



NLRP3 Inflammasome: A Possible Link Between Obesity-Associated Low-Grade Chronic Inflammation and Colorectal Cancer Development

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Emerging evidence reveals that adipose tissue-associated inflammation is a main mechanism whereby obesity promotes colorectal cancer risk and progression. Increased inflammasome activity in adipose tissue has been proposed as an important mediator of obesity-induced inflammation and insulin resistance development. Chronic inflammation in tumor microenvironments has a great impact on tumor development and immunity, representing a key factor in the response to therapy. In this context, the inflammasomes, main components of the innate immune system, play an important role in cancer development showing tumor promoting or tumor suppressive actions depending on the type of tumor, the specific inflammasome involved, and the downstream effector molecules. The inflammasomes are large multiprotein complexes with the capacity to regulate the activation of caspase-1. In turn, caspase-1 enhances the proteolytic cleavage and the secretion of the inflammatory cytokines interleukin (IL)-1 β and IL-18, leading to infiltration of more immune cells and resulting in the generation and maintenance of an inflammatory microenvironment surrounding cancer cells. The inflammasomes also regulate pyroptosis, a rapid and inflammation-associated form of cell death. Recent studies indicate that the inflammasomes can be activated by fatty acids and high glucose levels linking metabolic danger signals to the activation of inflammation and cancer development. These data suggest that activation of the inflammasomes may represent a crucial step in the obesity-associated cancer development. This review will also focus on the potential of inflammasome-activated pathways to develop new therapeutic strategies for the prevention and treatment of obesity-associated colorectal cancer development.

Keywords: inflammasome, NLRP3, inflammation, colon cancer, obesity, adipose tissue, immunity

INTRODUCTION

During the past decades, colorectal cancer (CRC) has become a major public health problem constituting the second most common type of cancer in females and the third most common in males, with its incidence being expected to continue increasing in the coming years (1, 2). Colorectal carcinogenesis is a heterogeneous process characterized by different sets of molecular

alterations influenced by gender, diet, environmental and microbial exposures as well as host immunity (3). Recently, global epidemiological and scientific studies suggest that obesity, a modifiable lifestyle factor, influences not only the risk of CRC incidence but also its morbidity and mortality (4–7). Different meta-analyses have revealed that an increased body mass index (BMI) is related with an elevated incidence of CRC (8–10) and with each unit increase of the BMI, the risk for CRC augments by 2–3% (11–13). Additionally, patients with type 2 diabetes (T2D) also have an increased risk for CRC development (14–16). These data are alarming because globally, the prevalence of obesity is reaching epidemic proportions worldwide (17–19). It is crucial to distinguish between the different anatomical distribution of the fat depots, rather than focusing exclusively on the BMI, given that abdominal obesity characterized by an accumulation of visceral fat is associated with metabolic risk whereas the peripheral subcutaneous fat depot confers protective effects on energy homeostasis (20, 21). In this line, cancer risk has been shown to be diminished among metabolically healthy overweight/obese adults as compared to overweight/obese adults with metabolic dysfunction (22).

Although mechanistic insights explaining these data are notably lacking, three main factors are considered to link excess body fat and CRC: (i) alterations in the metabolism of endogenous sex steroids, (ii) the insulin-like growth factor (IGF)-1 axis, and (iii) the adipocyte-derived cytokines (named adipokines) (6, 23–25). Importantly, obesity is defined not only by an excess of adipose tissue accumulation but also by an altered adipose biology and all these previous factors are closely connected to the typical dysfunction of adipose tissue in the obese state (26). It is widely accepted that adipose tissue from obese individuals exhibits a sustained chronic and unresolved inflammation (27, 28) that is associated with an imbalance of adaptive homeostatic mechanisms and leads to the development of obesity-associated comorbidities (29). Thus, growing evidence indicates that obesity-associated low grade chronic inflammation is a central mechanism whereby obesity promotes CRC risk and progression (30, 31). In this sense, multiple clinical studies have evaluated the role of inflammation as a possible mechanism linking adipose tissue excess with increased risk of CRC development (6).

INFLAMMATION, OBESITY, AND COLORECTAL CANCER

In 1863, Rudolf Virchow described the localization of leukocytes in neoplastic tissues suggesting a connection between inflammation and cancer. He proposed that the “lymphoreticular infiltrate” indicated the induction of carcinogenesis at sites of chronic inflammation (32). Much of our understanding of the close link between chronic inflammation and the development of CRC is illustrated by elegant studies showing that in patients suffering from chronic inflammatory bowel disease of the colon, the incidence of CRC increases progressively over time, reaching 19% after 30 years of disease (33–36). Furthermore, population-based studies have demonstrated an increased risk

