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Obesity-associated myeloid immunosuppressive cells, key players in cancer risk and response to immunotherapy.

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Abstract

Obesity is a risk factor for developing several cancers. The dysfunctional metabolism and chronic activation of inflammatory pathways in obesity create a milieu that supports tumor initiation, progression, and metastasis. Obesity-associated metabolic, endocrine, and inflammatory mediators, besides interacting with cells leading to a malignant transformation, also modify the intrinsic metabolic and functional characteristics of immune myeloid cells. Here we discuss the evidence supporting the hypothesis that obesity metabolically primes and promotes the expansion of myeloid cells with immunosuppressive and pro-oncogenic properties. In consequence, the accumulation of these cells, such as myeloid-derived suppressor cells (MDSCs) and some subtypes of adipose-tissue macrophages (ATMs), creates a microenvironment conducive to tumor development. In this review we emphasize the role of lipids, insulin, and leptin, which are dysregulated in obesity, and dietary nutrients in metabolic reprogramming of these myeloid cells. Moreover, we also summarize emerging evidence indicating that obesity enhances immunotherapy response and hypothesized mechanisms. Priorities in deeper exploration involving the mechanisms of crosstalk between metabolic disorders and myeloid cells related to cancer risk in patients with obesity are highlighted.

Keywords

Obesity; cancer; myeloid immunosuppressive cells; MDSC; macrophages

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INTRODUCTION

Obesity is associated with an elevated risk of developing or dying from at least 13 types of cancer. It is estimated that 11% of cancers in women and 5% of cancers in men are attributable to overweight and obesity. Data from animal models also demonstrate that obesity promotes tumorigenesis [1]; however, the specific biological mechanisms by which obesity stimulates carcinogenesis are incompletely understood. Tumorigenesis is influenced by several factors derived from dysfunctional and hypertrophic visceral adipose tissue. Excess adiposity induces systemic alterations in metabolism, immune, and endocrine systems that result in abnormal concentrations and signaling of insulin, insulin-like growth factors (IGF), sex hormones, lipids, cytokines, and adipokines including leptin. Additionally, impaired fat tissue promotes polarization shifts of myeloid cells and systemic and local chronic low-grade inflammation [2]. A feature of chronic inflammation is the induction of myeloid cells with the ability to restrain pro-inflammatory responses with carcinogenic properties. In obesity, the accumulation and polarization of myeloid cells towards an immune-regulatory phenotype are promoted to restore metabolic and inflammatory homeostasis; however, these myeloid cells are important drivers of immune suppression and inflammation that also facilitate tumor development [3, 4]. In this review, we examine the impact of obesity-primed myeloid immunosuppressive cells, specifically myeloid-derived suppressor cells (MDSCs) and the metabolically activated subtype of adipose-tissue macrophages (ATMs), in promoting cancer.

Chronic low-grade inflammation: a disorder that promotes cancer

The cellular and molecular mechanisms underlying chronic inflammation in obesity remain incompletely established. Adipocytes produce a diversity of inflammatory molecules that are dysregulated during adipose tissue expansion. Among these molecules include prostaglandin E2 (PGE2), cytokines (interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (IFNα), IFNγ) chemokines (IL-8, Monocyte chemoattractant protein-1 (MCP-1/CCL2), and macrophage inflammatory protein 1 (MIP-1)), and hormones with pro-inflammatory properties (leptin and resistin) [5]. Several of these inflammatory molecules promote tumorigenesis by activating signaling cascades related to cellular proliferation, suppression of apoptosis and angiogenesis on nascent malignant cells [6]. Additionally, hypertrophic adipocytes exhibit increased rates of lipolysis, hypoxia, and frequency of adipocyte death [7], which enhances cytokine production, activates resident macrophages and facilitates the recruitment of circulating leukocytes. In inflamed tissue, the continuous infiltration of myeloid cells such as neutrophils and macrophages results in high local levels of reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI), responsible for oxidative damage to DNA, proteins, and lipids [8]. Inflammation-associated oxidative stress causes genomic instability resulting in increased mutation rates that lead to cellular transformation into malignant cells [8, 9]. Together these events promote cellular damage, perpetuate and amplify the inflammatory process, support the proliferation of mutated cells, stimulate angiogenesis, and confer metastatic properties to tumor cells [10].

Myeloid cells in the obese milieu that foster cancer onset

It is generally accepted that with normal weight and metabolic homeostasis, ATMs with anti-inflammatory functions, traditionally termed as M2 macrophages, are the main macrophage subpopulation infiltrating adipose tissue. Once adiposity is increased (overweight), a switch from M2 towards M1 pro-inflammatory polarized macrophages occurs (Figure 1). This switch is considered critical for obesity-associated inflammation [11]. As obesity progresses and insulin resistance develops, ATMs proliferating within adipose tissue exhibit markers of an M2 alternatively activated state [12]. In the advanced stage of adiposity, the induction of other myeloid cells with immune-regulatory, angiogenic and tissue-remodeling activities, named MDSCs, also infiltrate the adipose tissue, perhaps in an attempt to resolve inflammation, repair tissue, and restore insulin sensitivity [3]. While these myeloid cells restore metabolic homeostasis and resolve inflammation, their sustained presence nurtures an immunosuppressive and pro-angiogenic microenvironment that facilitates immune escape of emerging malignant cells and tumor initiation [3]. The first key studies that established the role of these myeloid cells in promoting cancer development were originated in a mouse model by deletion of CCAAT/enhancer-binding protein β (C/EBPβ) [13], a transcription factor essential for myeloid M2-like polarization. In this model, when myeloid immunosuppressive cells were depleted, the host was protected from high-fat diet (HFD; 60% kcal fat, 6.8% kcal sucrose)-induced systemic inflammation, insulin resistance, and tumor development [14].

