Available online at www.sciencedirect.com

SCIENCE DIRECT®

Journal of Nutritional Biochemistry 17 (2006) 145–156

Journal of Nutritional Biochemistry

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

Received 26 May 2005; received in revised form 14 June 2005; accepted 15 June 2005

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.

Keywords: Body size; Obesity; Colorectal cancer; Insulin resistance; Genetics

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/m^2 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).

0955-2863/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.jnutbio.2005.06.011

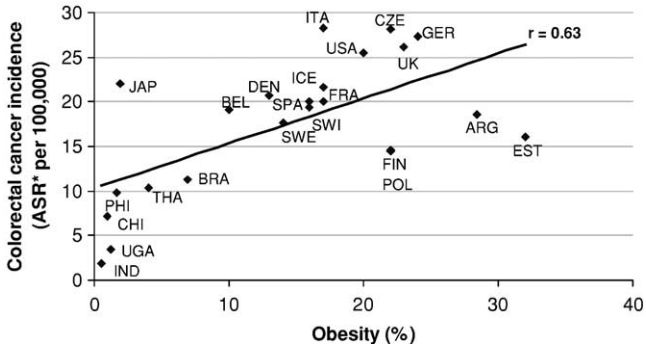

Fig. 1. A plot of age standardized colorectal cancer incidence vs. obesity prevalence (%) for 23 countries. *ASR, age standardized rates. Colorectal cancer ASR (2002) and obesity prevalence (percentage of the population with a BMI 30 kg/m^2 or more) data were obtained from IARC [4,5] .

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/m^2) or obese individuals (BMI>30 kg/m^2) compared with normal weight individuals (BMI 18.5–25 kg/m^2) 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/m^2) conferred a 1.7-fold increased risk of colon cancer compared to a BMI<24.8 kg/m^2 [33]. Following adjustment for BMI, a large prospective study found a twofold elevated risk for colorectal cancer among men and women

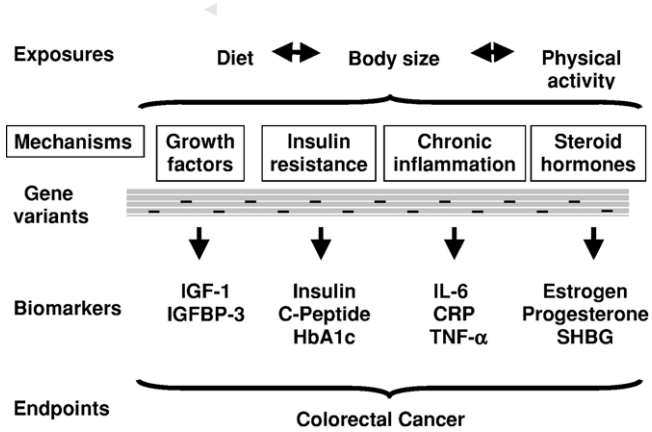

Fig. 2. Proposed mechanisms that link energy balance and colorectal cancer (HbA1c, glycated hemoglobin).

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 nonesterified 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 diacylglycerol 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

Table 1
Examples of groups of candidate genes for obesity and insulin resistance

Pathway	Gene	Polymorphism	Variant phenotype
Insulin signaling	*INS*	−315 (ins)	T2DM [91,92]
		−596 VNTR	Obesity, T2DM
	INSR	Val985Met	T2DM, obesity [93]
	IRS1	Gly972Arg	Insulin resistance
	IRS2	Gly1057Asp	T2DM, BMI [96,97,103]
	PI3K	Met326Ile	Insulin resistance [107]
IGF system	*IGF1*	−969[CA](*n*)	↓ IGF1, body fat [108,109]
	IGF2	*Apa*I	BMI [114]
			Visceral fat [112]
Adipokines and regulators of adipocyte metabolism and differentiation	*ACDC*	T+45G	T2DM [132]
		G+276T	T2DM [133]
	LEP	A19G,G-2548	Obesity [128,129]
	TNF	G-308A	WHR, obesity [117–119]
	PPARG	Pro12Ala	BMI, WHR, leptin, body fat, T2DM [135,136]
Peripheral regulation of energy expenditure and homeostasis	*UCP1*	−3826G	BMI, WHR [146]
	UCP-2	G-866A	T2DM [148,149]
			↑ TG, cholesterol [147]
	UCP-3	C-55T	BMI [143–145]
	ADRB2	Arg16Gly	Body weight increase [154]
		Gln27Glu	BMI [156]
		Thr164Ile	Lipolysis [157]
	ADRB3	Trp64Arg	WHR, BMI, T2DM [150–152]

resistance in a number of insulin-responsive tissues, and animal models have demonstrated that obese *tnf*$^{-/-}$ 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 Val985Met 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-inflammatory 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 *PPARG* 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*$^{-/-}$ knockout 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-adrenoreceptor (*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

[1] International Obesity Taskforce. http://www.iotf.org [accessed 2005].

