Diets link metabolic syndrome and colorectal cancer development (Review)

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Abstract. Diets have been believed to be an important factor in the development of metabolic syndrome and colorectal cancer (CRC). In recent years, many studies have shown an intimate relationship between mucosal immunity, metabolism and diets, which has led to a greater understanding of the pathophysiology of metabolic syndrome and CRC development. Although the precise effects of diets on oncogenesis have not been completely elucidated, microbiota changes and inflammation are believed to be important factors that influence the development of CRC. Moreover, increased release of pro-inflammatory cytokines and alteration of adipokine levels have been observed in patients with colorectal adenoma and/or CRC, and these all have been considered as the important mechanisms that link diets to the development of metabolic syndrome and CRC. Importantly, a high-fat, low-fiber diet is associated with dysbiosis, and as the gut signature becomes more important in metabolic syndrome and CRC, an increased understanding of diets on bacterial activity in the pathogenesis of metabolic syndrome and CRC will lead to new preventive and therapeutic strategies.

Contents

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1. Introduction

Visceral obesity or, in its broader terminology, metabolic syndrome is an emerging lifestyle-related health problem that has globally increased in prevalence in recent decades (1-5). Metabolic syndrome is clinically defined as a combination of visceral obesity, increased blood pressure, insulin resistance and dyslipidemia (6,7). This condition has been extensively investigated due to its correlation with various health problems in humans, including cardiovascular diseases, type 2 diabetes (T2D) and non-alcoholic fatty liver disease. In addition to these diseases, which are directly related to visceral adiposity, recent studies have also explored other consequences of metabolic syndrome, such as thromboembolic conditions, hypogonadism and various cancers (8-11). Recent studies have suggested that the pathophysiology of metabolic syndrome is partly associated with dysfunction of the intestinal flora (12-14), a condition called dysbiosis (15). Both brain functions and gut microbiota influence fat intake and increased body mass, which in turn is a source of cytokines that induce chronic, low-grade inflammation and carcinogenesis (16-18). Additionally, obesity itself influences the ecology of the gut microbiota population (19).

Colorectal cancer (CRC) is one the cancers that has been associated with metabolic syndrome. CRC is an epithelial cell-derived adenocarcinoma that develops through a multistep carcinogenic process known as the adenoma-carcinoma sequence. Epidemiological studies have demonstrated that colorectal adenomas and CRC risk are higher in individuals with metabolic syndrome or any of its components (20-22). A recent meta-analysis of cohort studies reported that metabolic syndrome was associated with higher relative risks of CRC in men at 1.25 (95% confidence interval; 1.19-1.32) and in women at 1.34 (1.09-1.64) (22). In recent decades, partly because of the improved resolution of high-throughput sequencing technology, the gut microbiome has been extensively investigated. Studies have suggested a link between diet-induced microbiota dysbiosis and colorectal carcinogenesis (22).

This review aims to update the current understanding of metabolic syndrome and its role as a pathogenic factor in colorectal pathogenesis.

2. Metabolic syndrome is a brain-, inflammatory- and microbial-related disease

Metabolic syndrome as a brain disease. Obesity is a major risk factor for several types of cardiovascular and metabolic diseases, such as hyperglycemia, T2D, hypertension and atherosclerosis (23). Individuals with more than three of these symptoms with or without obesity are diagnosed with 'metabolic syndrome'. Although obesity and metabolic syndrome are generally considered a problem of the gut, neurobiological studies have shown that the brain also plays an important role since neurobiological diseases, such as stroke, dementia, intracranial hypertension and sleep disorders are associated with obesity (24). Moreover, obesity can be initiated by pathological conditions of the brain and several neuropsychiatric drugs (25,26). Therefore, the brain appears to be a central regulator that directs energy fluxes within an organism.