Macrophage subsets as key players in the inflamed fat tissue—Macrophages are plastic cells that easily adjust to different sources of stimuli in the local environment by changing their metabolic and functional properties, a process defined as polarization. Based on the function, genomic signature, and protein expression profiles, a wide spectrum of macrophage activation states between the conventional pro-inflammatory M1 (classical activated) and anti-inflammatory M2 (alternative activated) phenotypes have been identified (Table 1) [15]. Generally, these M2 macrophages are thought to participate in tissue homeostasis, remodeling, and wound healing; however, because of the heterogeneous subpopulations found in different microenvironment settings, those macrophages designated as M2 have rapidly expanded to include several functionally distinct subtypes. Based on the *in vitro* stimuli applied for their activation, M2 macrophages can be further divided into subsets called M2a, M2b, M2c and M2d [16]. M2a, often termed as wound-healing macrophages, are induced by IL-4 and IL-13 leading to the increased expression of IL-10, TGF-β, and CCL17/18/22. These macrophages activate an anti-parasite Th2 response by producing IL-10 and TGF-β. M2b cells, also known as regulatory macrophages, are activated by immune complexes and TLRs ligands (i.e. lipopolysaccharides or by IL-1β). M2b cells release both pro- and anti-inflammatory cytokines such as IL-1β, IL-6, TNFα, IL-10, CCL1 and TNF superfamily member 14 (TNFSF14), and regulate the immune responses and inflammatory reaction. IL-10 or the combination of glucocorticoids and TGFβ induces M2c macrophages. These cells produce IL-10, TGFβ, CCL16, and CCL18 and play a role in immune suppression, tissue repair, matrix remodeling and phagocytosis of apoptotic cells. M2d macrophages are induced by co-stimulation with TLR ligands and A2 adenosine receptor (A2R) agonists or by IL-6. This leads to the high release of IL-10, TGFβ and vascular endothelial growth factors (VEGF) and low production of IL-12, TNFα and

IL1β which promotes angiogenesis and tumor progression. Within the tumor, infiltrating macrophages exhibit functions like those of M2 macrophages and can be classified as M2b and M2d subtypes [17, 18]. These cells display immunosuppressive and tumorigenic functions and express the enzyme arginase 1 (Arg-1), which depletes L-arginine thereby inhibiting anti-tumor T cell function [19] and promoting tumor initiation and progression. In addition to Arg-1 as the main signature of immunosuppressive macrophages, these cells also produce high levels of immune-regulatory cytokines such as IL-10 and TGFβ.

Signals found in the complex milieu of fat tissue from mice and humans with obesity also elicit multiple distinct subpopulations of ATM with distinctive function, transcriptome signature, and epigenetic landscapes [20]. For instance, macrophages in the peritoneal cavity and cecal tissue from mice with diet-induced obesity (DIO) exhibit an M2b polarization ($TNF\alpha^{high}$, $IL\text{-}10^{high}$, CD206+, Dectin1+) and produce TNFα, IL-1β and IL-10 [21]. Also, ATM that are metabolically activated by dysregulated mediators found in adiposity, named metabolically activated macrophages (MMe) [22, 23], exhibit both M1 pro- and M2 anti-inflammatory characteristics (as described for M2b cells) with functional properties of M2-like macrophages [23]. Potential immunosuppressive properties in these MMe may be modulated by PPARγ, a transcription factor that regulates the gene expression of M2-like markers including Arg-1 [24], which confers the ability to limit the pro-inflammatory response of MMe [23]. Interestingly, adipose-derived mesenchymal stem cells (ADMSCs), which are suspected to promote tumor development and progression, have an important role in immunosuppression in the local tissue. Culture of peritoneal macrophages with conditioned media derived from ADMSCs induces macrophage polarization towards M2b/c phenotype via IL-6. Although M2b/c macrophages can produce several pro-inflammatory cytokines, the most prominent feature of these cells is the large production of IL-10 [25]. However, whether DIO-induced macrophage subsets can block the protective anti-tumor T cell immune response has not been convincingly demonstrated. These observations suggest that M2b/c and MMe macrophages may be critical cell populations within tumor-associated macrophages (TAMs) in obesity. Despite the critical roles of macrophage subsets in adiposity progression and comorbidities associated with obesity such as cancer, the specific molecular and metabolic markers of M2b and MMe macrophages, as well as their ability to block protective T cell immune response have not yet been definitively established.

MDSCs as major contributors to chronic inflammation—MDSCs are a heterogeneous population of immature myeloid cells with pro-inflammatory and immune-suppressor capacity. Two major subtypes have been identified, monocytic- (M-MDSCs) and granulocytic polymorphonuclear-MDSCs (PMN-MDSCs). A third recently described subset of human MDSCs, named early (e)-MDSCs, is considered precursors of M- and PMN-MDSCs [26]. The knowledge about MDSCs biology is derived mostly from studies in cancer, but they are also found in other chronic inflammatory conditions, such as autoimmunity, transplantation, infections, and pregnancy [27, 28]. MDSCs are powerful inhibitors of the protective anti-tumor immune response through diverse mechanisms. Those include i) the expression of the enzymes Arg-1, inducible nitric oxide synthase (iNOS), and indoleamine 2,3-dioxygenase (IDO) that deplete essential amino acids for T cell activation; ii) the production of ROS, and peroxynitrite (PNT) that cause oxidative stress; iii) by

expressing molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLR4) and programmed death-ligand 1 (PD-L1) that block effector T cells responses; and iv) by secreting IL-10 and TGFβ that restrain the pro-inflammatory functions of immune cells. However, MDSCs also produce several pro-inflammatory molecules such as IL-1β and IL-6 that may contribute to chronic inflammation [29–31] (Table 1).

Obesity promotes an increase in circulating inflammatory cytokines leading to alteration of immune cell production, activation, and infiltration in tissues. Mechanisms of MDSCs expansion in obesity-associated inflamed tissue rely on VEGF, IL-1β, IL-6, TNFα, and PGE2 as well as growth factors that regulate myelopoiesis such as GM-CSF and G-CSF [32]. The role of MDSCs in the pathophysiology of obesity is still under extensive investigation. Recent studies showed an association between the elevated number of MDSCs with reduced insulin resistance [33], down-regulation of leptin [34], increased adiposity [34] and increased liver damage [35]. Furthermore, DIO tumor-bearing mice have increased accumulation and immunosuppressive activity of MDSCs and accelerated tumor growth compared to lean-tumor bearing counterparts in models of breast, renal and prostate cancer [34, 36, 37]. Meticulous dissection of the role of different dysfunctional factors in obesity on the emergence of MDSCs in cancer may provide important insight into the connection between obesity, tumor growth, and anti-tumor immunity.

