TNF-α in obesity-associated colon cancer

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Abstract: Obesity is leading to an unparalleled increase in the incidence of metabolic diseases and cancers, including colon cancer. Research over the last few decades revealed obesity as a low-grade chronic inflammatory state, which has recently been implicated in colon carcinogenesis. Understanding the molecular links of obesity-associated inflammation with colon carcinogenesis is therefore more critical than ever. In this review we discuss the central role of TNF-α, the prototypical pro-inflammatory cytokine, in the pathophysiology of obesity-associated colon carcinogenesis.

Keywords: Colorectal cancer; obesity; TNF-α

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Introduction

Modern societies are challenged by dramatic changes in the epidemiology of diseases. Scientific and technological advances have resulted in more efficient treatment of acute diseases and changes in human habits contributing to a high increase in the prevalence of chronic inflammatory conditions. In this context, obesity and cancer have emerged as two of the greatest threats to global human health. Here we will examine the evidence that links inflammation as a key mechanism to promote both obesity and cancer. We will extend the discussion to present the pathophysiological mechanisms that implicate obesity-associated inflammation in the development of colorectal cancer, with a special emphasis on the role of TNF-α.

Inflammation: basis for modern diseases

Inflammation is canonically defined as an essential biological response which promotes host repairs of tissue injury and infection (1). In the last decades, striking advances were made in our understanding of the biochemical and cellular mechanisms induced by acute inflammation, whilst the knowledge of the intracellular programs regulated by chronic inflammation advanced at a much slower rate (2). Nevertheless, the spectrum of prevailing inflammatory conditions has shifted from acute to chronic inflammatory states since the end of 20th century, significantly contributing to the pathogenesis of modern diseases such as obesity, type 2 diabetes (3,4), atherosclerosis (5), neurodegenerative diseases (6), and certain cancers (7).

The most obvious signs of inflammation are heat, pain, swelling, and redness, described by Celsius during the time of the Roman Empire. Initially, this inflammatory response was deemed as a biological reaction without deleterious effects, evoked just to protect from infection and normalize homeostasis. This theory influenced the understanding of the field until the 1970s, when it was recognized that inflammation not only preserves the integrity of the body but might also harm host tissues itself (8). Interestingly, recent research brought to light the fact that inflammation-mediated deleterious effects are closely linked to the pathophysiology of chronic multifactorial diseases (9-12). Accordingly, there is increasing interest in the mechanisms involved in the resolution of inflammatory response as much evidence links nonresolving inflammation to the pathophysiology of the ever-growing modern diseases of industrialized societies (10).

There is intense debate about the regulatory mechanisms that control inflammatory response, in part due to its complexity and also because of the multitude of agents

involved in its induction and resolution. However, it is now well recognized that there are two major stimuli that promote acute inflammation: infection and host cell necrosis from sterile tissue injury (13). Intriguingly, the products generated by both processes are recognizable by the same cluster of host molecules, which activate a common inflammatory pathway that eliminates triggering stimuli and repairs the damaged tissue (2). As a result, inflammation is often interrupted by an active and highly regulated process that restores the homeostatic state (2,14,15). One key regulating mechanism of inflammation resolution is the switch from pro-inflammatory prostaglandins and leukotrienes to anti-inflammatory resolution-inducing lipids, such as lipoxins and resolvins (14,16). Specifically, these anti-inflammatory mediators promote the transition from neutrophil to monocyte recruitment (17-19). The subsequent uptake of apoptotic neutrophils orchestrates the production of anti-inflammatory cytokines by monocytes and recruited macrophages, which are responsible for the clearance of dead cells and other debris and initiation of tissue repair at the damaged site (15,20,21). However, if the inflammatory trigger is not eliminated, a chronic state of inflammation is sustained for an undetermined period of time, although signs of acute phase may reappear throughout the course of the disease. This type of chronic inflammation is detected in a myriad of conditions including tuberculosis, unrepaired tissue damage, persistent allergens and undigestible foreign particles and endogenous crystals (10).

Chronic inflammation may also occur in diseases where the initiating trigger is not well defined and does not seem to be related to infection or tissue damage, therefore, without a physiological counterpart (2,9). In these conditions, inflammation appears to be chronic from the outset with infiltration of monocytes, dendritic cells and macrophages into the target tissue. Examples include obesity (22), atherosclerosis (5) and some cancers (23). Notably, in these cases of chronic inflammation there appears to be vicious cycles connecting inflammation and the pathological process it accompanies. Indeed, this reciprocal relationship may be responsible, at least in part, for the chronic nature of these inflammatory conditions and distinguishes them from the first type of chronic inflammation, which is caused by the persistence of the inflammatory inducer.