According to the 'selfish brain theory' (27) which states that the human brain fulfills its own comparably high energy needs with the highest priority, there are three types of behavioral components regulated by the central nervous system for energy requests: allocative, ingestive and exploratory behaviors (28). The allocation of energy from the body to the central nervous system is the 'allocative behavior' carried out by organs such as the liver, pancreas, muscles and adipose tissue (28). The second strategy is 'ingestive behavior', describing a situation where the brain acquires energy from its immediate environment, which is initiated by sensory metabolic input signals, including leptin and insulin (28-30), and afferent nerve fibers (31,32). The last component, exploratory behavior, enables foraging in distant locations when energy resources in the immediate vicinity become scarce. The brain integrates all three of these behaviors to introduce a feedback control for an 'energy on demand' process that maintains an adequate ATP concentration in the nerve cells of the brain. However, if this allocative behavior of the brain fails to satisfy its energy requirements, ingestive behavior increases, leading to the promotion of higher body mass.

Obesity development may be caused by this allocative defect, in which the brain requires energy from food consumption instead of blood sugar (28). The mechanism of this failure may result from an abnormality in various regions of the brain, such as the hypothalamus, amygdala or hippocampus. Clinical studies dating back more than a century have demonstrated that hyperphagia and obesity can be induced by lesions of the ventromedial hypothalamus (VMH), a part of the brain that plays a role in preserving body mass (28,33). In animal studies, lesions of the VMH have caused weight gain in dogs, while VMH stimulation led to satiety (28,34). It is possible that lesions of the VMH lead to increased parasympathetic activity, resulting in an inadequate allocation of glucose to the brain. Then, the animal becomes hyperinsulinemic, finally resulting in hypoglycemia, neuroglycopenia and excessive body mass (35-37). In addition, several defective signaling pathways in the hypothalamus have been reported to be involved in obesity development. For example, studies have shown that loss of the leptin receptors in the hypothalamus resulted in obesity, insulin resistance and diabetes in mice (38,39). Leptin signaling abnormalities have also been found in obese patients and were caused by a monogenetic defect or a leptin receptor mutation in the hypothalamus (40,41).

A regulator of insulin and leptin signaling, protein tyrosine phosphatase 1B, has also been associated with leptin and insulin resistance in hypothalamic neurons (42,43) as neuronal protein tyrosine phosphatase 1B-knockout mice showed improved glucose tolerance following chronic high-fat feeding (44). Moreover, VMH lesions may be associated with an unusual vagus nerve-hypothalamus interaction pathway leading to miscommunication between the adipose tissue and β-cells (45). Other factors that result in obesity include a lack of α-melanocyte-stimulating hormone (46), insulin (47) or interleukin-6 (IL-6) (48) or bilateral lesions of the amygdala (36,49). However, not all obese individuals develop obesity due to lesions of the brain. The core concept of the selfish brain theory, the brain-pull hypothesis, posits that 'brain-pull' is the force with which the brain actively demands energy from the body (50), indicating that the brain has an active approach associated with specific brain-pull mechanisms (51). Stress has been suggested as the major mechanism that causes the brain to enter a hypervigilant state. This leads to an increased requirement for cerebral energy and initiation of brain-pull mechanisms (52,53), such as 'cerebral insulin suppression' that over time results in the loss of subcutaneous adipose tissue, the accumulation of visceral fat and an increased cerebral glucose supply (51).

Metabolic syndrome as an inflammatory disease. Metabolic syndrome and obesity are related to a chronic, low-grade systemic inflammatory condition characterized by increasing levels of circulating inflammatory cytokines and free fatty acids (FFAs) (54). In contrast to classical inflammation, this 'metabolic inflammation' (55,56) does not necessarily involve pathogens but occurs as a result of metabolic homeostatic abnormalities. Nowadays, obesity has been associated with inflammatory adipose tissue, which may be caused by higher immune cell accumulation in the fatty tissue region (57). The immune cells associated with this metabolic inflammation include macrophage, neutrophil and lymphocyte.