Accumulation of MDSCs is observed in different tissues such as the liver, spleen, peripheral blood, and visceral fat tissue of mice fed with HFD (60% kcal fat, 6.8% kcal sucrose) [33, 35]. Furthermore, an increased number of MDSCs occurs in the peripheral blood of patients with overweight/obesity (BMI > 25) [38, 39]. Whether tissue residing MDSCs are involved in local or distant cancer development have not been explored. An increased number of MDSCs in different tissues could generate a systemic immunosuppressive environment attenuating the protective anti-tumor immune response in the site of tumor onset. In fact, increased levels of circulating Arg-1 have been shown in individuals with overweight [40] and higher Arg-1 activity in serum from women with obesity and metabolic syndrome [41]. Although it is unknown if MDSCs are the source of the increased levels of Arg-1 in circulation, it is plausible that Arg-1 produced by tissue infiltrating and circulating MDSCs creates a systemic immunosuppressive microenvironment. During cancer onset, these obesity-induced MDSCs could migrate to primary tumors in response to tumor-derived chemokines. Indeed, primary tumors and spleens of tumor-bearing mice are characterized by elevated CCL2 concentrations and hence increased infiltration of functionally immunosuppressive MDSCs [36].

Metabolic reprogramming of myeloid cells in obesity

The phenotype and function of macrophages rely on their flexibility to switch their metabolism in response to the local metabolic stimuli [42]. Macrophages with M1 pro-inflammatory function (M1-like) rely on glycolytic metabolism and pentose phosphate pathway (PPP) to achieve ATP requirements, with downregulation of oxidative phosphorylation (OXPHOS) and fatty acid beta-oxidation (FAO), and tricarboxylic acid (TCA) cycle interrupted. Conversely, macrophages with anti-inflammatory functions (M2-like) display increased uptake and catabolism of glutamine and lipids, enhanced FAO, and

OXPHOS with an intact TCA cycle, while glycolysis is abrogated [42, 43]. The increased lipid uptake and metabolism result in signaling cascades that promote the expression of Arg-1 [24, 43]. In contrast, MMe in metabolically dysfunctional adipose tissue display a unique hypermetabolic profile with both enhanced glycolysis and OXPHOS compared to ATMs from lean adipose tissue [42, 44]. This metabolic phenotype is the result of combinatorial signaling induced by elevated concentrations of saturated fatty acids (SFAs), insulin, and glucose [23]. It is unclear whether MDSCs exhibit a different activation status than macrophages that could be metabolically modulated; however, it is known that glycolysis, OXPHOS, and FAO are increased in MDSCs [45], and the immunosuppressive capacity of tumor-infiltrating MDSCs is enhanced by FA uptake and FAO [45, 46]. Together, this suggests that microenvironments rich in lipids, such as obesity, could potentiate the immunosuppressive properties of MDSCs. Inflammatory and metabolic alterations that occur in obesity, besides directly affecting malignant cells, are critical for shaping the metabolic and functional phenotype of myeloid cells.

Recent studies have shown that myeloid cells can adopt a long-term memory, named trained immunity, induced by sustained exposure to a stimulus that leads to long-term changes in intracellular metabolism and histone remodeling [47]. In consequence, this trained immunity phenotype yields an enhanced response upon a second triggering signal. Obesity-induced trained immunity in monocytes has been associated with increased cardiovascular risk [48]. However, whether obesity confers a trained immunity phenotype in MDSCs and ATMs subtypes is unknown. It is plausible that such training by obesity leads to an increased immunosuppressive response following a secondary stimulation such as tumor initiation contributing to cancer progression.

Although progress has been achieved in characterizing the intrinsic metabolic-associated profiles of macrophages and MDSCs, little is known about the impact of systemic metabolic disturbances in adiposity that play a role in obesity-related reprogramming of myeloid cells towards immunosuppressive pro-tumor cells. Next, we provide some evidence of the putative role of lipids, insulin, and leptin in mediating metabolic reprogramming of MDSCs and macrophages (Figure 1).

Role of lipids in the immunosuppressive function of myeloid cells—Alteration of lipid homeostasis is common in metabolic diseases that are characterized by chronic inflammation such as obesity, hepatic steatosis, and cardiovascular disease. Chronic intake of dietary fats and excessive release of lipids, including FFAs, triglycerides, and cholesterol, as a result of increased lipolysis and adipocyte cell death, is observed in obesity [49]. Hyperplastic and hypertrophic adipocytes provide a continuous source of lipid species including SFAs, which propagate the pro-inflammatory condition of obesity [50]. The elevated levels of FFAs and lipoproteins may cause a profound metabolic and functional reprogramming of myeloid cells priming their phenotype as immune-regulatory cells. In macrophages, SFAs, particularly lauric acid and palmitic acid, stimulate a pro-inflammatory response through the TLR4 signaling pathway priming macrophages towards an M1-like phenotype [51]. On contrary, polyunsaturated acids (ω−3 fatty acid docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), linoleic and) and the monosaturated oleic acid inhibit the expression of inflammatory genes, bind and activate PPAR signaling pathway, that

results in metabolic reprogramming of macrophages towards an anti-inflammatory M2-like profile [52].

Dietary linoleic acid, particularly consumed from refined omega-6 vegetable oils, is incorporated into lipoproteins increasing the susceptibility to be oxidized and may increase cardiovascular risk [53]. It has been shown that the exposition of M2-like macrophages to oxidized LDL enhances a pro-inflammatory response [54]. However, the exposition to oxidized phospholipids, that is accumulated in atherosclerotic lesions, instead activate macrophages towards a functionally distinct phenotype from the conventional M1 or M2 polarization [55]. In the same context of atherosclerosis, macrophages treated with desmosterol, the most prevalent sterol in atherosclerotic plaques, or macrophages that contain high cholesterol content which also leads to accumulation of desmosterol, have down-regulated gene expression involved in pro-inflammatory responses [56].