[2] Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002; 288:1723–7.

[3] Seidell JC. Obesity, insulin resistance and diabetes — a worldwide epidemic. Br J Nutr 2000;(83 Suppl 1):S5–S8.

[4] IARC. Weight control and physical activity. IARC handbooks of cancer prevention, vol.6. Lyon, France: IARC Press; 2002.

[5] Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents. Lyon, France: IARC Press; 2002.

[6] Steinbach G, Kumar SP, Reddy BS, Lipkin M, Holt PR. Effects of caloric restriction and dietary fat on epithelial cell proliferation in rat colon. Cancer Res 1993;53:2745–9.

[7] Premoselli F, Sesca E, Binasco V, Caderni G, Tessitore L. Fasting/re-feeding before initiation enhances the growth of aberrant crypt foci induced by azoxymethane in rat colon and rectum. Int J Cancer 1998;77:286–94.

[8] Bouchard C. Genetics of obesity: overview and research directions. Genetics Obesity 1994;223–233.

[9] Graham S, Marshall J, Haughey B, Mittelman A, Swanson M, Zielezny M, et al. Dietary epidemiology of cancer of the colon in western New York. Am J Epidemiol 1988;128:490–503.

[10] Kune GA, Kune S, Watson LF. Body weight and physical activity as predictors of colorectal cancer risk. Nutr Cancer 1990; 13:9–17.

[11] Gerhardsson de Verdier M, Hagman U, Steineck G, Rieger A, Norell SE. Diet, body mass and colorectal cancer: a case-referent study in Stockholm. Int J Cancer 1990;46:832–8.

[12] Le Marchand L, Wilkens LR, Kolonel LN, Hankin JH, Lyu LC. Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. Cancer Res 1997;57:4787–94.

[13] Caan BJ, Coates AO, Slattery ML, Potter JD, Quesenberry Jr CP, Edwards SM. Body size and the risk of colon cancer in a large case-control study. Int J Obes Relat Metab Disord 1998;22:178–84.

[14] Russo A, Franceschi S, La Vecchia C, Dal Maso L, Montella M, Conti E, et al. Body size and colorectal-cancer risk. Int J Cancer 1998;78:161–5.

[15] Dietz AT, Newcomb PA, Marcus PM, Storer BE. The association of body size and large bowel cancer risk in Wisconsin (United States) women. Cancer Causes Control 1995;6:30–6.

[16] Boutron-Ruault MC, Senesse P, Meance S, Belghiti C, Faivre J. Energy intake, body mass index, physical activity, and the colorectal adenoma-carcinoma sequence. Nutr Cancer 2001;39:50–7.

[17] Lee IM, Paffenbarger Jr RS. Quetelet's index and risk of colon cancer in college alumni. J Natl Cancer Inst 1992;84:1326–31.

[18] Bostick RM, Potter JD, Kushi LH, Sellers TA, Steinmetz KA, McKenzie DR, et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). Cancer Causes Control 1994;5:38–52.

[19] Chyou PH, Nomura AM, Stemmermann GN. A prospective study of weight, body mass index and other anthropometric measurements in relation to site-specific cancers. Int J Cancer 1994;57:313–7.

[20] Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327–34.

[21] Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J Natl Cancer Inst 1997;89:948–55.

[22] Ford ES. Body mass index and colon cancer in a national sample of adult US men and women. Am J Epidemiol 1999;150:390–8.

[23] Murphy TK, Calle EE, Rodriguez C, Kahn HS, Thun MJ. Body mass index and colon cancer mortality in a large prospective study. Am J Epidemiol 2000;152:847–54.

[24] Lin J, Zhang SM, Cook NR, Rexrode KM, Lee IM, Buring JE. Body mass index and risk of colorectal cancer in women (United States). Cancer Causes Control 2004;15:581–9.

[25] Tamakoshi K, Wakai K, Kojima M, Watanabe Y, Hayakawa N, Toyoshima H, et al. A prospective study of body size and colon cancer mortality in Japan: the JACC Study. Int J Obes Relat Metab Disord 2004;28:551–8.

[26] Moore LL, Bradlee ML, Singer MR, Splansky GL, Proctor MH, Ellison RC, et al. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. Int J Obes Relat Metab Disord 2004;28:559–67.

[27] Neugut AI, Lee WC, Garbowski GC, Waye JD, Forde KA, Treat MR, et al. Obesity and colorectal adenomatous polyps. J Natl Cancer Inst 1991;83:359–61.