Adipose tissue macrophages (ATMs). ATMs appear to play a major role in the regulation of obesity-induced inflammation as ATMs generally play a key role in most cases of chronic inflammation, and these cells can comprise up to 40% of the cells in the adipose tissue (58). It is possible that obesity-induced inflammation is regulated by macrophages (59), and ATM accumulation can be found after as little as 1 week on a high-fat diet (60). Moreover, numerous studies have indicated that accumulation of monocytes and macrophages is positively linked to subcutaneous fat accumulation and weight gain (61). Elevated monocyte levels can be found in the circulation of obese individuals, and the levels decrease when the fat is lost (62,63). These circulating monocytes can be attracted to recruit into the adipose tissue by macrophage chemoattractant protein-1 (MCP-1) (also as known as CCL2), which is secreted by enlarging adipocytes (64,65). Interestingly, mice that lack CCR2, the receptor for MCP-1, showed a decreased food intake and obesity development and increased eosinophil accumulation, which highly increase the expression of IL-4 and IL-13 in the adipose tissue during high-fat diet feeding, leading to the predominance of M2 macrophages (66,67). In addition to

CCL2, other studies have found that CXCL12, CXCL14 and CCL5 also play roles in macrophage migration (68-70).

In the tissues, macrophages can be subgrouped into 2 types: the classically activated macrophages, termed M1 and the alternatively activated macrophages, termed M2 (71). The M1 macrophage is a $CD11c^+$ pro-inflammatory cell that produces inducible nitric oxide synthase and inflammatory cytokines, such as IL-6 and tumor necrosis factor-α (TNF-α), while the M2 macrophages, which can be identified by the markers CD206, CD209 and CD301 (Mgl1/2), express arginase 1 (Arg1) and immunosuppressive cytokines, including IL-10, transforming growth factor-β (TGF-β), IL-1 receptor antagonist (IL-1RA)-α and IL-4 (59). Interestingly, in obese adipose tissue, the production of anti-inflammatory IL-10 is decreased, and increased levels of inflammatory TNF-α are observed (72). This may be the obvious evidence showing the dominance of the pro-inflammatory macrophage in adipose tissue of obese person. However, recent study demonstrated that inflammatory ATMs found in obese adipose tissue have a uniquely distinct phenotype from M1 macrophages called 'metabolically activated (MMe) macrophages' (73), and this phenotype can be induced *in vitro* by treating macrophages with palmitate, insulin and glucose (metabolic activation) (73). While M1 macrophages display cellular markers CD319, CD274 and CD38, ATMs from obese individuals express lipid transport proteins ATP-binding cassette member 1 (ABCA1) and fatty acid translocase (CD36) (73). Although, both types of macrophages have different phynotypes, they still shared the pro-inflammatory properties by producing TNF-α, IL-6 and IL-1β (73).

Neutrophil. Neutrophils are granulocytes that carry a large number of granules (intracellular vesicles), which contain anti-microbial agents, including lysozyme, neutrophil elastase (NE), myeloperoxidase (MPO) and defensins (59). Although neutrophils are known to play a role in inflammation, it is still unclear whether this type of immune cells is involved in obesity-induced inflammation. Several studies have found that neutrophil migration into the adipose tissue and classical inflammation occurred within 3 days of beginning a high-fat diet in mice (74,75). However, another study found that the neutrophils decreased after 1 week of high-fat feeding, which suggests that neutrophils may play different roles in different stages of obesity development. In this study, they appeared to induce early polarization of ATMs toward the M1 phenotype with corresponding increases in TNF-α and IL-6 (74). Increased percentages of peripheral blood neutrophils have also been found in obese males (76).