A causal relationship between chronic inflammation and cancer has long been suspected. It was first detected by Galen and later established in the 19th century by Rudolf Virchow who discovered leukocyte infiltration in malignant tissues. Interestingly, the inflammatory response is similar in many aspects to a wound-healing process and tumors have been considered as wounds that do not heal (24). Research over the last decade in the field of inflammation and cancer pathogenesis has produced abundant evidence of the functionally important tumor-promoting effects that immune cell have on neoplastic progression (7,23,25). Inflammation can contribute to multiple hallmark capabilities by supplying bioactive molecules to the tumor microenvironment, including growth factors that sustain proliferative signaling, survival factors that limit cell death, proangiogenic factors, extracellular matrix-modifying enzymes while enhancing cell proliferation, cell survival, cell migration and angiogenesis (7,23,25). Accordingly, the importance of inflammation for production of the "tumor microenvironment" is now widely recognized as an enabling characteristic of cancer (26).

As a modern epidemic disease, the concept of obesity-induced adipose tissue inflammation is much more recent, about 20 years old (27). Corresponding to Virchow's findings related to cancer tissue, large numbers of macrophages have been observed infiltrating adipose tissue from obese mice and humans (28,29). In obesity, the proinflammatory pathways in adipose tissue macrophages (ATM) are highly activated, leading to the secretion of a variety of cytokines such as TNF-α and interleukin-6 (IL-6) (3,30).

Inflammation is conspicuously associated with certain colon cancers. For instance, colitis-associated cancer (CAC) often arises in patients diagnosed with inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis (31). Moreover, the cumulative incidence of CAC among patients with ulcerative colitis 25 years after diagnosis ranges from 8% to 32%, accounting for one sixth of all deaths in this group (31). Furthermore, Crohn's disease is associated with a pooled estimated relative risk of 2.4 (32). The physiopathology of IBD is multifactorial and involves genetic, mucosal, microbiota and immune system abnormalities (for review see Xavier *et al*. and Danese *et al*.) (33,34). Interestingly, the disrupted communication between the epithelium and the intestinal flora has an important role in activating the immune system and maintaining the inflammatory response (35-40). Therefore, ulcerative colitis and CAC are mainly mediated by the first mentioned mechanism of nonresolving inflammation, whereby the inflammatory trigger is not eliminated and causes an acute inflammatory response to persist for a long period of time.

In addition to IBD, other well-known risk factors for colon cancer are obesity, diets low in fruits and vegetables,

and physical inactivity (41,42). As these habits were initially more prevalent in developed nations, obesity-associated cancer was once a disease primarily observed in longstanding industrialized societies; however nowadays it is a worldwide health burden (43). Specifically, the association between being overweight or obese with colon cancer are positive for both men (RR =1.24) and women (RR =1.09) at an elevation of 5 kg/m^2 in BMI (42). Intriguingly, obesity-associated colon cancer is, at least in part, mediated by the second mentioned mechanism of nonresolving inflammation, in which chronic low-grade inflammation arises without a clear trigger. In the next topics we will further explore these inflammatory features of obesity-associated colon cancer.

Obesity-associated inflammation

In the 1980s and 1990s, the world saw a striking increase in the prevalence of obesity and in the most recent years it trended to levelling out (44). This epidemic had begun in developed countries, but nowadays it is also common in many other regions over the world, such as Asia and Latin America (43,45-47). In conjunction with this epidemic, we faced a dramatic increase in the prevalence of diseases, such as hypertension, dyslipidemia, cardiovascular disease, type 2 diabetes mellitus and certain cancers, making obesity a worldwide public health concern (48).

Obesity-associated tissue inflammation is now recognized as a major driver in the pathogenesis of metabolic diseases (3,4,49,50). Activation of inflammatory pathways has since been observed in classical metabolic tissues, including fat, liver and muscle (27,51,52). At the molecular level, chronic low-grade inflammation induced by obesity leads to activation of protein kinases, such as Jun N-terminal kinase (JNKs) (53) and inhibitor of nuclear factor B kinaseβ (IKKβ) (51,54,55), which phosphorylates serine 307 (Ser307) of IRS-1 (56,57). As a result, the interaction of the PTB domain of IR with the phosphorylated NPEY motif of IRS-1 is inhibited, impairing the interaction of IRS-1 with the insulin receptor and causing insulin resistance (56). Obesity associated inflammation is also associated with increased activity of iNOS, which *S*-nitrosates insulin signaling pathway and promotes insulin resistance (58-61).