of cancer in individuals who are predisposed to develop specific types of chronic inflammatory diseases (37). Significantly, obesity is associated with chronic inflammation, both systemic and at the tissue level (38). Extensive experimentation has demonstrated that immune cells, including lymphocytes and macrophages, infiltrated visceral adipose tissue from patients with obesity inducing a complex immune response (38, 39). Indeed, adipose tissue macrophages (ATM) exhibit plasticity, changing their phenotype and functions in response to both the surrounding microenvironment and external stimuli (29). ATM in healthy fat depots generally exhibit a dominant M2 phenotype but during obesity, a polarization toward a pro-inflammatory M1 macrophage profile has been evidenced (39, 40). Pro-inflammatory ATM produce tumor-promoting cytokines, including tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-6, IL-8, IL-18, IL-32, interferon (IFN)- γ , vascular endothelial growth factor (VEGF), osteopontin (OPN), tenascin C (TNC), and monocyte chemoattractant protein (MCP)-1 (24, 41). Thereby, adipose tissue from patients with obesity becomes a chronically impaired tissue constituting an important source of proinflammatory mediators, potentially fostering tumor growth (30). In addition, increased circulating levels of pro-inflammatory cytokines are typically found in obese patients, promoting a microenvironment favorable for tumor growth (42–47). Unresolved inflammation favors a complex paracrine signaling mechanism between innate immune cells and cancer cells (48, 49). Studies performed in conditional-knockout mice treated with specific carcinogenic compounds to promote inflammation-induced colitis-associated cancer, have shown that the inactivation of the nuclear factor κ B (NF- κ B) signaling in tumor infiltrating inflammatory cells results in attenuated colon cancer formation (49). Therefore, one conceptual issue to define is that many of the immune cells subsets and molecules that control inflammation influence immune reactions, and vice versa (31).

Besides chronic inflammation, critically involved in tumor progression, experimental and clinical evidence has unveiled a protective role for immune cells in cancer progression (50). This evidence led to the hypothesis of a duality of the innate immune system in tumor evolution exhibiting both oncogenic and tumor suppressive properties (51). Specifically, inflammasomes, as major mediators of the innate immunity, also show a dual role in inflammation contributing to carcinogenesis or immunosurveillance in a highly context-dependent fashion (31, 52). This ambivalent contribution is most probably due to the specific activities and properties of the multiple inflammasome complexes that are dependent on the simultaneous expression of their specific constituents in the same cell type of damaged tissues (53).

ROLE OF HYPOXIA-ASSOCIATED INFLAMMATION IN OBESITY AND COLORECTAL CANCER

Maintenance of oxygen homeostasis is essential for cellular and tissue function. Hypoxia results from a constant inadequate

supply of oxygen (O₂), resulting in decreased O₂ tension that limits its availability to the demands of the surrounding tissue (54). Hypoxic stress is clinically relevant and plays a pivotal role in the pathogenesis of multiple human diseases, including cardiovascular diseases, diabetes, and cancer (55). In the obese state, adipose tissue depots become hypoxic as tissue mass expands, restricting the availability of oxygen particularly in clusters of adipocytes that are distant from the vasculature (56). This imbalance between the O₂ supply and demand in adipocytes promotes the release of pro-inflammatory mediators, an inhibition of the anti-inflammatory adipokine adiponectin, macrophage infiltration and adipocyte death. In this sense, hypoxia constitutes an important factor in the development of obesity-associated comorbidities (55–57). Although hypoxia was proposed as a new potential risk factor for chronic inflammation in obesity in 2004 (58), its biological significance was not disentangled until 2008 when new methods for detection of oxygen levels in the adipose tissue were developed (59). Since then, multiple studies have directly evidenced a significant increase in hypoxic stress in the adipose tissue of different obese mouse models and humans (59–61).

The hypoxia-inducible factor 1 (HIF-1) acts as a master regulator of oxygen homeostasis regulating the expression levels of a wide variety of genes that stimulate erythropoiesis, angiogenesis, and glycolysis in a cell-specific pattern (62, 63). Increased HIF-1 α gene expression in the subcutaneous adipose tissue of obese patients have been shown to be reduced after surgery-induced weight loss (64). Moreover, it is well established that levels of HIF-1 α are elevated in the adipose tissues of obese mice, exerting important roles in the development of obesity and insulin resistance (65, 66). Reportedly, *Hif1a* deficient mice under a high-fat diet exhibited beneficial effects in adipose tissue inflammation and insulin resistance development (67). Interestingly, an opposite role for *Hif-2 α* has been proposed. The deletion of *Hif2a* in adipocytes exerts protective effects by reducing the expression of inflammation- and fibrosis-related genes and also counteracting *Hif-1 α* effects (67).

Indeed, hypoxia is also a hallmark of cancer (68, 69). Hypoxia plays a main role in cancer by promoting changes in the tumoral microenvironment, inducing angiogenesis, sustained proliferative signaling, unlimited replicative potential, genetic instability and altering the metabolism of tumoral cells (70). Hypoxia induces a transcription programme that promotes an aggressive tumor phenotype by the activation of HIF-1 (71). Accumulated evidence has highlighted a strong link between hypoxia-induced inflammation and intestinal diseases including ulcerative colitis, intestinal ischemia, and CRC (72). Similar to obesity, HIF-1 α and HIF-2 α have divergent roles in colon cancer development (73). HIF1A overexpression was significantly associated with poor prognosis and higher colorectal cancer-specific mortality, whereas HIF-2 α was not related with clinical outcome and exhibited an inverse association with high tumor grade and obesity (74). Xenograft studies have revealed that loss of expression of HIF-1 α inhibited tumor growth and, in contrast, deficiency of HIF-2 α stimulated tumoral cell

proliferation (75). The potential of targeting hypoxia and HIFs as a possible therapy for different types of cancer has widely analyzed because of their significant involvement in cancer development (76, 77).

