism has, however, been associated with a type of T2DM characterized by obesity and severe insulin resistance [96,97]. Furthermore, there is evidence to suggest that this variant may contribute to colorectal cancer. A large study conducted in the United States found carriage of the Arg972 allele of IRS1 to be positively associated with colon cancer [98]. IRS2 has also been studied with respect to T2DM risk. Homozygous disruption of this gene in a murine model yields an insulin-resistant phenotype with similarities to T2DM [99]. Three nonsynonymous amino acid substitutions have been identified, but none have been linked to T2DM risk or insulin resistance [100–102]; however, an IRS2 haplotype has been associated with obesity [103].

The PI3K gene encodes phosphatidylinositol-3-kinase, an enzyme that engages and is activated by IRS to generate several phosphorylated inositol-signaling molecules. Among insulin-resistant and Type 2 diabetic individuals, a reduction in the activity of this enzyme has been observed [104]. The identification of insulin resistance susceptibility variants in this gene has been hampered by the sheer complexity of this protein. The enzyme comprises a catalytic subunit (p110) coupled to a regulatory subunit (p85), of which two isoforms exist encoded by different genes. Furthermore, a third regulatory subunit has been identified (p55γ), along with splice variants of p85α [105]. A Met326Ile amino acid substitution that occurs at relatively high frequency within the p85α isoform lies in close proximity to an SH2 domain that interacts with IRS [106]. The less frequent Ile326 allele has been associated with insulin resistance [107].

5.2. Genes involved in the GH/IGF pathway

A number of common variants in the GH/IGF pathway have been reported, some of which appear to predict circulating levels of components of the GH/IGF axis. Alleles that increase levels of IGF are hypothesized to increase colorectal cancer risk due to an enhanced mitogenic effect. Homozygosity for the IGF1 (CA)19 repeat polymorphism, located 1-kb upstream of the transcription start site, is associated with lower circulating levels of IGF-1 [108]. This variant has also been linked to body fat mass and changes in fat-free mass in response to endurance training [109]. The IGF1 (CA)19 polymorphism has been inconsistently associated with colorectal cancer. The IGF1 192/192 genotype is protective against colon cancer risk among individuals with high physical activity [110]. Carriage of the IGF1 non-192 allele in conjunction with the IRS1*972R allele was associated with a two-fold increased risk of colon cancer in a study conducted by Slattery et al. [98]. Variation at the IGF2 locus on chromosome 11p15 has been associated with muscle mass and fat deposition [111], visceral adiposity [112], circulating IGF-2 levels [113] and BMI [114]. A haplotype bearing an IGF2 variant, the INS VNTR Class III allele and a TH (tyrosine hydroxylase) variant is associated with percentage fat, fat mass and increased risk of the metabolic syndrome in a study conducted in the United Kingdom [115]. An association between the T1663A polymorphism of the GH1 gene and risk of colorectal cancer has been reported [116].

5.3. Genes involved in the regulation of adipocyte metabolism and differentiation

The adipocyte secretes a range of peptides that affect not only adipocyte metabolism, but also act on both central and peripheral targets to influence energy metabolism. Tumor necrosis factor is a pro-inflammatory cytokine and adipokine, secreted by adipocytes and macrophages in response to stress or infection. The principal physiological function of TNF-α is to stimulate recruitment of neutrophils and other cells of the innate immune system to sites of infection or irritation. Binding of TNF-α to its receptor initiates a signal transduction cascade leading to activation of NF-κB and transcription of inflammatory genes. TNF has also been
proposed as a candidate gene for obesity and insulin resistance. The TNF gene is highly polymorphic, and several common variants are known to render changes in TNF-α expression levels. In addition, TNF variants have been associated with percentage body fat, obesity and insulin resistance [117–119].

Leptin is a small adipocyte-derived hormone that transmits information on the size of energy stores to the brain and is believed to be a critical regulator of energy balance. The metabolic properties of leptin are believed to originate in its activation of 5’-AMP activated protein kinase with subsequent pro-catabolic and anti-anabolic effects. Overfeeding stimulates large increases in serum leptin levels, whereas caloric restriction leads to the converse [120,121]. Serum leptin levels are positively correlated with body mass, insulin resistance and insulin concentrations [122–124]. Interestingly, leptin also has mitogenic properties and has been shown to stimulate growth of colon cancer cells [125]. Further evidence for a role of leptin in obesity-induced colorectal cancer came from a Norwegian study, which found a positive association between incident colorectal cancer risk and serum levels of leptin [126]. The LEP gene is the homologue of the murine Ob gene, and homozygosity for a mutation in Ob causes severe obesity in mice. Although the LEP region of chromosome 7 has been linked with BMI, it is unlikely that a single mutation in LEP causes obesity in humans. Several common variants in LEP have been identified — each conferring modest associations with obesity. A five-marker LEP haplotype comprising probable transcription factor binding sites has been associated with obesity [127]. Other LEP polymorphisms that have been linked to obesity include the A19G and G-2548A substitutions [128,129].