Furthermore, intracellular accumulation of triglycerides, in form of lipid droplets, drives macrophages towards an M1-like phenotype [57], while enhanced lipid catabolism by FAO promotes the anti-inflammatory M2-like activation in mouse [58], but partially, in human macrophages [59]. Besides FAO, ATMs from DIO mice also activate the lysosomal lipid metabolism following a program towards M2-like polarization [60]. In MDSCs, lipid uptake and FAO is closely associated with functional responses [46, 61]. The high lipid content in the tumor microenvironment fuels the oxidative metabolism of MDSCs and increases the expression of immunosuppressive molecules in tumor-resident MDSCs [46]. Whether MDSCs in obesity-related dyslipidemia and lipolysis are functionally and phenotypically distinct to tumor-resident MDSCs remains uncharacterized. These findings suggest that in addition to promoting systemic insulin resistance [62], lipids differentially activate diverse polarization programs in myeloid cells depending on lipid species, modifications of their chemical structure by oxidation, and lipid catabolism.

Impact of insulin in myeloid cells polarization—Obesity is commonly associated with insulin resistance, which leads to increased concentrations of insulin, and amplified bioactivity of insulin growth factor-1 (IGF-1). Insulin mediates its signal through the insulin receptor (IR), but also by its highly homologous Insulin-like growth factor 1 receptor (IGF-1R). It is well known the important role of insulin signaling in adipocytes and cancer cells. In adipocytes, insulin receptor stimulation promotes glucose and FFA uptake, stimulates *de novo* lipogenesis, and inhibits lipolysis; however, these effects are dependent on the insulin resistance status [63]. Many cancer cells overexpress isoform A of the insulin receptor (IR-A) which has a higher affinity for insulin/IGF-1 compared to isoform B. Signaling through IR-A promotes a mitogenic response of cancer cells and inhibits apoptosis leading to enhanced cellular proliferation and support of tumor cell proliferation [64].

The insulin signaling in myeloid lineage cells may differentially influence cell activation and its effect may depend on the level and ability to trigger signaling pathways. Some studies showed the contribution of insulin on macrophage metabolism which promotes glycolysis causing polarization towards an M1-like profile [23, 43]. The pro-inflammatory polarization of Insulin/IGF-1 in macrophages has been demonstrated *in vitro* [65] and *in vivo* in the context of atherosclerosis [66], obesity-induced inflammation and systemic insulin

resistance [67]. Expression of IRS2, an adaptor protein that mediates both insulin and IGF-1 signaling, suppresses the M2-like polarization of macrophages *in vivo* in a model of allergic lung inflammation [68]. Macrophages also express other molecules involved in the insulin signaling cascade, including receptors (IR and IGF-1R), and Akt kinase isoforms which differentially influence the functional phenotypes; for example, the ablation of Akt2 renders macrophages prone to M2-like, whereas the absence of Akt1 renders them towards M1-like polarization [69].

Myeloid lineage-restricted insulin resistance has also been suggested. Peripheral macrophages from mice with systemic insulin resistance or *in vitro* exposure to elevated insulin become insulin resistant and exhibit a subtype of M2-like macrophages [69], termed as insulin resistance macrophages (M-InsR). These cells have a reduced expression of IR and IGF-1R, defective IR signaling, and increased glycolysis in response to insulin [69]. Genetic ablation of IR in macrophages protected against inflammation and systemic insulin resistance in HFD (55.2% kcal fat) fed mice [67], and also decreased pro-inflammatory gene expression in macrophages [70], suggesting a polarization towards M2-like profile. Certainly, M-InsR macrophages presented a reduced response to lipopolysaccharide (LPS; inducer of M1-like polarization), but express Arg-1 and found in inflammatory zone 1 (Fizz1) (M2 markers) [69]. Together, these findings suggest that defective IR signaling could promote MMe phenotype.

The biological functions of insulin signaling on MDSCs metabolism and its contribution to their immune-regulatory capacity are poorly studied. Although it is unknown whether insulin directly modulates transcriptional control on MDSCs, systemic insulin resistance appears to induce their expansion as a physiological response to promote insulin sensitivity. This was observed in a mouse model of DIO, where depletion of MDSCs exacerbated insulin resistance, while adoptive transfer of MDSCs significantly improved glucose tolerance and reduced inflammation [33]. This observation suggests that MDSCs may contribute to the maintenance of systemic metabolic functions. However, following the theory of trained immunity by obesity-related metabolic dysfunction, the permanent accumulation of MDSCs to restore insulin sensitivity also may impair immune surveillance and antitumor immunity contributing to tumor development.

Leptin as an immunomodulatory molecule with a potential role in polarizing myeloid cells—Leptin is another hormone found in high concentrations in obesity and has additional biological properties besides the regulation of energy balance. Leptin is a pro-inflammatory and pro-angiogenic adipokine that promotes survival, proliferation, and modulates the function of several immune cells [71]. Although the mechanism is not yet identified, the crosstalk between leptin and MDSCs was recently described *in vivo*. The over-production of leptin was associated with an increased frequency of MDSCs in DIO mice and counteracted by the inoculation of soluble leptin receptor [34]. In this study, the leptin-dependent accumulation of MDSCs was associated with suppression of anti-tumor CD8+ T cell response and further tumor progression and metastasis in DIO tumor-bearing mice. These findings suggest that higher levels of leptin drive MDSCs accumulation and immunosuppressive function fostering tumor growth and cancer progression. The effect of leptin on reprogramming myeloid cells has not been rigorously explored; however, leptin

receptor (ObR) is ubiquitously expressed on the surface of immune cells, regulates both innate and adaptive immunity [72], and stimulates differentiation and leukocyte migration [73]. Activation of leptin/ObR signaling on macrophages elicits the secretion of several pro-inflammatory and pro-angiogenic cytokines such as IL-1, TNFα, IL-6, IL-11 and facilitates the pro-inflammatory polarization [74]. These cytokines, in combination with other molecules such as prostaglandin E2 (PGE2), which is also elevated in obesity, could indirectly favor the induction of MDSCs [32]. Besides the impact of leptin through induction of cytokine production, leptin itself may have a direct effect on myeloid cells by activating the leptin/ObR/STAT3 signaling cascade. STAT3 is a transcription factor critical for MDSCs expansion and function and confers immunosuppressive abilities of TAMs [75], suggesting a plausible role of leptin in inducing a myeloid cell activation towards immunosuppressive cells.