A pivotal event in the pathophysiology of obesity-induced inflammation is the recruitment of macrophages into adipose tissue (62). The large accumulation of adipose tissue macrophages (ATMs), representing up to 40% of the cells in obese adipose tissue, determines locally increased levels of pro-inflammatory cytokines, such as TNF-α and IL-6, which sustain insulin resistance in a paracrine manner (28,29,55). In addition, these cytokines may also leak out the adipose tissue and exert systemic effects (28). Congruent with this data, macrophages are recruited to adipose tissue by chemokines secreted by adipocytes, which provide a chemotactic gradient that attracts Ly6C^{hi} monocytes into the adipose tissue, where they differentiate into ATMs (63-66). Once pro-inflammatory ATMs migrate into adipose tissue, they also secrete their own chemokines, attracting additional macrophages and establishing a vicious cycle that stimulates the inflammatory process (55).

Macrophages are dynamic cells that acquire different phenotypes in accordance with the microenvironment that they reside (62). These cells are often classified by their functional inflammatory state and the polarized states are often referred to as classically activated macrophages (CAMs), known as M1, and alternatively activated macrophages (AAMs), known as M2 (67). In adipose tissue these two subpopulations exert opposite immune actions: M1 inflammatory macrophages secrete proinflammatory cytokines whereas AAMs secrete anti-inflammatory ones (22). The majority of ATMs in obesity are M1-like, identified by the specific expression of CD11c, typically negative in M2-like macrophages that reside in lean adipose tissue (55,68). Along this line, macrophage specific JNK deficient mice are protected from insulin resistance induced by high fat diet (69). In contrast, repression of programs that control alternative activation of macrophages is associated with obesity and insulin resistance (70,71). Furthermore, obese animals exposed to a switch from a high-fat diet (HFD) to a chow diet or treated with omega-3-fatty acids or thiazolinediones have macrophages converted from an M1 to M2 phenotype, coincident with increased insulin sensitivity (72,73).

After the observation of the striking switch from AAM to inflammatory macrophages in obese adipose tissue, it was progressively described that not only are macrophages actively mobilized by the obese adipose tissue but also by other innate and adaptive immune cells (22,74). In a simplified way, there is an increase in inflammatory immune cells such as Th1 cells (75), CD8+ T cells (76) and B cells (77), which promote insulin resistance by further activating inflammatory macrophages or directly secreting pro-inflammatory cytokines or antibodies. Meanwhile, this pool of inflammatory cells takes place with resident tolerogenic immune cells, including eosinophils (68), innate lymphoid type 2 cells (ILC2s) (78), regulatory T cells