Importantly, apart from HIF-1 other transcription factors are involved in the response to hypoxia, including nuclear factor κ -B (NF- κ B), cyclic AMP response element binding protein (CREB), activating protein-1 (AP-1), early growth response-1 (EGR-1) and p53 (56). NF- κ B is a central transcriptional mediator of the inflammatory response and its activation leads to a coordinated expression of genes involved in the control of innate immunity, inflammation as well as cellular stress responses and cell survival (78–80). Reportedly, NF- κ B regulates gene expression levels of *Hif1a* under basal conditions and also during hypoxia in animal models, linking inflammation and the hypoxic response (81). Previous studies also demonstrated the dual regulation between NF- κ B and HIF-1 in cellular cultures (82, 83) Hypoxia also potentiates the NF- κ B signaling by modulating the expression of toll like receptors (TLRs), which are known for their functional roles in the inflammatory response in both, infectious and non-infectious diseases and in the production of IL-1 β , a main pro-inflammatory cytokine (55, 84).

INFLAMMASOME BIOLOGY AND ACTIVATION

The innate immune system include a wide range of pattern-recognition receptors (PRRs) for sensing cellular insults including the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), the retinoic acid-inducible gene I-like receptors (RLRs) and the toll-like receptors (TLRs) (53, 85). Among them, NLRs recognize diverse set of inflammation-inducing stimuli that include pathogen-associated molecular patterns (PAMPs) as well as host-derived danger signals (danger-associated molecular patterns, DAMPs) (53). Inflammasomes are intracellular multiprotein complexes that recognize both PAMPs and DAMPs. The essential components of inflammasomes comprise a sensor protein (NLR and PYHIN families), the adaptor apoptosis-associated speck-like protein containing a CARD (ASC) and the effector protease caspase-1. Hence, inflammasomes act as high-molecular weight platforms for caspase-1 activation (86) and once activated, caspase-1 triggers the maturation and release of important proinflammatory mediators such as IL-1 β and IL-18 (53, 87). IL-1 β is involved in the regulation of broadly systemic and local responses to infection and injury and, therefore, a tight control of its production is required (88, 89). In addition, inflammasomes also trigger the secretion of multiple proteins to coordinate cell proliferation and tissue repair such as fibroblast growth factor (FGF)-2, high mobility group box 1 (HMGB1), galectin-1, galectin-3, and IL-1 α through an unconventional pathway (90, 91). Moreover, inflammasomes are required to coordinate other important mechanisms of inflammation and tissue repair including (i) pyroptosis, a type of lytic programmed cell death mediated by activation of caspase-1

and (ii) necrosis, a passive cell death resulting from external factors (92–94). Inflammasomes-induced processes are of great importance not only in the antimicrobial response but also in governing metabolic pathways and mucosal immune responses. An altered inflammasome function has been shown to be implicated in the pathogenesis of human diseases (92, 94).

According to their main constituent, inflammasomes can be categorized in two main groups: (i) the NLR family that includes the members NLRP1, NLRP2, NLRP3, NLRP6, NLRC4 and, potentially, NLRP12 and (ii) the PYHIN family that comprises the AIM2 and IFI16 members (95, 96). Among them, the NLRP3 inflammasome is the best characterized. Unlike other inflammasomes, the endogenous expression of NLRP3 in inactive immune cells is not enough to allow its activation representing a key limiting factor for its regulation (97). These evidences show that the activation of the NLRP3 inflammasome depends on a two-signal step process with a minimum of two stimuli being needed (98); first a priming step is required followed by a second activation step to induce the NLRP3 inflammasome formation (99, 100). The priming step can be mediated through PRRs, toll-like receptors (TLR), cytokine receptors or other factors upstream the nuclear factor NF- κ B pathway (99–101) and then, the NLRP3 inflammasome assembles in response to a wide array of signals including PAMPs, bacterial toxins and DAMPs (ATP, uric acid, amyloid β fibrils, cholesterol crystals ceramides, palmitate and hyaluronan) (102–104). Saturated fatty acids induce the activation of the NLRP3 inflammasome in macrophages by increasing mitochondrial reactive oxygen species as well as by activating the AMP-activated protein kinase and autophagy signaling cascades (105, 106). Hypoxia has been also described to be involved in the regulation of NLRP3 activation in adipocytes. A recent study has elegantly demonstrated that the increased gene expression levels of the NLRP3 inflammasome components induced by homocystein, were downregulated in the epididymal adipose tissue of an adipocyte-specific *Hif1a* knockout mice (107). Moreover, reduced circulating levels of IL-1 β and active caspase-1 were found in both adipocytes and macrophages infiltrating adipose tissue (107). Extracellular ATP is another key DAMP that induces NLRP3 inflammasome formation. The mechanism for producing ATP is dependent on the levels of O₂ and regulated by HIF-1, that directs cells to produce ATP via glycolysis during O₂ deprivation (54, 63, 108). Therefore, the increase in ATP under hypoxia conditions might be also involved in the activation of the NLRP3 inflammasome. While TLRs recognize PAMPs in the extracellular component and endosomes, NLRs act in the cytoplasm (109). Recent evidences have connected the NLRP3 inflammasome and TLRs in immune and metabolic regulation (108). The activation of TLRs offers a priming signal for inflammasome activation independent from the transcription of NLRP3 and involving critical factors such as IRAK1 and TRAF6 (110–113). Moreover, LPS has been shown to induce the expression of HIF-1 α by a TLR4-dependent pattern in macrophages and in turn, HIF-1 α up-regulated TLR4 expression under hypoxic stress (108, 114, 115), suggesting that both NLRP3 and TLR4 are under hypoxia control. The role of hypoxia,