[28] Shinchi K, Kono S, Honjo S, Todoroki I, Sakurai Y, Imanishi K, et al. Obesity and adenomatous polyps of the sigmoid colon. Jpn J Cancer Res 1994;85:479–84.

[29] Davidow AL, Neugut AI, Jacobson JS, Ahsan H, Garbowski GC, Forde KA, et al. Recurrent adenomatous polyps and body mass index. Cancer Epidemiol Biomarkers Prev 1996;5:313–5.

[30] Giovannucci E, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk of colorectal adenoma in women (United States). Cancer Causes Control 1996;7:253–63.

[31] Bird CL, Frankl HD, Lee ER, Haile RW. Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. Am J Epidemiol 1998;147:670–80.

[32] Kono S, Handa K, Hayabuchi H, Kiyohara C, Inoue H, Marugame T, et al. Obesity, weight gain and risk of colon adenomas in Japanese men. Jpn J Cancer Res 1999;90:805–11.

[33] MacInnis RJ, English DR, Hopper JL, Haydon AM, Gertig DM, Giles GG. Body size and composition and colon cancer risk in men. Cancer Epidemiol Biomarkers Prev 2004;13:553–9.

[34] Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
[35] Slattery ML, Caan BJ, Potter JD, Berry TD, Coates A, Duncan D, et al. Dietary energy sources and colon cancer risk. Am J Epidemiol 1997;145:199–210.
[36] Franceschi S, Dal Maso L, Augustin L, Negri E, Parpinel M, Boyle P, et al. Dietary glycemic load and colorectal cancer risk. Ann Oncol 2001;12:173–8.
[37] Higginbotham S, Zhang ZF, Lee IM, Cook NR, Giovannucci E, Buring JE, et al. Dietary glycemic load and risk of colorectal cancer in the Women's Health Study. J Natl Cancer Inst 2004;96: 229–33.
[38] Michaud DS, Fuchs CS, Liu S, Willett WC, Colditz GA, Giovannucci E. Dietary glycemic load, carbohydrate, sugar, and colorectal cancer risk in men and women. Cancer Epidemiol Biomarkers Prev 2005;14:138–47.
[39] Kushi L, Giovannucci E. Dietary fat and cancer. Am J Med 2002;(113 Suppl 9B):63S–70S.
[40] Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. J Nutr 2002;132:3456S–64S.
[41] Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Preliminary communication: glycated hemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European prospective investigation into cancer — Norfolk study. Cancer Epidemiol Biomarkers Prev 2004;13:915–9.
[42] Yam D, Fink A, Mashiah A, Ben-Hur E. Hyperinsulinemia in colon, stomach and breast cancer patients. Cancer Lett 1996;104:129–32.
[43] Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. Br J Cancer 2001;84:417–22.
[44] Platz EA, Hankinson SE, Rifai N, Colditz GA, Speizer FE, Giovannucci E. Glycosylated hemoglobin and risk of colorectal cancer and adenoma (United States). Cancer Causes Control 1999;10:379–86.
[45] Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, et al. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. J Natl Cancer Inst 2000;92:1592–600.
[46] Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194–202.
[47] Saydah SH, Platz EA, Rifai N, Pollak MN, Brancati FL, Helzlsouer KJ. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2003;12:412–8.
[48] Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. J Natl Cancer Inst 1999;91:620–5.
[49] Yamada K, Araki S, Tamura M, Sakai I, Takahashi Y, Kashihara H, et al. Relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma in situ. Int J Epidemiol 1998;27:794–8.
[50] Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst 1999;91:1147–54.
[51] McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? Cancer Epidemiol Biomarkers Prev 1994;3:687–95.
[52] Kim YI. Diet, lifestyle, and colorectal cancer: is hyperinsulinemia the missing link? Nutr Rev 1998;56:275–9.
[53] Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 2001;131:3109S–20S.
[54] Koenuma M, Yamori T, Tsuruo T. Insulin and insulin-like growth factor 1 stimulate proliferation of metastatic variants of colon carcinoma 26. Jpn J Cancer Res 1989;80:51–8.
[55] Wu X, Fan Z, Masui H, Rosen N, Mendelsohn J. Apoptosis induced by an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin. J Clin Invest 1995;95:1897–905.
[56] Bjork J, Nilsson J, Hultcrantz R, Johansson C. Growth-regulatory effects of sensory neuropeptides, epidermal growth factor, insulin, and somatostatin on the non-transformed intestinal epithelial cell line IEC-6 and the colon cancer cell line HT 29. Scand J Gastroenterol 1993;28:879–84.
[57] Tran TT, Medline A, Bruce WR. Insulin promotion of colon tumors in rats. Cancer Epidemiol Biomarkers Prev 1996;5:1013–5.
[58] Corpet DE, Jacquinet C, Peiffer G, Tache S. Insulin injections promote the growth of aberrant crypt foci in the colon of rats. Nutr Cancer 1997;27:316–20.
[59] Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001;414:799–806.
[60] Prentki M. New insights into pancreatic beta-cell metabolic signaling in insulin secretion. Eur J Endocrinol 1996;134:272–86.
[61] Torra IP, Chinetti G, Duval C, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice. Curr Opin Lipidol 2001;12:245–54.
[62] Sarraf P, Mueller E, Smith WM, Wright HM, Kum JB, Aaltonen LA, et al. Loss-of-function mutations in PPAR gamma associated with human colon cancer. Mol Cell 1999;3:799–804.
[63] Doney AS, Fischer B, Cecil JE, Boylan K, McGuigan FE, Ralston SH, et al. Association of the Pro12Ala and C1431T variants of PPARG and their haplotypes with susceptibility to Type 2 diabetes. Diabetologia 2004;47:555–8.
[64] Draper HH, Bettger WJ. Role of nutrients in the cause and prevention of oxygen radical pathology. Adv Exp Med Biol 1994; 366:269–89.
[65] Paolisso G, Giugliano D. Oxidative stress and insulin action: is there a relationship? Diabetologia 1996;39:357–63.
[66] Dandona P, Thusu K, Cook S, Snyder B, Makowski J, Armstrong D, et al. Oxidative damage to DNA in diabetes mellitus. Lancet 1996; 347:444–5.
[67] Rechler MM. Growth inhibition by insulin-like growth factor (IGF) binding protein-3 — what's IGF got to do with it? Endocrinology 1997;138:2645–7.
[68] Jenkins PJ, Fairclough PD, Richards T, Lowe DG, Monson J, Grossman A, et al. Acromegaly, colonic polyps and carcinoma. Clin Endocrinol (Oxf) 1997;47:17–22.
[69] Kaaks R, Lukanova A, Sommersberg B. Plasma androgens, IGF-1, body size, and prostate cancer risk: a synthetic review. Prostate Cancer Prostatic Dis 2000;3:157–72.
[70] Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002;106:2067–72.
[71] Mohanty P, Hamouda W, Garg R, Aljada A, Ghanim H, Dandona P. Glucose challenge stimulates reactive oxygen species (ROS) generation by leukocytes. J Clin Endocrinol Metab 2000; 85:2970–3.
[72] Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87–91.
[73] Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab 2001;280:E745–51.
[74] Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526–35.
[75] IARC. Non-steroidal anti-inflammatory drugs. IARC handbooks of cancer prevention, vol. 1. Lyon, France: IARC Press; 1997.
[76] Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ. C-reactive protein and the risk of incident colorectal cancer. JAMA 2004; 291:585–90.