Dietary immunomodulation

A recent study has revealed that different nutritional components, besides influencing metabolism, also affect critical pathways to inflammation [76]. This could be explained by the ability of dietary patterns and nutrients to modulate immune cells response via several broad mechanisms related to circulating hormones, excess of nutrients, and alteration in the gastrointestinal (GI) tract. The GI tract is the initial intersection between diet and immunity. Gut-associated lymphoid tissue, a component of the mucosa-associated lymphoid tissue, is the largest immune organ in the body [77, 78]. Complex interactions among diet and microbiome alter activation and function of resident immune cells. Also, diet can alter gut microbiota diversity and function. Microbial dysbiosis is related to local and systemic inflammation [79] and alteration of the host immune system composition [80]. Maintaining gut microbiota diversity is important as gut microbiota produce short-chain fatty acids (SCFA) as a byproduct of fiber fermentation. These SCFA have an important role in regulating and maintaining normal function of the innate and adaptive immune system. Indeed, SCFA activate anti-inflammatory effects including reduction of pro-inflammatory cytokines, modulating the proliferation, differentiation, and activation of T cells, and downregulate the pro-inflammatory response of myeloid cells [81, 82]. In consequence, the anti-inflammatory high fiber diet improves host immunity by maintaining microbial diversity, increasing SCFA production and lowering local and systemic inflammation all while slowing glucose and decreasing cholesterol absorption [82].

Mouse models have increased understanding of the role different diets have in the alteration of metabolism, inflammation, and obesity. Pro-inflammatory diets including the commonly used HFD, in which the proportion of calories deriving from different nutrients is 60% fat, 20% protein, 20% carbohydrate (6.8% sucrose) or high-fat high sucrose diet (HFHSD; 45% fat, 24% protein, 35% carbohydrate (17% sucrose)) are highly obesogenic. Conversely, ketogenic diets (KD; 89–94% fat, 5–10% protein, 1% carbohydrate (0% sucrose)) have an anti-inflammatory effect by activating metabolically protective γδT cells and lowering pro-inflammatory cytokines (e.g. TNFα, IFN, IL-1, and IL-6) [83, 84]. In some preclinical rodent models, KD has shown to slow tumor growth, reduce angiogenesis, inflammation, migration, invasion by boosting tumor-reactive immune response in mice (i.e. increased CD4+ T cell infiltration and increased cytokine production by tumor-reactive CD8+ T cells)

and increase survival [85, 86]. The decrease of inflammatory cytokines and increase in CD4+ T cells infiltration into the tumor suggests that manipulation of metabolism by this specific diet may abrogate the function of immunosuppressive myeloid cells immunotherapy allowing the anti-tumor T cell response. In fact, KD depletes MDSCs and Tregs, thereby improving the immunological profile of pancreatic tumor-bearing animals [87]. Interestingly, the impact of nutrition and systemic metabolism on myeloid cells function also influences the responses to cancer therapy. Several animal studies with fasting, hypocaloric, ketogenic and western diets have shown a different effect on the efficacy of chemotherapy and toxicity of cancer therapies [88]. However, more research is warranted to understand the molecular, metabolic, or epigenetic mechanisms by which macro- and micronutrients influence immune cell functions and response to anticancer therapies.

In humans, the impact of diets on inflammation has been calculated by the dietary inflammatory index (DII), which has been used to evaluate the contribution of diet to cancer risk. Women who consumed diets with high inflammatory potential indicated by the DII score, had an increased risk of breast cancer, compared to women who consumed more anti-inflammatory diets [89]. The promising effect of dietary intervention on cancer risk was also observed in African Americans when increasing dietary fibers changed the microbiome and increased SCFA production, mainly butyrate, resulting in a reduction of biomarkers of cancer risk [90]. The positive impact of dietary intervention on inducting protracted anticancer immune response after chemotherapy has also been observed [91]. The mechanisms involved in the response are still under investigation; however, patients with a low-calorie KD have shown improvements in levels of insulin and glucose suggesting an important impact on cellular metabolism. The consumption of a SFA-rich diet results in a pro-inflammatory gene expression profile in subcutaneous adipose tissue (i.e., IL-1β, IL-6, and TNF-α), while a monounsaturated fatty acid-rich diet causes different profiles depending on the category of subjects [92]. Whether such dietary effects might involve a major impact on immunity and immunotherapy response has been poorly explored. Nevertheless, different nutritional interventions to boost the efficacy of different cancer therapy in patients with a variety of advanced solid malignancies have begun [91].

The intriguing finding of obesity improve response to immunotherapy

Surprisingly, while augmented weight is associated with increased cancer risk and patients with obesity and certain types of cancer have a poorer prognosis, obesity seems also to confer survival advantages to some cancer treatments [93]. The improved outcome was recently shown in patients with obesity and cancer receiving programmed death receptor-1/programmed death-ligand (PD-1/PD-L1) blockade therapy (checkpoint blockade immunotherapy. PD-L1 is expressed by tumor and immune cells that interact with the corresponding receptor PD-1 which is expressed on T and NK cells. Sustained PD-1 stimulation by PD-L1/PD-1 interaction interferes with T cell receptor signal transduction causing T cell exhaustion and apoptosis [94], supporting tumor cell ability to evade the immune system [95]. The mechanisms for the efficiency of the immunotherapy in obesity are incompletely understood; however, the expression of PD-L1 on MDSCs [96], macrophages [97], and the surface of tumor cells [95] could be higher in obesity which may facilitate an enhanced immunotherapy response. In fact, infiltrated MDSCs in HFD (60%

kcal fat, 6.8% kcal sucrose) fed mice have elevated immunosuppression capacity by expressing higher levels of PD-L1 compared to tumor-infiltrating MDSCs in mice fed with low-fat diet [34]. Although the mechanisms of obesity to amplify the expression of PD-L1 on cells are under investigation, pro-inflammatory molecules such as IFNγ and leptin are potentially involved [93, 98]. These findings indicate that IFNγ and leptin upregulate the expression of PD-L1 and PD-1 providing a broader target for checkpoint blockade immunotherapy in patients with obesity. Although the evidence supporting improved outcomes is markedly strong for PD-1/PD-L1 blockade therapies, anti-Cytotoxic T-lymphocyte-associated Protein (CTLA)-4 therapy in patients with obesity has also been shown to be beneficial. CTLA-4 is expressed by activated T-cells and a subset of regulatory T-cells and acts as a competitive inhibitor by counteracting the signaling through costimulatory receptors during antigen-presenting cell (APC) and T cell interaction. Recently, a review of studies demonstrated improved survival in men with obesity and metastatic melanoma who were treated with anti-CTL4 with or without combination with chemotherapy [93]. Interestingly, the response to anti-CTL4 therapy in DIO mice was only achieved when leptin levels were reduced [99], inferring a potential inverse relationship between leptin concentration and CTLA-4 expression.