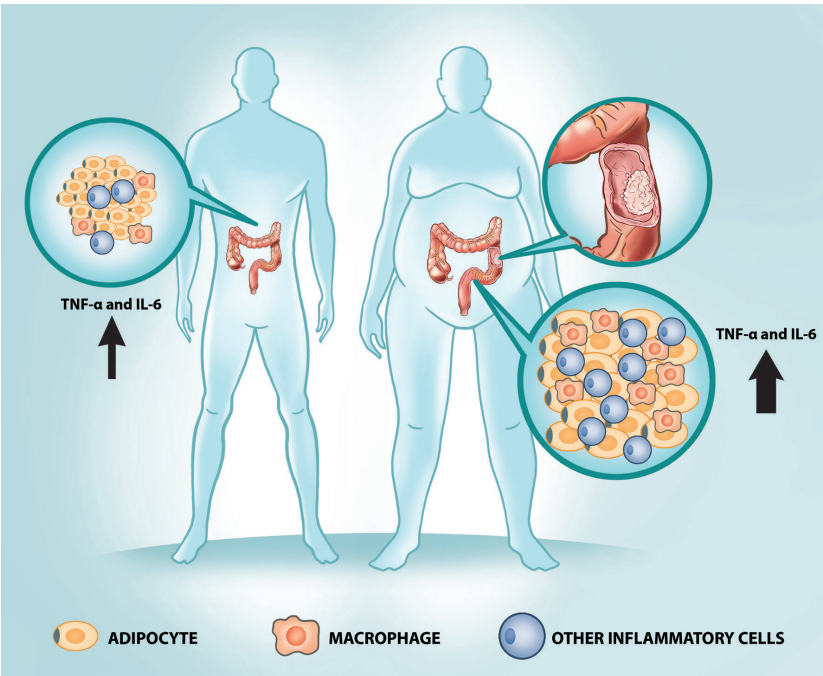

Figure 1 Adipose tissue of obese individuals is highly infiltrated by machophages and other active inflammatory cells. These cells present a pro-inflammatory phenotype characterized by increased levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) secretion, which promote obesity-associated colon cancer by acting through both endocrine and paracrine ways.

(Tregs) (79), invariant natural killer (iNKT) cells (80,81) and Th2 cells (75), which secrete IL-4, IL-5 and/or IL-10 and, therefore, promote direct anti-inflammatory effects or activate the alternative program of resident macrophages to sustain metabolic homeostasis. Despite the debate about the sequence of cells that infiltrate the adipose tissue, obesity assembles a large number of immune cells that promote and amplify the inflammatory response in the adipose tissue.

Another critical mechanism that mediates inflammation in obesity is the interaction with the host-microbiota (82,83). The gut microbiota contains expressive amounts of lipopolysaccharides (LPS) derived from Gram-negative bacteria, which can leak into circulation and may cause inflammation and macrophage recruitment into adipose tissue (84,85). Interestingly, recent studies revealed that obesity changes in microbiota are associated with increased circulating LPS levels (86,87). Accordingly, exercise-induced decreases in LPS circulating levels parallels the increase in insulin sensitivity (88). Mechanistically, LPS binds to TLR-4 Toll-like receptors (TLRs), which exert a central role as a major regulator in microbe-associated molecules recognition and free fatty acids (89). Importantly, TLR4 activation promotes increased JNK and IKK activity and insulin resistance in obesity (76). In addition, TLR4 genetically deficient animals were protected from free fatty acids- and obesity-induced insulin resistance (89,90). Interestingly, gut microbiota modulation by antibiotic treatment decreases LPS and TLR4 activation sustains insulin sensitivity in different animal models (85,87,91).

In aggregate, the studies discussed in this section suggest that obesity is a unique systemic chronic inflammatory disease. Importantly, the interplay between cytokines secreted by inflammatory cells, free fatty acids and gut microbiota products signal through the two prototypical pro-inflammatory receptors, TNF-α and TLR-4 promoting the activation of specific intracellular cascades that include IKK-β, NF-κB and JNK and resulting in the inhibition of insulin signaling and deregulation of metabolic homeostasis. Interestingly, insulin resistance has been suggested to be an adaptive and protective response that properly balances the metabolic homeostasis during the noxious stimulus of overnutrition (3). Since the protective effects of inflammation cannot be dissociated from a cost to homeostasis (92), it is important to better understand how obesity-associated inflammation also promotes human modern diseases including cancer (*Figure 1*).

Obesity-associated inflammation and colon cancer

Besides type 2 diabetes, hyperlipidemia and hypertension, which are classically linked to obesity, other diseases, including cancer, were recently associated with obesity (93). Obesity not only promotes colorectal cancer (CRC) but it is also specifically associated with esophageal, pancreatic, post-menopausal breast, endometrial, thyroid, gallbladder and renal cancers (42). Notably, a meta-analysis of 56 studies, where more than 7 million individuals were evaluated, demonstrated that for each 5 kg/m^2 increment in body mass index BMI there was an increase of 18% in the risk of developing colon cancer (94).

In spite of the prominent epidemiological importance of obesity as a risk factor for colon cancer, the initial evidence that implicates inflammation as a promoter of colon cancer comes from CAC studies. Remarkably, TNF-α production is increased in ulcerative colitis and has been implicated in its pathogenesis (95,96). Although, it is long recognized that TNF-α activates the oncogenic transcription factors NF-κB and AP-1 only recently the importance of inflammatory cytokines in CAC became better understood (97,98). In an elegant study by Greten *et al*., the conditional ablation of IKKβ in epithelial cells resulted in a marked reduction in the development of colonic adenomas, but had little effect on adenoma size (99). Otherwise, lack of NF-κB in myeloid cells, principally lamina propria macrophages, led to a significant reduction in both colonic tumor quantity and size (99). Although IKKβ ablation did not resulted in decreased TNF-α production, it is not clear whether the LysM-Cre deleter used in this study is non-functional in a specific subset of colonic macrophage, or whether TNF-α may be produced by other cell types in CAC, including T cells and epithelial cells (99). Additionally, a very interesting study demonstrated that TNF-α expression is elevated in CAC carcinogenesis and genetic inactivation of the type 1 TNF receptor (TNFR1) or TNF signaling inhibition with a soluble decoy receptor reduced CAC promotion (100). Moreover, the dependence of TNF-α to carcinogenesis in a distinct model of CAC than AOM + DSS, as T-bet deficiency was observed in dendritic cells, reinforces its importance in CAC tumorigenesis (101). Thus, the same prototypical cytokines, TNF-α and IL-6, which are increased in obesity-associated inflammation, have been found to be crucial in promoting colitis induced cancer.