[77] Gunter MJ, Stolzenberg-Solomon R, Cross AJ, Leitzmann MF, Wood R, Taylor P, et al. Serum C-reactive protein levels and incident colorectal cancer risk in a cohort of Finnish male smokers. 2005 [Manuscript in preparation].
[78] Zhang SM, Buring JE, Lee IM, Cook NR, Ridker PM. C-reactive protein levels are not associated with increased risk for colorectal cancer in women. Ann Intern Med 2005;142:425–32.
[79] Jaiswal M, LaRusso NF, Burgart LJ, Gores GJ. Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. Cancer Res 2000;60:184–90.
[80] Jackson JR, Seed MP, Kircher CH, Willoughby DA, Winkler JD. The codependence of angiogenesis and chronic inflammation. FASEB J 1997;11:457–65.
[81] Grimble RF. Inflammatory status and insulin resistance. Curr Opin Clin Nutr Metab Care 2002;5:551–9.
[82] Ford ES, Giles WH, Mokdad AH, Myers GL. Distribution and correlates of C-reactive protein concentrations among adult US women. Clin Chem 2004;50:574–81.
[83] Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327–34.
[84] Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature 1997;389:610–4.
[85] Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM. Tumor necrosis factor alpha inhibits signaling from the insulin receptor. Proc Natl Acad Sci U S A 1994;91:4854–8.
[86] Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 1996;271:665–8.
[87] Emanuelli B, Peraldi P, Filloux C, Chavey C, Freidinger K, Hilton DJ, et al. Obberghen, SOCS-3 inhibits insulin signaling and is up-regulated in response to tumor necrosis factor-alpha in the adipose tissue of obese mice. J Biol Chem 2001;276:47944–9.
[88] Nonogaki K, Fuller GM, Fuentes NL, Moser AH, Staprans I, Grunfeld C, et al. Interleukin-6 stimulates hepatic triglyceride secretion in rats. Endocrinology 1995;136:2143–9.
[89] Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest 2000;106:171–6.
[90] Coady SA, Jaquish CE, Fabsitz RR, Larson MG, Cupples LA, Myers RH. Genetic variability of adult body mass index: a longitudinal assessment in Framingham families. Obes Res 2002; 10:675–81.
[91] Ong KK, Phillips DI, Fall C, Poulton J, Bennett ST, Golding J, et al. The insulin gene VNTR, type 2 diabetes and birth weight. Nat Genet 1999;21:262–3.
[92] Le Stunff C, Fallin D, Schork NJ, Bougneres P. The insulin gene VNTR is associated with fasting insulin levels and development of juvenile obesity. Nat Genet 2000;26:444–6.
[93] Hart LM, Stolk RP, Heine RJ, Grobbee DE, van der Does FE, Maassen JA. Association of the insulin-receptor variant Met-985 with hyperglycemia and non-insulin-dependent diabetes mellitus in the Netherlands: a population-based study. Am J Hum Genet 1996;59:1119–25.
[94] Almind K, Inoue G, Pedersen O, Kahn CR. A common amino acid polymorphism in insulin receptor substrate-1 causes impaired insulin signaling. Evidence from transfection studies. J Clin Invest 1996;97:2569–75.
[95] Yoshimura R, Araki E, Ura S, Todaka M, Tsuruzoe K, Furukawa N, et al. Impact of natural IRS-1 mutations on insulin signals: mutations of IRS-1 in the PTB domain and near SH2 protein binding sites result in impaired function at different steps of IRS-1 signaling. Diabetes 1997;46:929–36.
[96] Hitman GA, Hawrami K, McCarthy MI, Viswanathan M, Snehalatha C, Ramachandran A, et al. Insulin receptor substrate-1 gene mutations in NIDDM; implications for the study of polygenic disease. Diabetologia 1995;38:481–6.
[97] Clausen JO, Hansen T, Bjorbaek C, Echwald SM, Urhammer SA, Rasmussen S, et al. Insulin resistance: interactions between obesity and a common variant of insulin receptor substrate-1. Lancet 1995;346:397–402.