Concluding remarks and future directions.

There is compelling evidence linking obesity to cancer; however, the underlying molecular mechanisms driving this association remain incompletely established. One of the major factors associated with the metabolic inflammation of obesity is the expansion of myeloid cells with immunosuppressive and pro-oncogenic abilities. Obesity is a complex disease with a malfunction of multiple factors that independently, or in combination, lead to the accumulation of myeloid cells. Although it is partly defined, several alterations that promote low-grade inflammation and expansion of myeloid immunosuppressive cells may include i) nutrient over-supply, ii) tissue hypoxia, iii) excess of growth factors, cytokines and lipolysis, and iv) metabolic and endocrine abnormalities, such as dyslipidemia, deregulated signaling by insulin and leptin, altered levels of resistin and adiponectin, elevated bioavailable estrogen and hypovitaminosis due to sequestration of fat-soluble vitamins such as the immuno-modulator vitamin D in body fat depots. All together may create the milieu for obesity-induced trained immunity.

The sustained presence of inflammatory myeloid cells keeps the vicious cycle skewed towards adipogenesis, perpetuating chronic inflammation, and creates an ideal microenvironment that supports cancer initiation, growth, and metastasis. Myeloid immunosuppressive cells inhibit anti-tumor immune response and present an obstacle to cancer immunotherapy. In this review, we focused on the view towards MDSCs and subtypes of macrophages as critical contributors to cancer development induced by obesity-associated inflammation and metabolic disorder. We discussed the role of insulin, IGF-1, lipids and leptin in metabolically priming, or training, macrophages and MDSCs in obesity. These cells may adopt an enhanced immunosuppressive capacity followed by a subsequent stimulation derived from the tumor onset.

Despite the progressive evidence about metabolic and functional characteristics of macrophages and MDSCs in different diseases, including cancer and obesity, important gaps remain. As research continues, there are outstanding questions to be considered:

1. Is the elevated cancer risk in obesity due to the reprogramming of immune cells by the systemic metabolic abnormalities? If so, do patients with obesity without metabolic syndrome have less accumulation of myeloid immunosuppressive cells and therefore a reduced risk of cancer? Conversely, are normal-weight individuals with metabolic syndrome predisposed to the oncogenic microenvironment because of the increased myeloid immunosuppressive cells? Efforts are needed to compare metabolically healthy versus unhealthy individuals. Also, the detailed molecular mechanisms and crosstalk of cytokines, hormones, lipids, among others, to expand and activate myeloid immunosuppressive cells in the settings of obesity-associated disturbances, are critically needed.

2. Several studies have shown that patients who have had bariatric surgery have a reduction in cancer incidence and mortality [100]. Does bariatric surgery lower the risk of cancer by reversing the accumulation or function of immunosuppressive myeloid cells in patients with obesity? Is the normal-weight inflammatory (untrained) phenotype restored upon weight loss and resolution of metabolic disorders induced by bariatric surgery? Do patients resistant to anti-obesity interventions or those having difficulty achieving sustained weight loss have increased accumulation of metabolically trained myeloid cells? Biomarkers to properly identify these cells in peripheral blood or fat tissue residents are required.

3. Following our hypothesis that the risk of cancer is driven by the expansion and function of myeloid immunosuppressive cells in obesity, could the use of drugs known to target MDSCs and TAMs prevent cancer initiation in patients with morbid obesity? However, strategies for partially blocking the MDSCs functions should be counted to assure the maintenance of their ability to restore insulin sensitivity while simultaneously preventing their capacity to restrain the anti-tumor immune response.

4. What is the immunological profile of primary, advanced, and metastatic tumors in patients with obesity? Is there any degree and specific activation subtypes of infiltrating myeloid cells in the tumor milieu that predict a better response to checkpoint-inhibitors therapy in patients with obesity? Enrollment of patients across the body mass index (BMI), metabolic, and inflammatory spectrum is crucial to study the response of immunotherapy. These studies can facilitate the identification of potential biomarkers to distinguish patients that will respond to immunotherapy. It will also allow the detection of patients that may need an initial therapeutic approach that enables immunologic and metabolic tumor profile modification before the immunotherapy initiation to improve outcomes.

5. Many more research questions remain: What is the causal relationship between metabolic alterations, epigenetics, and functional phenotype in obesity? Can any

of these mechanisms be targeted by therapies to reprogram the immune-regulatory myeloid cells? How is this relationship at the molecular level relevant for the development of effective anti-cancer therapeutics in obesity? What is the interaction between metabolic factors and the intrinsic molecular characteristics of myeloid immunosuppressive cells that facilitate their anti-tumor hallmarks?

We acknowledge that the relationships between obesity, cancer, and the immune system are very complex. We propose a hypothesis that the multi-factorial metabolic and inflammatory abnormalities in obesity, independently or in combination, lead to the expansion and activation of metabolically primed myeloid immunosuppressive cells. Although their induction seems to be promoted to restore the metabolic homeostasis and curtail overt immune responses, obesity may also prime these myeloid cells that enhance their pro-oncogenic properties promoting tumor growth. Furthermore, although the maintenance of a healthy weight is an essential principle to prevent cancer, obesity, within the context of a certain metabolic and inflammatory phenotype that remains to be defined, may be advantageous for the response of immune checkpoint therapy.

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Study importance questions:

What major reviews have already been published on this subject?

- The majority of reviews have been focused on obesity inducing cellular transformation into malignant cells and broadly the role of obesity-related inflammatory mediators on cancer.

What are the new findings in your manuscript?

- We discuss in the manuscript a perspective of the pro-tumor impact of obesity where myeloid cells with immunosuppressive capacity are the key players.
- The concepts of reprogramming and trained immunity are used to elucidate the molecular mechanisms of metabolic disturbances in obesity for enhancing the pro-oncogenic capabilities of MDSCs and subtypes of ATMs with immune-regulatory properties.
- Finally, the recent controversial finding of obesity improving immunotherapy response is reviewed, and our hypothesis is offered.