mitochondrial reactive oxygen species as well as glucose and lipid metabolism in NLRP3 activation and dysregulation has been exhaustively reviewed supporting their high potential in the design of innovative therapies for inflammasome-associated diseases (108, 116).

Therefore, NLRP3 activation is tightly regulated at multiple levels highlighting the significance of this protein complex in the development and progression of chronic inflammatory diseases and its potential for designing innovative therapeutic strategies (92, 94). Notably, recent studies have linked the activation of the NLRP3 inflammasome to different metabolic diseases including obesity, metabolic syndrome, T2D and cardiovascular alterations and the role of NLRP3 in cancer, especially in inflammation-induced cancers, has been extensively explored (101). However, the molecular pathways underlying the organ- and cell-specific activation of the NLRP3 inflammasome in the context of obesity have just stated to be elucidated.

NLRP3 IN THE DEVELOPMENT OF OBESITY AND INSULIN RESISTANCE

Immune and metabolic responses must be tightly regulated for normal cellular homeostasis and both are highly conserved across species and throughout evolution (117). The NLRP3 inflammasome was first suggested to regulate adiposity and insulin sensitivity during obesity by Zhou et al. (118) demonstrating that mice lacking *Nlrp3* showed improved glucose homeostasis under a high fat diet (119). A novel study corroborated this finding reporting that *Nlrp3*-, *Caspase-1*-, or *Il1b*-knockout mice under a normal diet exhibited a reduction in their weight gain and fat mass, as well as an improvement in insulin sensitivity. These data suggest that the *Nlrp3* inflammasome is involved in the regulation of glucose homeostasis (120). Indeed, mice lacking *Nlrp3* were resistant to the development of high fat diet-induced obesity and were also protected from obesity-induced insulin resistance. In this knockout mice model, the impaired inflammasome activation was associated with a reduction in the expression of the proinflammatory factor MCP-1 in adipose tissue as well as with a decrease in the size of adipocytes, in the number of infiltrated macrophages in adipose tissue and in the content of triglycerides in the liver (121). The improved metabolic phenotype of *Nlrp3*^{-/-} mice has been also linked to an attenuated *Il1b* expression in adipose tissue and lower serum concentrations of IL-18 (122). These observations are partly paralleled in humans, in whom the expression of the different components of the NLRP3 inflammasome in adipose tissue is directly associated with body weight in obese individuals with T2D as well as with the severity of T2D (122). Furthermore, weight loss in obese patients with T2D was correlated with a significant downregulation in *NLRP3* and *IL1B* gene expression in subcutaneous adipose tissue. Another evidence for a pathogenic role of NLRP3 in T2D comes from a study reporting that glyburide, a sulfonylurea drug for the treatment of T2D, inhibits NLRP3-mediated IL-1 β release in monocytes (123). In addition, the islet amyloid polypeptide

(IAPP or amilin), a hallmark feature in the pancreas of most patients with T2D, triggers IL-1 β production via NLRP3 in lipopolysaccharide (LPS)-primed macrophages or dendritic cells (124).

Considering that the development of obesity is associated with hypoxia and adipocyte death, NLRP3 is preferentially expressed in ATMs from the crown-like structures. Lipotoxic ceramides and the saturated fatty acid palmitate can also trigger NLRP3 activation through a mechanism that involves defective autophagy and the accumulation of mitochondrial reactive oxygen species (ROS) (94, 106). Importantly, obesity is associated with increased circulating levels of palmitate, constituting one of the most abundant free fatty acids in the obese state (101). Obesity itself also promotes the assembly of the NLRP3 inflammasome in ATMs, inducing macrophage-mediated T cell activation that, through the release of INF- γ , mediates insulin resistance (101, 122). In addition, the activation of caspase-1 in ATM induces detrimental effects in insulin-sensitive tissues: (i) IL-1 β impairs insulin signaling by direct phosphorylation of insulin receptor substrate 1 and by inducing the expression of TNF- α , a well-characterized pro-inflammatory and insulin resistance promoting cytokine; and (ii) IL-1 β induces type 1 CD4T helper cells in adipose tissue leading to lymphocyte accumulation and activation and promoting insulin resistance (94, 125). Despite unequivocal evidences causally link IL-1 β to the development of obesity-associated comorbidities, IL-18, also activated by caspase-1, has been shown to ameliorate the development of obesity and insulin resistance (126). Obese individuals have increased levels of circulating IL-18 that are markedly correlated with metabolic syndrome and insulin resistance (127–129). However, somewhat paradoxically, IL-18 has anti-obesity effects (129). *Il-18*- and *Il-18* receptor-deficient mice exhibit a notably increase in their body weight compared to wild-type littermates of the same age (126). Mice treated intracerebrally with recombinant IL-18 showed an inhibition in food intake as well as an improvement in glucose homeostasis (126). Recently, IL-18 production from the NLRP1 inflammasome has been associated to the prevention of obesity and metabolic syndrome (129). Reportedly, *Caspase-1* knockout mice also deficient in both IL-18 and IL-1 β exhibited an improvement in glucose metabolism, suggesting that the insulin desensitizing effects of IL-1 β override IL-18 action (126, 130, 131).