[98] Slattery ML, Samowitz W, Curtin K, Ma KN, Hoffman M, Caan B, et al. Associations among IRS1, IRS2, IGF1, and IGFBP3 genetic polymorphisms and colorectal cancer. Cancer Epidemiol Biomarkers Prev 2004;13:1206–14.
[99] Withers DJ, Gutierrez JS, Towery H, Burks DJ, Ren JM, Previs S, et al. Disruption of IRS-2 causes type 2 diabetes in mice. Nature 1998;391:900–4.
[100] Bernal D, Almind K, Yenush L, Ayoub M, Zhang Y, Rosshani L, et al. Insulin receptor substrate-2 amino acid polymorphisms are not associated with random type 2 diabetes among Caucasians. Diabetes 1998;47:976–9.
[101] Kalidas K, Wasson J, Glaser B, Meyer JM, Duprat LJ, White MF, et al. Mapping of the human insulin receptor substrate-2 gene, identification of a linked polymorphic marker and linkage analysis in families with type II diabetes: no evidence for a major susceptibility role. Diabetologia 1998;41:1389–91.
[102] Bektas A, Warram JH, White MF, Krolewski AS, Doria A. Exclusion of insulin receptor substrate 2 (IRS-2) as a major locus for early-onset autosomal dominant type 2 diabetes. Diabetes 1999;48:640–2.
[103] Lautier C, El Mkadem SA, Renard E, Brun JF, Gris JC, Bringer J, et al. Complex haplotypes of IRS2 gene are associated with severe obesity and reveal heterogeneity in the effect of Gly1057Asp mutation. Hum Genet 2003;113:34–43.
[104] Bjornholm M, Kawano Y, Lehtihet M, Zierath JR. Insulin receptor substrate-1 phosphorylation and phosphatidylinositol 3-kinase activity in skeletal muscle from NIDDM subjects after in vivo insulin stimulation. Diabetes 1997;46:524–7.
[105] Otsu M, Hiles I, Gout I, Fry MJ, Ruiz-Larrea F, Panayotou G, et al. Characterization of two 85 kd proteins that associate with receptor tyrosine kinases, middle-T/pp60c-src complexes, and PI3-kinase. Cell 1991;65:91–104.
[106] Antonetti DA, Algenstaedt P, Kahn CR. Insulin receptor substrate 1 binds two novel splice variants of the regulatory subunit of phosphatidylinositol 3-kinase in muscle and brain. Mol Cell Biol 1996;16:2195–203.
[107] Hansen T, Andersen CB, Echwald SM, Urhammer SA, Clausen JO, Vestergaard H, et al. Identification of a common amino acid polymorphism in the p85alpha regulatory subunit of phosphatidylinositol 3-kinase: effects on glucose disappearance constant, glucose effectiveness, and the insulin sensitivity index. Diabetes 1997;46: 494–501.
[108] Rosen CJ, Kurland ES, Vereault D, Adler RA, Rackoff PJ, Craig WY, et al. Association between serum insulin growth factor-I (IGF-I) and a simple sequence repeat in IGF-I gene: implications for genetic studies of bone mineral density. J Clin Endocrinol Metab 1998;83:2286–90.
[109] Sun G, Gagnon J, Chagnon YC, Perusse L, Despres JP, Leon AS, et al. Association and linkage between an insulin-like growth factor-1 gene polymorphism and fat free mass in the HERITAGE Family Study. Int J Obes Relat Metab Disord 1999;23:929–35.
[110] Slattery ML, Murtaugh M, Caan B, Ma KN, Neuhausen S, Samowitz W. Energy balance, insulin-related genes and risk of colon and rectal cancer. Int J Cancer 2005;115:148–54.
[111] Nezer C, Moreau L, Brouwers B, Coppieters W, Detilleux J, Hanset R, et al. An imprinted QTL with major effect on muscle mass and fat deposition maps to the IGF2 locus in pigs. Nat Genet 1999;21: 155–156.
[112] Rice T, Chagnon YC, Perusse L, Borecki IB, Ukkola O, Rankinen T, et al. A genomewide linkage scan for abdominal subcutaneous and visceral fat in black and white families: the HERITAGE Family Study. Diabetes 2002;51:848–55.