T lymphocyte. Lymphocytes are strongly associated with inflammatory processes in obesity. Although there are several lymphocyte cell types that are related to obesity and metabolic syndrome, pro-inflammatory Th1, Th17 and $CD8^+$ T cells predominate over anti-inflammatory regulatory T cells (Treg) and Th2 cells, which are found in higher proportions in lean adipose tissue (77,78). One study found that mice fed a high-fat diet displayed more Th1 polarization and interferon-γ (IFN-γ) production, which occurred several months after macrophage accumulation and insulin resistance (79). However, the number of Treg cells was decreased in the adipose tissue of obese mice, but insulin sensitivity can also be improved when these cells are increased (78). An increased number of Th17 cells in the spleen has been found in mice fed a high-fat diet, but this cell was absent in *IL-6*$^{-/-}$ mice fed the same high-fat diet, indicating that IL-6 is important for Th17 expansion in obesity (80).

$CD8^+$ T cells are another type of lymphocytes that may be involved in obesity development since co-cultures of splenic $CD8^+$ T cells with adipose tissue from high-fat diet mice showed a higher proliferation rate of $CD8^+$ T cells than those of the lean controls (81). Several studies have also found that higher numbers of $CD8^+$ T cells were positively correlated with an increased risk of insulin resistance (78,81,82). The recovery of $CD8^+$ T cells in knockout mice exacerbated obesity-induced insulin resistance, and this was correlated with increased M1 macrophages and IL-6 and TNF-α gene expression in adipose tissue (81).

B lymphocyte. In addition to T cells, B cells have also shown a positive association with obesity in high-fat diet-fed mice because infiltration of B cells can be found in the adipose tissue of obese mice, and these cells can activate T cells and polarize macrophages toward the M1 type (83). One study found that the number of IgG-associated B cells increased rapidly after 4 weeks on a high-fat diet (84), and the cell numbers then remained consistent during the weight gain (83,85). By using neutralizing antibodies against the B cells, other studies have found that obesity-induced insulin resistance in mice could be improved, and a reduction in M1 macrophages and activation of $CD8^+$ T cells along with an increase in Treg numbers and M2 signatures could be observed in the adipose tissue (83,86). Although B cells are associated with the inflammatory condition in obesity, regulatory B cells, which produce IL-10, have been shown to improve insulin resistance and reduce pro-inflammatory cytokine production in the skeletal muscles of mice fed a high-fat diet (83). These results support the findings from other studies, which found that low levels of IL-10 were associated with metabolic syndrome and T2D (87,88).

Metabolic syndrome as a microbial-related disease. The human intestine contains a unique group of microorganisms comprising up to 1,000 different species with ~100 trillion cells of bacteria, yeasts and parasites (89). There are over 50 bacterial phyla that comprise the gastrointestinal (GI) microbiota, but ~90% consists of *Bacteroidetes* and *Firmicutes* (90,91), and diet is clearly seemed to be a major influence on microbiota compositions.

Various evidences have shown that alteration of the diet can result in changes in the bacterial composition that also affected gut metabolic activity, especially the production of short-chain fatty acids (Fig. 1) (92). This scenario can be found in obese individuals (93) as high-fat diets or diets low in fiber have been associated with a higher abundance of *Firmicutes* (94). Studies comparing obese individuals and their lean twins have also shown a higher predominance of *Firmicutes* and lower abundance of *Bacteroidetes* (93,95) in the obese subjects. Other studies, however, have not found a difference (96,97).

Alternatively, the association studies between gut microbiota in obesity and metabolic syndrome have been performed by using germ-free mice. Researchers found that conventionalization of germ-free C57BL/6 mice with normal microbiota harvested from conventionally raised, genetically obese mice resulted in 60% higher levels of body fat and the development of insulin resistance in 2 weeks, despite reduced