Obesity-associated inflammation is clearly not restricted to adipocytes but disseminated in all metabolic tissues (51,52,102-104). Furthermore, it was recently observed that non-metabolic glandular organs, including colon, also present signs of low-grade inflammation in obesity (105-109). Importantly, TNF-α overexpression was consistently elevated in colons of genetically- or diet-induced obesity rodents (106-109). Congruent with an increased inflammatory response IL-6 and other cytokines are also upregulated in the colons of obese animals (110,111) suggesting that the obese colonic tissue recapitulates the inflammatory timbre constantly observed in metabolic tissues of obese individuals. Accordingly, obese Zucker rats treated with azoxymethane (AOM) manifested higher incidence of tubular adenomas and TNF-α than their lean matched controls (112). Recently, it was observed that leptin deficient and high fat diet fed mice exposed to a combination of AOM + DSS developed higher colonic inflammation than their lean counterparts and increased colonic adenoma numbers in a TNF-α dependent manner (109). Importantly, treatment with infliximab, a monoclonal antibody that neutralizes TNF-α, inhibited the activation of colonic JNK and IKK resulting in the decreased quantity of colonic adenoma and the growth of colon cancer xenografts (109). Interestingly, enhanced production of IL-6 and TNF-α was also observed in a hepatocarcinoma (HCC) mouse model (113). In these animals HFD induced increased expression of TNF-α and ablation of TNFR1 significantly reduced obesity-enhanced HCC development (113). Altogether, these studies suggest that the inflammatory milieu instigated by obesity may be a general mechanism that links obesity to gastrointestinal cancers.

Activation of IKK/NF-κB pathway is consistently associated with both colitis- and obesity-associated carcinogenesis (99,109,113,114). Interestingly, the outcome of TNF mediated NF-κB activation, considering target gene expression, may alternate, depending on the tissue or cell type stimulated. In this context, NF-κB exerts not only intrinsic effects within pre-malignant epithelial cells, but also modulates actions of infiltrating lymphocytes and macrophages (115,116). In normal physiology, NF-κB response is self-limited by the induction of negative feedback loops (117,118). However in chronic inflammation induced by obesity, continuous cytokine release by immune cells of the stromal vascular fraction results in sustained IKK activation, which deregulates NF-κB activity (109).

The pro-oncogenic effects of NF-κB involve other intracellular mechanisms, besides continuous activation of IKK. Transcription factors, including STAT3, may

play a role in NF-κB dependent tumorigenesis (7). In tumors, accumulation of the prototypical NF-κB complex (p50/RelA) in the cellular nucleus is regulated through acetylation by p300 (119,120). It is relevant that STAT3 though p300 mediates RelA acetylation to promote and sustain NF-κB activity (121). Importantly, cytokines and growth factors encoded by NF-κB target genes, especially IL-6, are critical STAT3 activators (122-124). Interestingly, other inflammatory cytokines, such as IL-17, promotes STAT3 activation through NF-κB mediated IL-6 expression (125,126). Congruent with this data, expression of several inflammatory mediators, such as IL-6, COX2, IL-17 and IL-23, is also dependent of STAT3 as a RelA co-transcriptional factor (127-130).