[113] O'Dell SD, Miller GJ, Cooper JA, Hindmarsh PC, Pringle PJ, Ford H, et al. Apal polymorphism in insulin-like growth factor II (IGF2) gene and weight in middle-aged males. Int J Obes Relat Metab Disord 1997;21:822–5.

[114] Gaunt TR, Cooper JA, Miller GJ, Day IN, O'Dell SD. Positive associations between single nucleotide polymorphisms in the IGF2 gene region and body mass index in adult males. Hum Mol Genet 2001;10:1491–501.

[115] Rodriguez S, Gaunt TR, O'Dell SD, Chen XH, Gu D, Hawe E, et al. Haplotypic analyses of the IGF2-INS-TH gene cluster in relation to cardiovascular risk traits. Hum Mol Genet 2004;13:715–25.

[116] Le Marchand L, Donlon T, Seifried A, Kaaks R, Rinaldi S, Wilkens LR. Association of a common polymorphism in the human GH1 gene with colorectal neoplasia. J Natl Cancer Inst 2002;94:454–60.

[117] Fernandez-Real JM, Gutierrez C, Ricart W, Casamitjana R, Fernandez-Castaner M, Vendrell J, et al. The TNF-alpha gene Nco I polymorphism influences the relationship among insulin resistance, percent body fat, and increased serum leptin levels. Diabetes 1997;46:1468–72.

[118] Herrmann SM, Ricard S, Nicaud V, Mallet C, Arveiler D, Evans A, et al. Polymorphisms of the tumour necrosis factor-alpha gene, coronary heart disease and obesity. Eur J Clin Invest 1998; 28:59–66.

[119] Hoffstedt J, Eriksson P, Hellstrom L, Rossner S, Ryden M, Arner P. Excessive fat accumulation is associated with the TNF alpha-308 G/A promoter polymorphism in women but not in men. Diabetologia 2000;43:117–20.

[120] Kolaczynski JW, Ohannesian JP, Considine RV, Marco CC, Caro JF. Response of leptin to short-term and prolonged overfeeding in humans. J Clin Endocrinol Metab 1996;81:4162–5.

[121] Dallongeville J, Hecquet B, Lebel P, Edme JL, Le Fur C, Fruchart JC, et al. Short term response of circulating leptin to feeding and fasting in man: influence of circadian cycle. Int J Obes Relat Metab Disord 1998;22:728–33.

[122] Zimmet PZ, Collins VR, de Courten MP, Hodge AM, Collier GR, Dowse GK, et al. Is there a relationship between leptin and insulin sensitivity independent of obesity? A population-based study in the Indian Ocean nation of Mauritius. Mauritius NCD Study Group. Int J Obes Relat Metab Disord 1998;22:171–7.