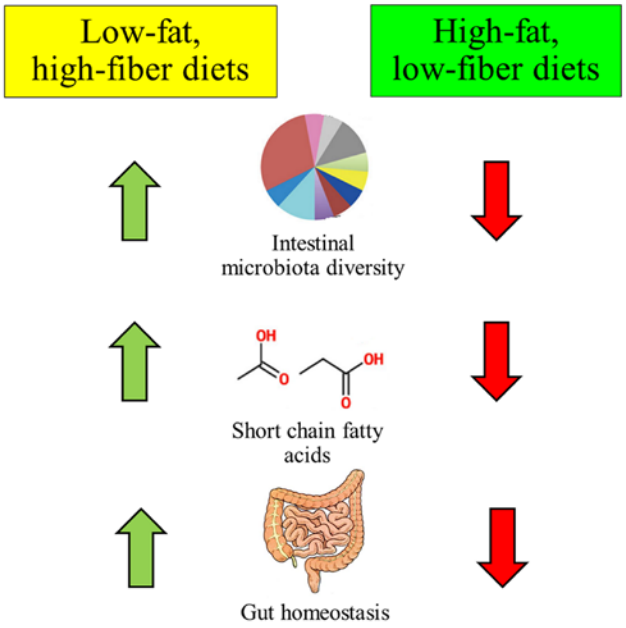

Figure 1. The effects of diets on the gut. High-fat diets affect the composition of microbiota, leading to the alteration of SCFA production in the gut, which influences intestinal homeostasis.

food consumption (98). Furthermore, a large human study found that low bacterial richness showed a positive correlation with higher weight gain supporting the concept that some bacteria may be more abundant than other types in obese individuals (99). Another study also found that obesity could be transmissible because microbiota derived from discordant obese twins caused germ-free mice to become obese when they were transplanted with these microbiota (100). This study also demonstrated that diet played a major role in gut microbiota diversity because the gut of low-fat, high-fiber diet-fed obese mice was finally dominated by the lean microbiota, which prevented increased adiposity, even when the mice were cohoused with mice with obese microbiota, suggesting that diet is responsible for the development of this phenotype (100).

3. Colonic carcinogenesis may be promoted by diet-related carcinogenic metabolites

CRC is a common, worldwide cancer causing up to 690,000 deaths/year (101). Although the exact etiology of CRC remains unknown, gradual accumulation of genetic mutations are essential for CRC tumorigenesis (102).

It is clear that the incidence of CRC is higher in developed countries, but in recent years, it has also become a public health problem in developing countries due to economic growth and an increasingly westernized lifestyle, including high consumption of red meats and high-calorie diets, which are associated with an increased incidence of CRC (103,104). This dietary pattern of higher consumption of animal protein (Western diet) that is related to the epidemiology of CRC demonstrates the role of diet in CRC development.

The composition and activity of the intestinal microbiota can be influenced by diet (105), and there is considerable evidence linking diet-induced microbiota dysbiosis to CRC tumorigenesis (106) (Fig. 2). This relationship may be mediated by metabolites and inflammatory induction, which induce genetic mutations and inhibit apoptosis or stimulate angiogenesis and cell proliferation (107). One study found that the increased consumption of red meat was associated with higher levels of sulfur, nitrates, ammonia, amines, branched-chain amino acids, and H_2S in the colon (108), which all have been shown to be pro-inflammatory and genotoxic, that in turn facilitates colon tumorigenesis by causing DNA damage and inhibiting the oxidation of butyrate (109,110). Moreover, several species of *Bacteroides* and some *Firmicutes* have shown the ability to ferment aromatic amino acids, leading to the production of toxic compounds, such as phenylacetic acid, phenols, indoles, and p-cresol, that promote colon carcinogenesis by DNA alkylation and mutations (111).

Lipid metabolism byproducts, such as bile acids, appear to be associated with the development of CRCs. Secondary bile acids, such as deoxycholic acid (DCA), are involved in the higher levels of reactive oxygen species (ROS), DNA damage, genomic instability and tumor growth (112,113). Moreover, an increased risk of CRC via the higher secondary bile acid production and ROS has been found in individuals consuming a high-fat, low-fiber diet who have a higher composition of inflammatory 7α-dehydroxylating bacteria and sulfur-reducing bacteria, which produce H_2S and secondary bile acids, respectively (109). Nitric oxide is another compound produced by specific types of bacteria. Its secondary reactive species can activate inflammation and damage DNA. An investigation by Sobko *et al* demonstrated that nitrite and nitrate-supplemented diets are sources for nitric oxide production by *Lactobacilli* and *Bifidobacteria*, leading to colonic mucosal inflammation and DNA damage (114,115).