Investigations on the influence of IL-6 in CAC showed that knockout mice for this cytokine developed less and smaller colonic adenomas than controls in a CAC model (123). Moreover, pharmacological inhibition of the common signaling receptor gp130 by a soluble gp130-Fc fusion protein also resulted in decreased tumor number and size in animals exposed to a CAC model (131). In consonance, genetic activation of gp130 in enterocytes of mice in a CAC model promoted increased tumor number and growth (132) whereas STAT3 deletion in intestinal epithelial cells markedly decreased the incidence and volume of AOM + DSS induced tumors (123). IL-6 is mostly produced by myeloid cells, primarily by lamina propria macrophages and dendritic cells during tumor initiation and by T cells during tumor progression, in CAC models (123,131,133). This is probably a consequence of the high inflammatory activity of CAC tumors and the continuous injury and death of enterocytes during tumor development (123). In other words, epithelial cells and cancer cells, as well as tumor-associated fibroblasts can also produce IL-6 and may contribute to the total amount of this cytokine, particularly in sporadic colorectal and obesity-associated colorectal cancers.

Taken together, these data provide strike evidence for the involvement of TNF-α by promoting continuous stimulation of IKK/NF-κB pathway in the pathogenesis of obesity-associated colon cancers. Furthermore, interactions between IL-6, STAT3 and NF-κB may have a role in this phenomenon.

TNF-α influence on obesity-associated colon carcinogenesis phases

Carcinogenesis can be didactically divided into three mechanistic phases: initiation (which involves stable genomic alterations), promotion (which involves the proliferation of genetically altered cells) and progression (which involves an increase in tumor size, its spreading and acquisition of additional genetic changes) (134). Notably, TNF-α may influence all those stages of tumor development (*Figure 2*).

Initiation

More than six decades ago, Peyton Rous defined initiation phase as a "*subthreshold neoplastic state*", in which "*latent tumor cells*" wait for the promotion stimuli to proliferate (134-136). Since the majority of cancers need at least 4-5 mutations to acquire a neoplastic phenotype (26,137) the initiation phase in current words corresponds to the early mutations observed in premalignant cells. TNF-α modulates the initiation phase by at least three mechanisms. First, TNF-α released by inflammatory cells in the tumor microenvironment may induce reactive oxygen and nitrogen species (RNOS) in adjacent epithelial cells, inducing DNA damage and genomic instability (138,139). Second, colorectal tumors may be initiated by increased activity of Wnt/β-catenin signaling in colon progenitor cells (140-142). Importantly, TNF-α through activation of NF-κB or repression of GSK3β promotes Wnt/β-catenin signaling in gastrointestinal mucosa (143,144). Finally, NF-κB regulates several tumor suppressor pathways; specifically it inhibits p53 activity through competition for the p300 and CBP co-activator proteins (145,146).

In spite of the effects of TNF-α in a number of important molecules involved in tumoral initiation, experimental evidence from obese Zucker rats and high fatty diet fed mice demonstrate that treatment with AOM does not changed the total number of aberrant crypt foci (147,148). Furthermore, recent data showed that obese individuals have an increased risk to develop β-catenin negative colon cancer, but not β-catenin positive (149). Overall, these findings are consistent with minor effects of obesity low-grade inflammation on the colonic tumor initiation.

Promotion

Initiation is an irreversible process, whereas promotion may be modulated by the stimuli intensity and even reversible if the stimuli are removed (134-136). The promotion phase is characterized by increased cell proliferation and reduced cell death. It may be an early or late event in tumor