Besides its functions in ATMs, the NLRP3 inflammasome is also an important regulator of intrinsic adipocyte functions, controlling adipocyte differentiation. Caspase-1 is upregulated during adipocyte differentiation and, through the activation of IL-1 β , directs adipocytes toward a more insulin-resistant phenotype. In addition, *Nlrp3*- and *Caspase-1*-deficient preadipocytes resulted in more metabolically efficient fat cells (120). Importantly, the loss of function of NLRP3 is associated with a decrease in the activation of caspase-1 but does not completely inhibit its function, suggesting that additional non-NLRP3 inflammasome sensors might be controlling its activation. This reveals the interesting possibility of specific inflammasome components present in macrophages, adipocytes, or pancreatic β cells inducing the development of

obesity-associated low-grade chronic inflammation and hence, its associated comorbidities (130).

ROLE OF NLRP3 IN COLORECTAL CANCER

The gastrointestinal mucosa homeostasis depends on complex interactions between diverse regulatory mechanisms: the microbiota, the intestinal epithelial cells and the host immune system with a breakdown in these pathways plausibly precipitating a chronic inflammatory pathology (94, 132). The ability of inflammasomes to recognize exogenous and endogenous pathogenic insults (91) has led to analyze their roles in intestinal inflammatory bowel diseases (IBD), including ulcerative colitis, Crohn's disease, and CRC development. However, conflicting results regarding the role of the NLRP3 inflammasome have been reported by several groups. Whereas, some studies have reported reduced disease severity in *Nlrp3* or *Caspase-1* knockout mice due to a lower IL-1 β production, other groups have found that *Nlrp3*-, *Asc*- and *Caspase-1*-deficient mice showed an increased disease severity (133–136). Indeed, the cytokines IL-1 β and IL-18, the main downstream signaling molecules from NLRP3 pathway, exert pleiotropic effects in inflammation and tumorigenesis with both, pro- and anti-tumorigenic functions having been extensively studied (137, 138). This seemingly contradictory function has been proposed to be context-dependent and tissue-specific. In an elegant study, ASC, a main component of the inflammasomes, was shown to promote tumor development favoring inflammation in infiltrating immune cells, and, oppositely, to limit the proliferation of cancer cells via the activation of p53 in epithelial cells (139). Thus, a model in which the hypo- or hyper-functionality of the inflammasome led to an imbalance of the intestinal homeostasis has been proposed. In this sense, the specific function of the inflammasome in the intestinal tissue depends on the affected cell type: the activation of the inflammasome is required for controlling epithelium permeability and regeneration but its excessive activation within the lamina propria promotes severe intestinal inflammation (140). Reportedly, the IL-22–IL-22 binding protein (IL-22BP) axis is critically involved in both, intestinal cellular renovation and colon tumor development. Colon tissue damage triggers the activation of the NLRP3 inflammasome that downregulates the expression levels of IL-22BP through the activation of IL-18 via caspase-1. It leads to an increase in the ratio of IL-22/IL-22BP allowing IL-22 exert its protective roles during the peak of damage. However, an uncontrolled and prolonged expression of IL-22 may promote CRC development (141). This observation suggests a critical role for IL-18 in colon carcinogenesis. In this regard, differential actions of IL-18 have been also described during the acute and chronic stages of colitis (142).

Relevant studies focused on the activity of the inflammasome in cancer development have demonstrated that NLRP3 is highly expressed in a cell line of mesenchymal-like colon cancer cells with its expression being upregulated by TNF- α

and transforming growth factor- β 1 (TGF- β 1) during the epithelial-mesenchymal transition (143). In addition, the knockdown of *NLRP3* in colon carcinoma cells has been associated with a decreased capacity of migration and invasion (143). Furthermore, a high cholesterol diet has been shown to promote colon carcinogenesis in azoxymethane (AOM)-treated mice via the activation of the NLRP3 inflammasome (144). Consistently, cholesterol inhibited the activity of AMP-activated protein kinase (AMPK)- α in macrophages, increasing the production of mitochondrial ROS, which in turn activated the NLRP3 inflammasome (144). These data underline the influence of diet in controlling molecular pathways associated with chronic inflammatory disorders and CRC. The inhibition of the NLRP3 inflammasome in macrophages from an AOM-dextran sulfate sodium (DSS) mouse model of colon carcinoma significantly protected against colitis-associated cancer (145). Despite mounting evidence about its pro-carcinogenic activities, *NLRP3* deficiency has been linked not only to an increased number of colon polyps but also to a greater susceptibility to colon cancer development in an AOM-DSS mouse model, suggesting a protective role for NLRP3 in colon carcinogenesis (133). Recently, genome-wide association studies have linked single nucleotide polymorphisms in the gene encoding NLRP3 with increased susceptibility to Crohn's disease (146) as well as with poor survival rate for colorectal cancer (92, 147).