How might your results change the direction of research or the focus of clinical practice?

- The manuscript highlights several questions where is emphasized the importance of finding biomarkers related to the identification of myeloid immunosuppressive cell activation status, as well as the systemic metabolic and inflammatory grades in patients with obesity to predict outcomes in terms of anti-obesity interventions such as bariatric surgery, cancer progression, and immunotherapy.

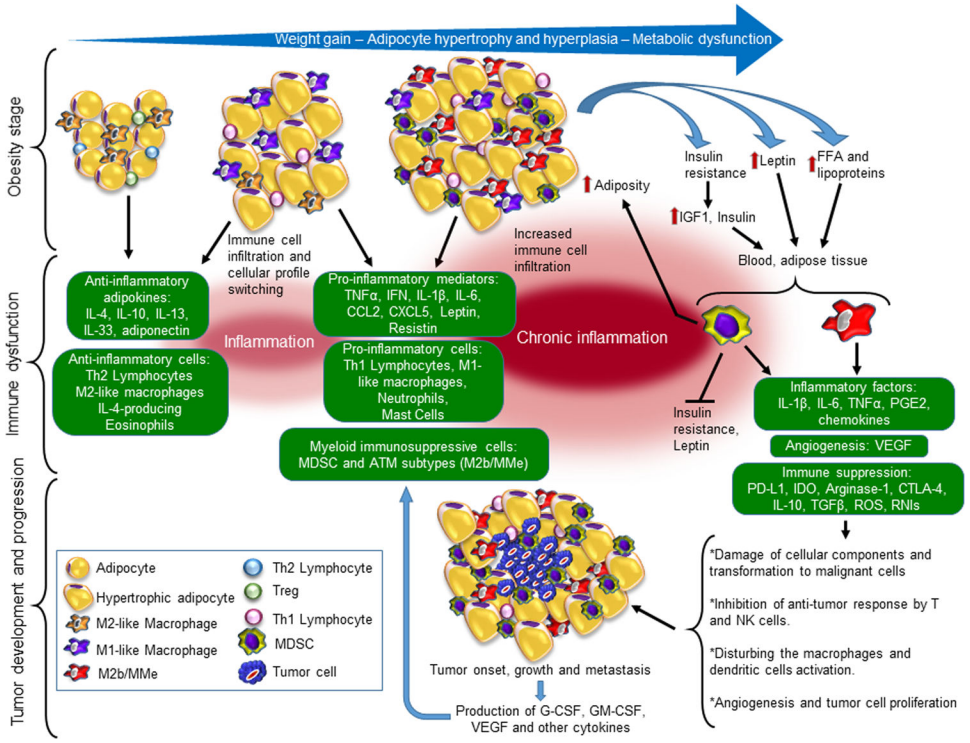

Figure 1. Role of obesity-induced inflammation in the evolution of tumor development.

In the lean stage with metabolic homeostasis, scarce immune cells in the adipose tissue are characterized by adipose tissue-associated macrophages (ATMs) with an anti-inflammatory M2-like phenotype, Tregs and Th2 lymphocytes in an anti-inflammatory milieu. In early obesity, dysregulated inflammatory microenvironment polarizes M2-like macrophages towards M1-like phenotype producing pro-inflammatory cytokines. In turn, the cytokines impair adipocyte biology and perpetuate the unbalanced composition of leukocytes in the adipose tissue. As hypertrophy and hyperplasia of adipocytes progress with obesity, metabolic dysfunction and inflammation are exacerbated. Chronic inflammation comprises an accumulation of pro-inflammatory immune cells (i.e. Th1 and Th17 lymphocytes), subtypes of ATMs with pro- and anti-inflammatory functions and the metabolically activated phenotype (M2b/MMe), and MDSC. The molecules produced by both dysfunctional adipocytes and infiltrating immune cells perpetuate low-chronic inflammation and establish a proangiogenic condition. Chronic inflammation in fat tissue leads to insulin resistance, over-production of leptin, and increased levels of free fatty acids (FFA) that contribute to the expansion and enhance the immunosuppressive function of MDSCs and subtypes of ATMs, including MMe. MDSCs limit obesity-associated metabolic dysfunction and down-regulate leptin production while increase adiposity. When tumor onset occurs, infiltrating MDSC, different subtypes of ATMs, and tumor-associated macrophages (TAMs), may facilitate tumor progression and metastasis. Within the tumor microenvironment (TME), the enrichment of cytokines (i.e. G-CSF, IL-6 and GM-CSF) and FFA enhance the immunosuppressive potency of myeloid cells, which in consequence, the protective anti-tumor immune response becomes inhibited, and production of pro-inflammatory and proangiogenic mediators is enhanced, supporting tumor growth and metastasis. IL indicates interleukin; Th1/2, T helper type 1 or 2; TNFα, tumor necrosis factor-alpha; IFN, interferon;

CCL2, C-C Motif Chemokine Ligand 2; CXCL5, C-X-C Motif Chemokine Ligand 5; IGF1, Insulin-Like Growth Factor 1; FFA, free fatty acid; GM-CSF, Granulocyte-macrophage colony-stimulating factor; G-CSF, colony-stimulating factor; PGE2, prostaglandin E2; VEGF, Vascular endothelial growth factor; PD-L1, Programmed death-ligand 1; IDO, indoleamine 2,3-dioxygenase; CTLA-4, Cytotoxic T-lymphocyte-associated Protein; TGFβ, transforming growth factor-beta; ROS, reactive oxygen species; RNIs, reactive nitrogen intermediates.