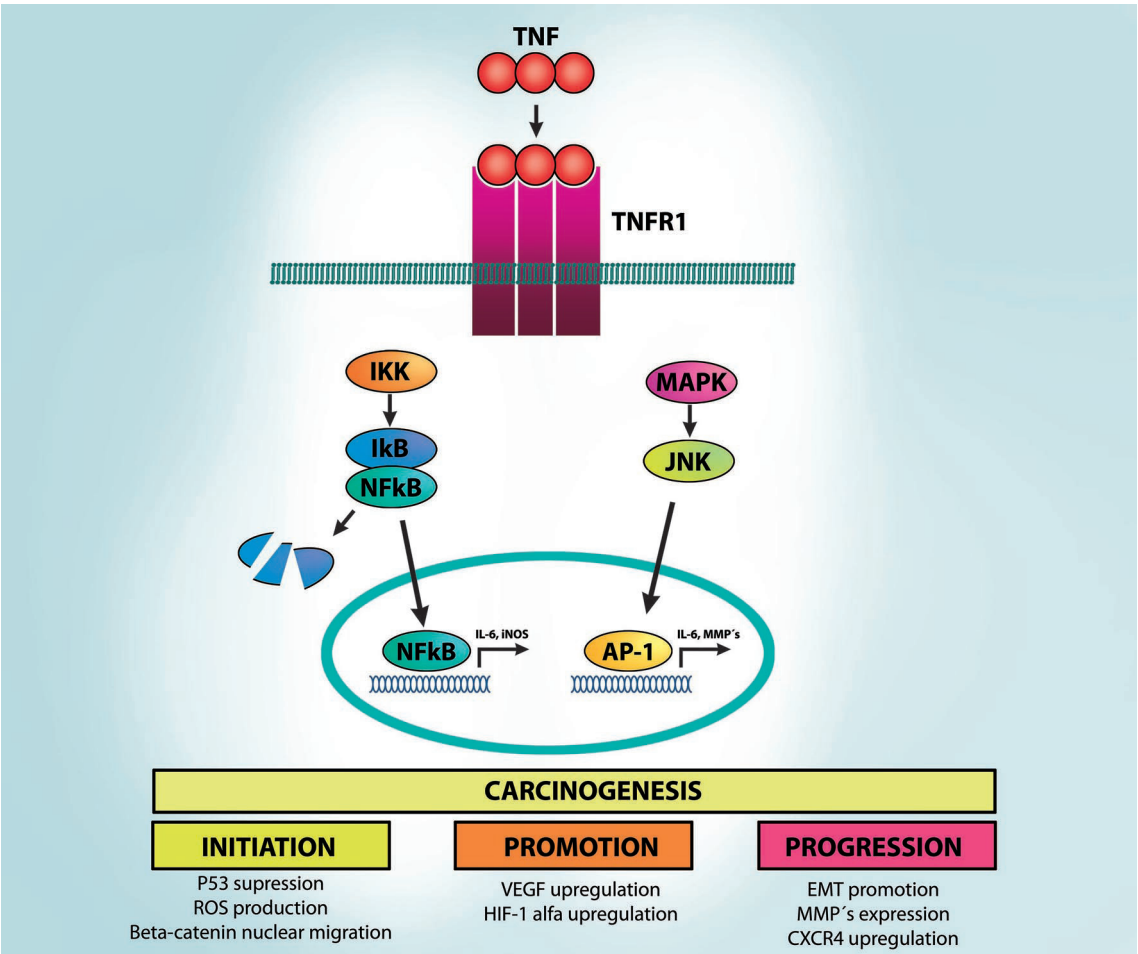

Figure 2 Tumor necrosis factor alpha (TNF-α) sensed by TNF-receptor 1 (TNFR1) phosphorylates inhibitor of nuclear factor kappa B (IKKβ) leading to degradation of inhibitor of kappa B (IκB) and nuclear migration of nuclear factor kappa B (NF-κB). TNF-α also promotes phosphoryation of mitogen-activated protein kinases (MAPK) pathway, resulting in Jun N-terminal kinase (JNK) and the activator protein 1 (AP-1) activity. Sustained activity of both NF-κB and AP-1 mediate important processes in distinct phases of colon carcinogenesis.

development, as late proliferation of dormant malignant lesions may also occur (150). Evidence for TNF-α-mediated colonic adenoma promotion in obesity came from observing elevated numbers and larger tumors size in obese animals compared to their lean controls, which was associated to IKK overexpression in these tumors (109). Accordingly, neutralization of TNF-α reverted the growth rate of colon cancer xenograft implanted in high fat diet fed animals to lean settings (109). Furthermore, obese animals switched from a HFD to regular chow after carcinogen exposure developed more tumors than lean controls, but similar number of aberrant crypt foci, the colonic pre-neoplastic lesion (148).

During tumor promotion, it is necessary to increase tumoral blood supply, mainly by angiogenesis triggered by tumor hypoxia (151). Interestingly, activation of NF-κB, STAT3 and AP-1 in tumoral microenvironment cells, such as tumor-associated macrophages (TAMs) and fibroblasts directly regulate important pro-angiogenic genes, including IL-8, CXCL1, CXCL8, VEGF, and hypoxia inducible factor 1 alpha (HIF1α) (152-154). Inactivation of NF-κB or STAT3, neutralization of CCL2 or CXCL12, or TAM depletion leads to ineffective angiogenesis and reduced tumor growth. Interestingly, the visceral adipose tissue of patients with colon cancer presents concomitantly increases in TNF-α and the pro-angiogenic factors, such as HIF1α and VEGF (155). Altogether, these data indicate that obesity-associated inflammation strongly affects colon

cancer promotion phase.