IL-1 β AND IL-18 IN OBESITY AND COLON CANCER

IL-1 β is an "alarmin cytokine" with pleiotropic functions mainly produced and released by inflammatory or stress signals (148). A dysregulated expression of IL-1 β has been linked to tumor development and growth in different types of cancer including CRC (149–153). In this sense, an increased IL-1 β expression associated with a high-grade inflammation in colonic mucosa has been described in patients with IBD as well as in several animal models of the disease (154–157). IL-1 β is also able to act on intestinal epithelial cells promoting epithelial-mesenchymal transition and hence, contributing to colon tumor cell invasiveness (158, 159). Moreover, IL-1 β stimulates the production of reactive oxidative species that induce DNA damage and cancer development. An increased expression of the microRNA-301a promoted by IL-1 β has been recently described in patients with CC. The microRNA-301a induced colon inflammation and cancer development by the production of strong pro-inflammatory cytokines that compromised colonic mucosa of patients with IBD (160). IL-1 β also stimulates the expression of syndecan-2, not only a well-known colon cancer marker but also an inflammatory hypoxia marker, strengthening the relationship between chronic inflammation and the development of CC (161). Consistently, mutations in the IL-1 β gene resulted in increased protein levels and therefore, in a higher risk of colon cancer development (162) and mutations in the nucleotide binding oligomerization domain containing (NOD)-2 gene have been shown to increase

NF- κ B activity and IL-1 β processing in patients with severe forms of Crohn's disease, indicating an association between IL-1 β and the development of IBD (163). Further studies in *Il1b*-deficient mice have shown an impairment of the potent IL-1 β -mediated inflammation limiting tumor development (152, 155).

Tumor-associated macrophages (TAM) are key effectors in cancer-related inflammation and reportedly, activated macrophages secrete IL-1 β resulting in the activation of NF- κ B signaling favoring tumorigenic progression (164, 165). In this line, the AW264.7 macrophage cell line is unable to secrete the mature form of IL-1 β because of the absence of a specific component of the inflammasome, the caspase-activating recruiting domain (ASC), suggesting the existence of different release pathways (166). The secretion of IL-1 β by macrophages is also required to activate Wnt signaling and β -catenin/TCF4 transcriptional activity in tumor cells promoting tumor growth (167–169). Obesity-associated adipose tissue inflammation is characterized by an infiltration of M1 activated macrophages. Based on growing evidence, excess adipose tissue has been linked to cancer promotion by its capacity to recruit pro-inflammatory macrophages that release pro-inflammatory cytokines with pro-carcinogenic effects including IL-1 β as well as by the great variety of inflammatory adipokines synthesized by the adipocytes (40, 41). In obesity-associated breast cancer, adipocytes are able to recruit macrophages by a novel signaling pathway involving IL-1 β and the chemotactic factor CCL2 (also known as MCP-1) that in turn activate CXCL12 promoting angiogenesis and tumor development (170). The relationship of CCL2 and IL-1 β has been previously reported since *Ccl2* knockout mice exhibited a reduced angiogenesis induced by IL-1 β (171).

IL-18 also known as interferon- γ inducing factor (IGIF) is a central cytokine in the regulation of both innate and acquired immune responses (172, 173). IL-18 also exhibits lymphocyte chemoattractant properties and induces the expression of pro-inflammatory mediators as well as angiogenesis- and adhesion-related factors (174). IL-18 is widely overexpressed in patients with IBD, especially in patients with Crohn's disease (155, 175). Furthermore, gene and circulating expression levels of IL-18 are increased in gastrointestinal-associated cancers (176). However, IL-18 has a dual activity in the pathogenesis of CC (155). Whereas, during early stages of CC IL-18 exerts a protective role including epithelial repair processes (177) during later stages, it promotes tumor growth and cellular invasion (178). Significantly, the importance of cell specificity for IL-18 signaling in colitis has been previously described (179).

Obesity and obesity-associated insulin resistance have been also associated with increased circulating IL-18 levels (180, 181). In accordance, a hypocaloric diet induced a reduction in plasma IL-18 levels (182). Although human adipocytes express IL-18, they are unlikely to contribute significant amounts of IL-18 into circulation and their increased levels associated with obesity (183). However, an independent study has demonstrated that human adipose tissue contributes to systemic IL-18 concentrations (184). Increased levels of IL-18 and TNF- α have been described in the colon of diet-induced obese mice

in parallel with alterations in the Wnt signaling pathway suggesting a mechanism for obesity-associated CC development (185).