[123] Falorni A, Bini V, Molinari D, Papi F, Celi F, Di Stefano G, et al. Leptin serum levels in normal weight and obese children and adolescents: relationship with age, sex, pubertal development, body mass index and insulin. Int J Obes Relat Metab Disord 1997;21:881–90.

[124] Kennedy A, Gettys TW, Watson P, Wallace P, Ganaway E, Pan Q, et al. The metabolic significance of leptin in humans: gender-based differences in relationship to adiposity, insulin sensitivity, and energy expenditure. J Clin Endocrinol Metab 1997;82:1293–300.

[125] Hardwick JC, Van Den Brink GR, Offerhaus GJ, Van Deventer SJ, Peppelenbosch MP. Leptin is a growth factor for colonic epithelial cells. Gastroenterology 2001;121:79–90.

[126] Stattin P, Palmqvist R, Soderberg S, Biessy C, Ardnor B, Hallmans G, et al. Plasma leptin and colorectal cancer risk: a prospective study in Northern Sweden. Oncol Rep 2003;10:2015–21.

[127] Jiang Y, Wilk JB, Borecki I, Williamson S, DeStefano AL, Xu G, et al. Common variants in the 5′ region of the leptin gene are associated with body mass index in men from the National Heart, Lung, and Blood Institute Family Heart Study. Am J Hum Genet 2004;75:220–30.

[128] Mammes O, Betoulle D, Aubert R, Herbeth B, Siest G, Fumeron F. Association of the G-2548A polymorphism in the 5′ region of the LEP gene with overweight. Ann Hum Genet 2000;64:391–4.

[129] Hager J, Clement K, Francke S, Dina C, Raison J, Lahlou N, et al. A polymorphism in the 5′ untranslated region of the human ob gene is associated with low leptin levels. Int J Obes Relat Metab Disord 1998;22:200–5.

[130] Kissebah AH, Sonnenberg GE, Myklebust J, Goldstein M, Broman RG, James RG, et al. Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. Proc Natl Acad Sci U S A 2000;97:14478–83.

[131] Vionnet N, Hani El H, Dupont S, Gallina S, Francke S, Dotte S, et al. Genomewide search for type 2 diabetes-susceptibility genes in French whites: evidence for a novel susceptibility locus for early-onset diabetes on chromosome 3q27-qter and independent replication of a type 2-diabetes locus on chromosome 1q21-q24. Am J Hum Genet 2000;67:1470–80.

[132] Menzaghi C, Ercolino T, Di Paola R, Berg AH, Warram JH, Scherer PE, et al. A haplotype at the adiponectin locus is associated with obesity and other features of the insulin resistance syndrome. Diabetes 2002;51:2306–12.

[133] Filippi E, Sentinelli F, Trischitta V, Romeo S, Arca M, Leonetti F, et al. Association of the human adiponectin gene and insulin resistance. Eur J Hum Genet 2004;12:199–205.

[134] Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). J Biol Chem 1995;270:12953–6.

[135] Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, et al. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. Nature 1999;402:880–3.

[136] Deeb SS, Fajas L, Nemoto M, Pihlajamaki J, Mykkanen L, Kuusisto J, et al. A Pro12Ala substitution in PPARgamma2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. Nat Genet 1998;20:284–7.

[137] Jones JR, Barrick C, Kim KA, Lindner J, Blondeau B, Fujimoto Y, et al. Deletion of PPAR{gamma} in adipose tissues of mice protects against high fat diet-induced obesity and insulin resistance. Proc Natl Acad Sci U S A 2005;102:6207–12.

[138] Landi S, Moreno V, Gioia-Patricola L, Guino E, Navarro M, de Oca J, et al. Association of common polymorphisms in inflammatory genes interleukin (IL)6, IL8, tumor necrosis factor alpha, NFKB1, and peroxisome proliferator-activated receptor gamma with colorectal cancer. Cancer Res 2003;63:3560–6.

[139] Gong Z, Xie D, Deng Z, Bostick RM, Muga SJ, Hurley TG, et al. The PPAR{gamma} Pro12Ala polymorphism and risk for incident sporadic colorectal adenomas. Carcinogenesis 2005;26: 579–85.

[140] Cassell PG, Saker PJ, Huxtable SJ, Kousta E, Jackson AE, Hattersley AT, et al. Evidence that single nucleotide polymorphism in the uncoupling protein 3 (UCP3) gene influences fat distribution in women of European and Asian origin. Diabetologia 2000; 43:1558–64.

[141] Kim OY, Cho EY, Park HY, Jang Y, Lee JH. Additive effect of the mutations in the beta3-adrenoceptor gene and UCP3 gene promoter on body fat distribution and glycemic control after weight reduction in overweight subjects with CAD or metabolic syndrome. Int J Obes Relat Metab Disord 2004;28:434–41.