Progression

Metastatic disease is the most critical feature of cancer in a clinical setting as it is responsible for over 90% of disease mortality (156). The process of invasion and metastasis can be schematically divided into four major steps. First, epithelial-mesenchimal transition (EMT) is required for acquisition of a fibroblastoid phenotype by an epithelial malignant cell, resulting in increased motility and capacity to invade basal membranes and reach blood vessels or lymphatics (157). Second, cancer cells intravasate into blood vessels and lymphatics, with possible involvement of cytokines and inflammatory effectors by promoting increased vascular permeability (158,159). Third, metastatic cells should survive and travel in circulation (158,159). Fourth, circulating cancer cells should adhere and extravasate in a distant site, in which they need to interact with immune, inflammatory, and stromal cells to proliferate (158,159). Some of these cells may already be targeted to a pre-metastatic niche, in which soluble growth factors secreted by the primary tumor prime certain tissues for tumor cell engraftment, known as 'metastatic niche' theory (160-162). Obesity is associated not only with an increased incidence of colon cancer, but also with a more aggressive natural history; the patients are younger, present more metastasis to lymph nodes and the disease free and overall survival are reduced (163). In spite of the lack of direct evidence that obesity-associated inflammation interferes in these endpoints, TNF-α may exert effects in all metastatic phases.

TNF-α may contribute to cell migration-promoting EMT through stabilization of Snail, an inhibitor of E-cadherin expression, a key event in EMT (164-166). Interestingly, TNF-α, through NF-κB signaling, can also induce overexpression of other important regulators of EMT such as Twist, ZEB1 and SLUG, contributing to its induction (165,167-169). Another mechanism by which TNF-α can induce EMT is through synergistic action with transforming growth factor β1 (TGFβ) (170,171). Importantly, in a model of colon cancer, cancer cell invasiveness was associated to extracellular matrix proteolysis, a process that is dependent of matrix metalloproteinases (MMP) release, which may also be regulated by TNF-α induced activation of NF-κB (172,173).

After intravasation in circulation, metastatic cells need to survive in suspension and resist detachment-induced death, named anoikis (174). Notably, TNF-α, and other cytokines can promote survival of circulating metastatic cells, through activation of NF-κB in either inflammatory and cancer cells or by promoting a physical link between cancer cells and TAMs, allowing them to travel together throughout the circulation and evading immunological attacks (175,176). Furthermore, migration of metastatic cells is directed by chemokine gradients that are sensed by many receptors, including CXCR4, which expression is upregulated by TNF-α (177).

In a distant site, circulating metastatic cells are arrested on the endothelium in an integrin-dependent process. Therefore, adhesion between malignant and endothelial cells are important mediators of this process (175). Importantly, bone marrow-derived haematopoietic cells that express vascular endothelial growth factor (VEGF) receptor 1 (VEGFR) migrate and determine the metastatic sites before the arrival of neoplastic cells (160). Interestingly, the pre-metastatic niche is also defined by the tumor-secreted matrix protein versican, which activates TLR2 on host macrophages and promotes release of TNF-α (178). Accordingly, metastasis formation was dramatically reduced, by TLR2 or TNF-α suppression (178). Furthermore, VEGFA, TGFβ, and TNF-α secreted by the primary tumor promoted the expression of inflammatory proteins S100A8 and S100A9, leading to infiltration of lungs, the target site of metastasis, by myeloid cells expressing the cell surface antigens integrin αM (also known as MAC1) or CD11b (161). As a result, treatment with S100A8 and S100A9 antibodies diminished infiltration of MAC1 myeloid cells, resulting in a remarkable reduction in metastasis incidence (161). Specifically in regard to colon cancer, it was observed that targeting VEGF2 and other cytokines involved in the pre-metastatic niche formation reduced liver metastasis formation (179).

Conclusions

Recent clinical and experimental data provide support for the involvement of TNF-α in the pathogenesis of obesity-associated colon cancer. TNF-α promotes colon cancer in obese states through direct effects on premalignant cells and by orchestrating a tumor-promoting microenvironment through actions on several distinct cell types. However, how the cellular component of obese adipose tissue microenvironment promotes a "fertile soil" to carcinogenesis and whether interactions between inflammatory cells and adipocytes contribute to promotion

and progression of cancer is still largely unknown. Since these studies may contribute to a better understanding of carcinogenesis in general and give clues to cancer treatment, it will be critical in the future to systematically evaluate how an obesity-associated inflammatory microenvironment contributes to colon carcinogenesis.

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