NLRP3 INFLAMMASOME IN OBESITY AND COLON CANCER

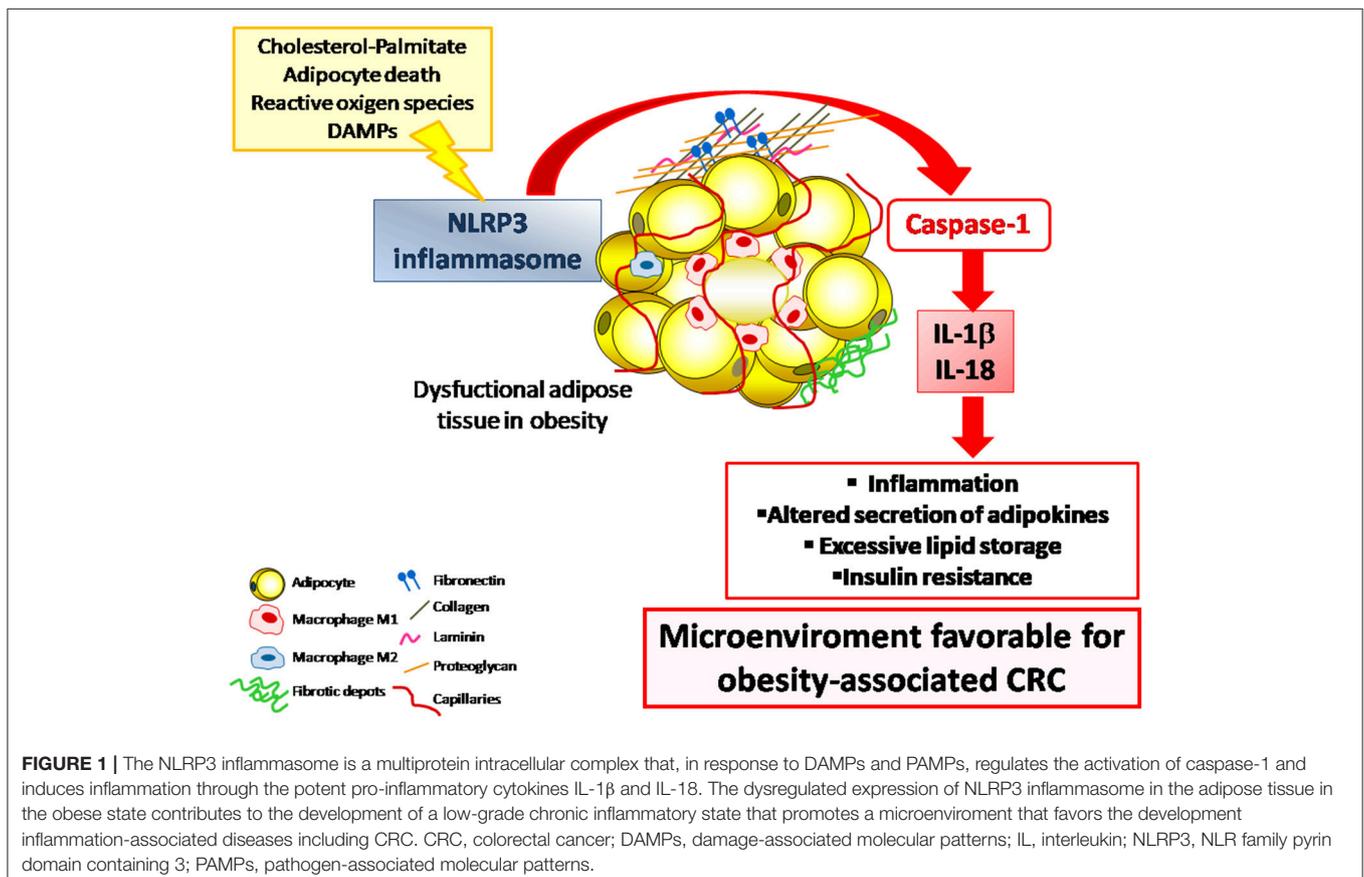
Chronic inflammation and excessive adipose tissue accumulation are known risk factors for numerous chronic conditions including CRC (6, 69, 186). Whether obesity has an impact on CRC development by enhancing inflammatory signaling pathways or through a direct mechanism remain largely unclear and the role of NLRP3 in colon cancer is still controversial. A causal mechanism by which obesity promotes the progression of breast cancer via the NLRP3 inflammasome activation has been recently described (187) but no results showing the impact of NLRP3 in obesity-associated CRC have been reported. A possible mechanism in this association may involve the IL-1 β pathway, strongly upregulated in obese patients with CRC (188). In this sense, IL-1 β has been shown to promote CRC progression by inducing the release of inflammatory and extracellular matrix remodeling factors by acting directly on adipocytes or indirectly on macrophages (189) (Figure 1).