The barrier dysfunction mediated by microbial products during CRC development also leads to adenoma invasion by stimulating inflammatory cytokines, such as IL-17 and IL-23, which, in turn, support tumor growth (116). The colonic inflammation model has also demonstrated the loss of the mucosal barrier in dextran sulfate sodium (DSS)-induced

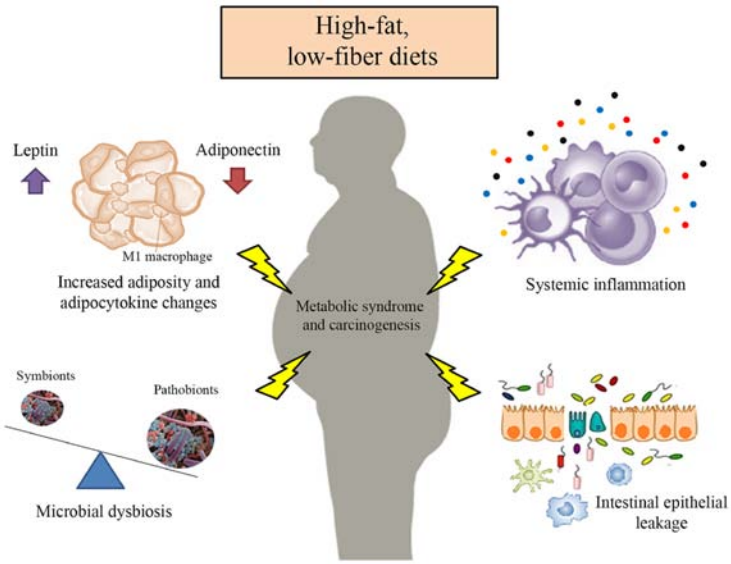

Figure 2. High-fat diets promote metabolic syndrome and colon carcinogenesis via increased adiposity, dysbiosis, gut barrier dysfunction and systemic inflammation.

colitis. However, when feeding rats with cheese whey protein, colitis markers were reduced, and fecal mucin, a family of glycosylated proteins that play a role in the intestinal mucus layer, and fecal *Lactobacilli* and *Bifidobacteria* counts were then increased (117).

4. Adipocytokines link metabolic syndrome to the risk of CRC

Numerous growth factors, hormones and cytokines, known as adipocytokines, can be secreted by adipose tissue and have pleiotropic effects, including regulation of food intake and metabolism, crosstalk with insulin signaling and inflammatory pathways, and promotion of angiogenesis and cellular proliferation (118,119). These adipocytokines include leptin, resistin, adiponectin and various cytokines, such as TNF-α and IL-6. In obese patients, the levels of these adipocytokines are altered, further contributing to an increased risk of CRC (120,121) (Fig. 2).

Adiponectin. Adiponectin, also known as Acrp30, ADIPOQ, apM1 or GBP28, is a 30 kDa protein that shares homologies with complement factors and TNF-α, and is predominantly secreted by adipocytes (122-124). This protein stimulates insulin secretion, increases fatty acid metabolism, activates energy consumption, and is also believed to have an anti-inflammatory role (124,125). The results from epidemiological and preclinical studies have indicated a protective role of adiponectin against tumorigenesis because the levels of adiponectin were negatively correlated with the risk of CRC development (126,127). Recent meta-analyses have shown that, in men, a 1 μg/ml increase in adiponectin levels was associated with a 2% reduced risk of CRC (128-130). Studies in animal models have also shown that adiponectin is involved in the suppression of colon carcinogenesis. High-fat diet-fed mice had significantly more polyps when the adiponectin gene was suppressed (131). Moreover, *in vitro* experiment showed that the growth of CRC cells can be inhibited by adiponectin through the activation of adenosine monophosphate-activated protein kinase (AMPK) and suppression of mammalian target of rapamycin (mTOR) pathways (132). As anti-angiogenic function, neovascularization suppression can be found in adiponectin-treated mice fed a high-fat diet, resulting in significant inhibition of CRC cell growth (133). Adiponectin also showed immunoregulatory functions because this protein induces macrophage infiltration in tumor area (134).