Adiponectin is an adipocyte-derived cytokine, and its expression is suppressed in obesity. In addition to its insulin-sensitizing properties, adiponectin possesses anti-inflammatoryatory roles and inhibits macrophage adhesion to endothelia. Reduced presence of adiponectin in adipose tissue may therefore engender insulin resistance through increased macrophage-induced inflammation. The adiponectin gene (ACDC) lies on a region of chromosome 3 that has been linked to Type 2 diabetes susceptibility [130,131]. Two common polymorphisms in ACDC, T45G in exon 2 and G276T in intron 2, have been associated with obesity, T2DM and insulin resistance in a number of studies [132,133].

Peroxisome proliferator-activated receptor gamma is a transcription factor receptor that regulates several genes involved in glucose homeostasis, lipid metabolism, inflammation and tumorigenesis. Activation of PPARγ enhances insulin sensitivity, and pharmacological activators of PPARγ such as thiazolidinediones are used to treat T2DM [134]. Further evidence as to the role played by PPARγ in insulin resistance came from the identification of loss-of-function mutations in PPARγ that cause insulin resistance [135]. Interestingly, a nonsynonymous single nucleotide polymorphism termed Pro12Ala has been associated with elevated insulin sensitivity, despite reduced receptor activity among *Ala-carriers [136]. Furthermore, pparg<sup>−/−</sup> knock-out mice are protected against high-fat diet-induced obesity and insulin resistance [137]. Variation at the PPARG locus has been associated with BMI, WHR, circulating leptin levels and T2DM. In addition, the Pro12Ala polymorphism has been linked to colorectal cancer and adenoma risk [138,139], and loss of function heterozygous mutations of PPARG have been identified in tumors from human colorectal cancer patients [62].

5.4. Genes involved in regulation of energy expenditure

The energy imbalance that results in obesity is caused by an excess of energy input over energy output. In humans, energy expenditure is represented by resting metabolic requirements, physical activity and adaptive thermogenesis. The genetics of physical activity are likely to be complex and integrate both physiological and behavioral mechanisms. The propensity to be physically active certainly varies between individuals, but there is scarce data on the genetic basis for this variation thus far.

Adaptive thermogenesis entails the expenditure of energy as heat and seeks to maintain the body temperature within a narrow, physiologically viable range. The mitochondrial respiratory chain yields potential energy in the form of a proton gradient, which may be harnessed by the ATP synthase but can also be dissipated as heat by the action of a set of uncoupling proteins (UCPs). To date, three members of the UCP family have been identified with varying tissue distribution, but little is known of their function in humans. A C(−55)T polymorphism of the UCP3 gene has been linked to fat distribution [140–142] and BMI [143–145], whereas a variant in the 5’-region of UCP1 has been associated with obesity [146]. Carriage of the UCP2*866A allele has been linked to elevated triglyceride and cholesterol levels [147]. Polymorphisms of UCP2 have been associated with risk of T2DM [148,149].

The β-adrenoceptors regulate adaptive thermogenesis, integrating peripheral signals from the sympathetic nervous system to the adipose tissue. This important role in the regulation of energy expenditure has prompted many researchers to investigate whether variants of beta-adrenoceptor (ADRB) genes encoding the beta-adrenergic receptors are linked to body size. The ADRB3*Arg64 allele has been associated with obesity in some [150–152] but not all studies [153,154]. Several variants of the ADRB2 gene have also been linked to obesity, although not all studies have found associations. Three ADRB2 polymorphisms that lead to nonsynonymous amino acid substitutions in the ADRB2 have been associated with weight gain [155], BMI [156] and serum triglyceride and insulin levels [157].

6. Conclusions and perspective

Obesity is a result of an imbalance between energy intake and expenditure and integrates environmental and genetic factors. The worldwide obesity phenomenon that has been
attributed to “westernization” has been paralleled by dramatic increases in the incidence of colorectal cancer in the previous two or three decades, and mechanistic and observational work have implicated increased body size as a risk factor for colorectal cancer. Among the putative mechanisms advanced to explain this relation, insulin resistance and its plethora of metabolic consequences have been studied most intensively. In addition, the emergence of the notion that obesity is an inflammatory disease has provided an additional mechanism, which may mediate the obesity-colorectal cancer relation.

Advances in genomics have permitted the identification of chromosomal regions and genes, which bear obesity-associated variants. In combination with candidate gene approaches to identifying obesity-related loci, studies have highlighted potential body-size susceptibility loci and have provided clues to mechanisms, which may underlie the pathogenesis of obesity. Preliminary findings require replication, and exploration of pathways beyond those described here warrants attention. Potential areas of future work include the components of the lipostatic regulatory system such as orexigenic and anorexigenic signals. In addition, the genetics of physical activity is a relatively uncharted domain. Further elucidation of the genetic and biological determinants of obesity may facilitate appropriate pharmacological and dietary interventions targeted at pathways related to increased colorectal cancer risk.

References


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