[142] Shen H, Xiang K, Jia W. Effects of uncoupling protein 3 gene −55 C→T variant on lipid metabolism, body fat, its distribution and non-insulin-dependent diabetes mellitus in Chinese. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2002;19:317–21.

[143] Walder K, Norman RA, Hanson RL, Schrauwen P, Neverova M, Jenkinson CP, et al. Association between uncoupling protein polymorphisms (UCP2–UCP3) and energy metabolism/obesity in Pima Indians. Hum Mol Genet 1998;7:1431–5.

[144] Otabe S, Clement K, Dina C, Pelloux V, Guy-Grand B, Froguel P, et al. A genetic variation in the 5′ flanking region of the UCP3 gene is associated with body mass index in humans in interaction with physical activity. Diabetologia 2000;43:245–9.

[145] Halsall DJ, Luan J, Saker P, Huxtable S, Farooqi IS, Keogh J, et al. Uncoupling protein 3 genetic variants in human obesity: the c-55t promoter polymorphism is negatively correlated with body mass

index in a UK Caucasian population. Int J Obes Relat Metab Disord 2001;25:472–7.

[146] Matsushita H, Kurabayashi T, Tomita M, Kato N, Tanaka K. Effects of uncoupling protein 1 and beta3-adrenergic receptor gene polymorphisms on body size and serum lipid concentrations in Japanese women. Maturitas 2003;45:39–45.

[147] Reis AF, Dubois-Laforgue D, Bellanne-Chantelot C, Timsit J, Velho G. A polymorphism in the promoter of UCP2 gene modulates lipid levels in patients with type 2 diabetes. Mol Genet Metab 2004;82:339–44.

[148] Krempler F, Esterbauer H, Weitgasser R, Ebenbichler C, Patsch JR, Miller K, et al. A functional polymorphism in the promoter of UCP2 enhances obesity risk but reduces type 2 diabetes risk in obese middle-aged humans. Diabetes 2002;51:3331–5.

[149] Wang H, Chu WS, Lu T, Hasstedt SJ, Kern PA, Elbein SC. Uncoupling protein-2 polymorphisms in type 2 diabetes, obesity, and insulin secretion. Am J Physiol Endocrinol Metab 2004; 286:E1–E7.

[150] Corella D, Guillen M, Portoles O, Sorli JV, Alonso V, Folch J, et al. Gender specific associations of the Trp64Arg mutation in the beta3-adrenergic receptor gene with obesity-related phenotypes in a Mediterranean population: interaction with a common lipoprotein lipase gene variation. J Intern Med 2001;250:348–60.

[151] Marti A, Corbalan MS, Martinez-Gonzalez MA, Martinez JA. TRP64ARG polymorphism of the beta 3-adrenergic receptor gene and obesity risk: effect modification by a sedentary lifestyle. Diabetes Obes Metab 2002;4:428–30.

[152] Hao K, Peng S, Xing H, Yu Y, Huang A, Hong X, et al. beta(3) Adrenergic receptor polymorphism and obesity-related phenotypes in hypertensive patients. Obes Res 2004;12:125–30.

[153] Gagnon J, Mauriege P, Roy S, Sjostrom D, Chagnon YC, Dionne FT, et al. The Trp64Arg mutation of the beta3 adrenergic receptor gene has no effect on obesity phenotypes in the Quebec Family Study and Swedish Obese Subjects cohorts. J Clin Invest 1996;98:2086–93.

[154] Hegele RA, Harris SB, Hanley AJ, Azouz H, Connelly PW, Zinman B. Absence of association between genetic variation of the beta 3-adrenergic receptor and metabolic phenotypes in Oji-Cree. Diabetes Care 1998;21:851–4.

[155] Ukkola O, Tremblay A, Bouchard C. Beta-2 adrenergic receptor variants are associated with subcutaneous fat accumulation in response to long-term overfeeding. Int J Obes Relat Metab Disord 2001;25:1604–8.

[156] Ukkola O, Rankinen T, Weisnagel SJ, Sun G, Perusse L, Chagnon YC, et al. Interactions among the alpha2-, beta2-, and beta3-adrenergic receptor genes and obesity-related phenotypes in the Quebec Family Study. Metabolism 2000;49:1063–70.

[157] Carlsson M, Orho-Melander M, Hedenbro J, Groop LC. Common variants in the beta2-(Gln27Glu) and beta3-(Trp64Arg)-adrenoceptor genes are associated with elevated serum NEFA concentrations and type II diabetes. Diabetologia 2001;44:629–36.