Leptin. Leptin is an adipocyte-derived *Ob* gene product that plays a major role in the modulation of appetite and energy homeostasis. This is through the feedback regulation between the central nervous system and the peripheral adipose tissue (135,136). Leptin levels appear to be positively associated with obesity and CRC (137,138), and they are believed to be an important factor in the intercellular interactions between adipocytes, fibroblasts, epithelial cells and immune cells (139). An investigation of 108 CRC patients indicated a relationship between leptin levels and progression of cancer, such as lymph node metastasis, distant metastasis and differentiation, suggesting that leptin is involved in cancer proliferation and apoptosis, which may be through the PI3K/Akt/mTOR signaling pathway (140). Leptin also has an anti-apoptotic role in human colon cancer cell lines and promotes the proliferation of normal colonic epithelial and cancer cells as the Wnt signaling pathway, a key pathway in CRC, can be activated by leptin, leading to CRC cell proliferation *in vitro* (141), while leptin-deficient mice showed a dramatic inhibition of tumor growth (142). Moreover, leptin can also promote CRC progression by stimulating VEGF secretion through hypoxia-inducible factor-1 (HIF-1) and nuclear factor-κB (NF-κB) activation (17,143). Interestingly, it is clear that leptin and adiponectin can neutralize each other's proliferative function because leptin plays a role in blocking the anti-proliferative effects of adiponectin in cancer cells (144), while adiponectin has a negative effect on the proliferative function of leptin (145). This suggests that the cancer risk related to metabolic syndrome can be accurately assessed by the leptin-to-adiponectin ratio.

TNF-α. TNF-α levels in systemic and adipose tissue are higher in obese individuals than in lean subjects (145). Although this cytokine has a functional role in apoptosis, cell necrosis, tumorigenesis inhibition, and appetite reduction (143), its pro-inflammatory role now has been associated with all steps of tumorigenesis (145). High levels of TNF-α in the colonic mucosa of high-fat diet mice resulted in β-catenin activation, leading to increased transcription of *c-Myc*, a downstream molecule in the Wnt signaling pathway (146). Moreover, this pro-inflammatory cytokine can activate NF-κB, a transcription factor associated with cell proliferation, apoptosis inhibition, tissue invasion, angiogenesis and metastasis, implying that this stimulation is involved in the progression of carcinogenesis (147,148).

Insulin and insulin-like growth factors (IGFs). Although insulin and IGFs are produced by β-cells in the pancreas and liver, respectively, not in adipose tissue, these factors still play a role in CRC cell proliferation and the progression of cancer both *in vitro* and *in vivo*. Circulating total IGF-1 has been positively associated with obesity and thus also contributes to an increased CRC risk (149); one study showed that IGF receptors were found in CRC cells (150). Importantly, several investigations have demonstrated that by binding to these receptors, insulin stimulates proliferation of cultured colonocytes and CRC cells directly, leading to the activation of the MAPK pathway (151,152). This scenario was supported in a study that used monoclonal antibodies against IGF1 and found inhibition of CRC stem cells in mice (153).

5. Conclusion

Over the last centuries, diets have been shown to affect the pathophysiological development of metabolic syndrome and CRC. Although the precise mechanisms have not been clearly elucidated, it is believed that intestinal inflammation and alteration of adipokines, which may result from a high-fat, low-fiber diet, plays a key role in these processes. This type of diet influences the metabolic activity of the gut and changes the composition of the microbiota, resulting in inflammation and carcinogenesis. Importantly, further investigations are needed for a deeper understanding of the effect of these abnormalities on metabolic imbalance and CRC development. This may lead to the development of new strategies that improve or even treat metabolic syndrome and CRC.

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