Table 1:

Phenotypic, functional, and metabolic characteristics of macrophages and MDSCs

	M1-like macrophages	M2-like macrophages	Metabolically activated macrophages (MMe)	Tumor-associated macrophages (TAMs)	Myeloid-derived suppressor cells (MDSCs)	
Surface markers	CD11c, CD38, CD62L, CD274, CD319, CD80, CD86, HLA-DR, CCR2/5/7	CD163, CD206, TFRC, CD36, CD204, CXCR1, CXCR2, CD206, CD209, CD163, FIZZ1, Ym1/2	CD36+, CD11c-, CD163-, CD206-	CD36, CD204, CD206, Scavenger Receptor A, CD52, CD163, CD39, CD73	**Mouse PMN-MDSC**: CD11b+, Gr1+, Ly6C^{dim}, Ly6G+ **Mouse M-MDSC**: CD11b+, Gr1+, Ly6C^{high}, Ly6G+	**Human PMN-MDSC**: CD11b^{+} (CD33^{+}), CD14^{-}, HLA-DR^{-}, CD15^{+}(CD66b^{+}). **Human M-MDSC**: CD11b^{+}(CD66b^{+}), CD14^{+}, HLA-DR$^{-/low}$
Activators	TLR, TNFa, IFNg, GM-CSF, LPS	IL-4, IL-10, IL-13, TGFb, COX2-derived PGE2, VEGF, PPARg agonist	Metabolically dysfunctional adipose tissue: ↑Insulin, ↑glucose, ↑FFA	Tumor microenvironment: IL-1b, IL-4, IL-6, IL-8, IL-10, IL-13, IL-23, IL-27, COX2-derived PGE2, PDGF, MIF, CXCL12, CCL2/3/4/17/18/22; hypoxia, FFA	GM-CSF, G-CSF, IL-1b, IL-4, IL-6, IL-13, IL-17, IFNg, TNFa, PGE2, VEGF, TLR ligands, cellular stress, exogenous fatty acid uptake and lipid metabolism	
Functional and metabolic markers. Key transcription factors	ROS, iNOS, pro-inflammatory cytokines: TNFa, IFNg, IL-6, IL-12, IL-23. pSTAT1, HIF-1a, IRF5, SOCS3	Arginase-1, Dectin-1, ABCA1, PLIN2, pSTAT6, IL-10, TGFb, IL-1β, IL-6, TNFα, IL-10, CCL1/16/18, TNFSF14, VEGF, IRF4, JMJD3, PPARg/PGC1b, PPARd.	ABCA1, CD36, PLIN2, p62, IL-1b, TNFa, arginase-1, PPARg	↓iNOS, ↑Arginase-1, ↑ROS, ↑IDO, COX2, arginase-1, captesin B, MMP2, MMP7, MMP9, VEGF, EGF, PDGF, MIF, TNFa, TGFb, IL-8, IL-1b, TP, CCL2, CXCL8, PPARs, PI-3K/AKT/mTOR pathway	iNOS, IDO, Arginase-1, ROS, PD-L1, CTLA4, IL-1b, IL-6, MMPs, COX2-derived PGE2, pSTAT3, pSTAT6, C/EBPb, IRF8, Notch, HIF-1a, ER-stress response pathway	
Metabolic profile	Glycolysis, PPP, FA synthesis, truncated TCA cycle, triglycerides accumulated in lipid droplets	↓Glycolysis, ↓PPP, OXPHOS, FAO, intact TCA, ↑Glutamine and lipid metabolism	↑Glycolysis, ↑OXPHOS	Dynamic metabolic profile, although predominant glutamine and FA metabolism, ↓PPP, Glycolysis, ↑OXPHOS, FAO, broken TCA	Glycolysis, OXPHOS, ↑FAO	
Function	Pro-inflammatory, antimicrobial, and anti-tumor activity	Wound-healing and anti-parasite (M2a), regulatory cells and immunosuppression (M2b/c), tissue repair and matrix remodeling (M2c), angiogenesis and tumor progression (M2d)	Pro-and anti-inflammatory with potentially immunosuppressive abilities (M2b-like phenotype)	Immunosuppressive capabilities: Inhibit cytotoxic T lymphocytes (CTL) responses. Support angiogenesis, oncogenesis and metastasis, production of pro- and anti-inflammatory cytokines		

HLA-DR indicates Human Leukocyte Antigen – DR isotype; TLR, Toll-like receptor; TNFa, tumor necrosis factor alpha; IFNg, interferon gamma; GM-CSF, Granulocyte-macrophage colony-stimulating factor; LPS, lipopolysaccharide; ROS, reactive oxygen species; pSTAT, phosphorylated Signal transducer and activator of transcription; iNOS, inducible nitric oxide synthase; TFRC, transferrin receptor; CCR2, C-C Motif Chemokine Receptor 2; CXCR1/2, Chemokine (C-X-C motif) receptor 1/2; CXCL, C-X-C motif Chemokine Ligand; CCL, C-C Motif Chemokine Ligand; IL, interleukin; HIF1a, hypoxia-inducible factor 1-alpha; IRF, Interferon Regulatory Factor; SOCS3, Suppressor of cytokine signaling 3; PPP, pentose phosphate pathway; FA, fatty acid; TCA, tricarboxylic acid; TGFb, transforming growth factor beta; COX2, cyclooxygenase-2; PGE2, prostaglandin E2; VEGF, Vascular endothelial growth factor; ABCA1, ATP Binding Cassette Subfamily A Member 1; PLIN2, Perilipin 2; TNF superfamily member 14, TNFSF14; JMJD3, Jumonji domain-containing protein D3; PPARd/g, Peroxisome proliferator activated receptor delta/gamma; PGC1b, peroxisome proliferator-activated receptor-gamma coactivator 1-beta; OXPHOS, Oxidative phosphorylation pathway; FAO, fatty acid phosphorylation; FFA, free fatty acid; p62, 62 kDa protein; PDGF, platelet-derived growth factor; MIF, Macrophage Migration Inhibitory Factor; IDO, indoleamine 2,3-dioxygenase; MMP, metallopetidase; PI-3K, Phosphoinositide 3-kinase; AKT, Protein kinase B, PKB; mTOR, mechanistic Target Of Rapamycin Kinase; EGF, epidermal growth factor; PDGF, Platelet-derived growth factor; TP, Thymidine Phosphorylase; PMN-MDSC, Polymorphonuclear Myeloid-derived suppressor cell; M-MDSC,

Monocytic Myeloid-derived suppressor cell; G-CSF, Granulocyte colony-stimulating factor; PD-L1, Programmed death-ligand 1; CTLA4, cytotoxic T-lymphocyte-associated protein 4; C/EBPb, CCAAT/enhancer-binding protein beta; ER, endoplasmic reticulum.