Obesity has been also broadly associated to poor prognosis of CRC by influencing tumor microenvironment through the

release of pro-inflammatory adipokines by adipocytes and inflammatory factors by tumor-associated adipocytes (TAAs). TAAs are able to modulate and recruit TAM which, in turn, can promote tumor angiogenesis and metastatic spread (190). TAMs display an increased activation of the NLRP3 inflammasome, resulting in a significant increase in IL-1 β expression that aggravates colon inflammation and favors CRC development. Importantly, improved survival as well as reduced lymph node invasion and distant metastasis have been reported for patients with invasive breast cancer with low levels of infiltrating NLRP3⁺ macrophages (191). These data sustain the concept that the enhanced expression of *NLRP3* in TAM correlates with disease aggressiveness and metastasis (191, 192). Further studies are required to fully explain the molecular pathways underlying the impact of NLRP3-IL-1 β in obesity-associated CRC.

THERAPEUTIC INTERVENTIONS

A huge body of knowledge supports the link between cancer and obesity, or more specifically with excess adiposity. Thus, it seems reasonable to translate these findings to the clinical practice and focus our attention more on adipose tissue by performing body composition analyses or at least estimating body fat by available validated equations (193). In this line, it is also important to gain more insight into the impact of adipobiology



given its direct relationship with energy homeostasis (21, 194), inflammation (195), T2D-insulin resistance (196, 197) and lipid metabolism (198–200). Moreover, the influence of already well-known adipokines or as yet unidentified additional factors with cancer development should be considered (201–205).

The well-established inflammatory potential of NLRP3 together with its central role for immune sensing as well as its key function in different diseases makes NLRP3 an attractive therapy target. The agonists of NLRP3 may be useful in immunotherapy of specific solid tumors by enhancing the immune function to reverse the immunosuppressive microenvironment (206). For instance, the activation of IL-18 signaling by the inflammasome controls colon tissue regeneration following CRC by inducing a process of intestinal re-epithelialization (207). The inflammasome signaling is also involved in the regulation of immunosurveillance, which by its combination with chemotherapy treatments induce immunogenic cell death (208) and by its interactions with TLR pathways promote an efficient antitumoral immunity (209). Since the activation of NLRP3 drives pyroptotic and immunogenic cell death, its direct activation within the tumor has been described as an efficient mechanism to mediate a potent and persistent antitumor immunity (210). However, in specific conditions such as obesity, the chronic activation of NLRP3 can promote tumor cell growth, migration and invasion (97). Thus, while long-term chronic inflammation may constitute a mechanism to support the growth of several tumors, the acute and robust activation of NLRP3 may have the capacity to activate the immune system for tumor destruction (97).

On the other hand, pharmacological inhibitors of the NLRP3 pathway could offer a better treatment option in a wide array of chronic- and auto-inflammatory diseases for which no adequate therapies exist (97). The development of NLRP3 antagonists constitutes an important research topic since only a specific subset of NLRP3-associated pathologies can be efficiently treated with agents that block the signaling pathway of IL-1 β , including (i) anakinra, a recombinant and slightly modified version of the IL-1 receptor antagonist, (ii) canakinumab, a monoclonal antibody to neutralize IL-1 β , and (iii) riloncept, a long-acting soluble decoy IL-1 β receptor engineered as a dimeric fusion protein (211). Different NLRP3 inflammasome inhibitors, including sulforaphane, β -hydroxybutyrate, glyburide, flufenamic acid, mefenamic acid, parthenolide, BAY 11-7082, INF39, and MCC950 have been developed, but there is no evidence demonstrating that these compounds directly and specifically target NLRP3 itself (212). Among these compounds, BAY 11-7082 has been shown to attenuate the increase of the NLRP3 inflammasome expression

after a high fat diet leading to the repression of caspase-1 activation as well as to the reduction of IL-1 β and IL-18 release, normalizing the diet-induced impairment of metabolic parameters (213). The fasting- or exercise-induced ketone metabolite β -hydroxybutyrate exhibited the potential to inhibit the NLRP3 inflammasome in human macrophages dampening innate immune responses and sparing ATP for the function of ketone-dependent organs. These results suggest that dietary approaches to increase the β -hydroxybutyrate levels may be a promise in decreasing the severity of NLRP3-associated chronic inflammatory diseases (214). However, the direct target of NLRP3 has potentially increased efficacy and decreased side effects over these current treatments. Recently, CY-09 has been reported to directly target NLRP3, inhibiting its activation *in vivo* and reversing metabolic disorders through inhibition of NLRP3-dependent IL-1 β production in a mouse model of T2D (212, 214). Further research characterizing the molecular mechanisms in which these compounds are involved will help us to establish the specific functions of NLRP3.

In light of the fact that the prevalence of obesity and CRC is increasing in an alarming rate, a more detailed studies identifying the roles and mechanisms of action of NLRP3 as well as the clinical development of molecules to selectively antagonize the NLRP3 inflammasome may lead to a better understanding of the pathogenesis of obesity-associated comorbidities as well as to the develop of innovative precision medicine approaches for the management of obesity and its complications (215, 216).

AUTHOR CONTRIBUTIONS

PA, GF, and VC: wrote and edited the manuscript; GZ, PM, JH-L, JB and XU: contributed to writing and critically revised the paper; VC and GF: designed the figure. All authors read, corrected, and approved the final manuscript.

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