Impact of obesity-associated myeloid-derived suppressor cells on cancer risk and progression (Review)

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Abstract. Obesity is a chronic disease caused by the accumulation of excessive adipose tissue. This disorder is characterized by chronic low-grade inflammation, which promotes the release of proinflammatory mediators, including cytokines, chemokines and leptin. Simultaneously, chronic inflammation can predispose to cancer development, progression and metastasis. Proinflammatory molecules are involved in the recruitment of specific cell populations in the tumor microenvironment. These cell populations include myeloid-derived suppressor cells (MDSCs), a heterogeneous, immature myeloid population with immunosuppressive abilities. Obesity-associated MDSCs have been linked with tumor dissemination, progression and poor clinical outcomes. A comprehensive literature review was conducted to assess the impact of obesity-associated MDSCs on cancer in both preclinical models and oncological patients with obesity. A secondary objective was to examine the key role that leptin, the most important proinflammatory mediator released by adipocytes, plays in MDSC-driven immunosuppression Finally, an overview is provided of the different therapeutic approaches available to target MDSCs in the context of obesity-related cancer.

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Abbreviations: Ad5-TRAIL/CpG, adenovirus 5-TNF-related apoptosis inducing ligand/cytosine-phosphate-guanosine; ARG1, arginase type 1; BC, breast cancer; BMI, body mass index; CCL, C-C motif chemokine ligand; CXCL, C-X-C chemokine ligand; DC, dendritic cell; G-CSF, granulocyte colony-stimulating factor; G-MDSC, granulocytic myeloid-derived suppressor cell; GM-CSF, granulocyte-macrophage colony stimulating factor; HFD, high-fat diet; IDO, indoleamine 2,3-dyoxygenase; IFN, interferon; IL, interleukin; IMC, immature myeloid cell; LEPR, leptin receptor; LFD, low-fat diet; M-MDSC, monocytic MDSC; MHC, major histocompatibility complex; MRP, migration inhibitory factor-related protein; RNS, reactive nitrogen species; OSCC, oral squamous cell carcinoma; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TCR, T-cell receptor; TGF, transforming growth factor; TME, tumor microenvironment; TNF, tumor necrosis factor; Treg, T-regulatory cell; VEGF, vascular endothelial growth factor

Key words: myeloid-derived suppressor cells, cancer, tumor, obesity, leptin, chronic inflammation

Contents

1. Introduction

Obesity is a metabolic disease caused by the overaccumulation of subcutaneous or abdominal adipose tissue characterized by chronic low-grade inflammation (1). This status ultimately leads to the development of diseases such as cancer, cardiovascular disease, type 2 diabetes, hypertension, dyslipidemia and reproductive disorders (2-5).

Adipocytes release proinflammatory mediators such as tumor necrosis factor (TNF)-α, interferon (IFN), interleukin (IL)-1β and leptin, (6), which also play a key role in tumor dissemination and metastasis (7,8). Proinflammatory molecules are involved in the recruitment of suppressive cells, including myeloid-derived suppressor cells (MDSCs), in the tumor microenvironment (TME). MDSCs are a heterogeneous population of immature myeloid cells (IMCs) with potent immunosuppressive effects in cancer (9).

According to the literature, obesity and cancer create similar chronic inflammatory environments. Indeed, evidence has been provided of the impact of obesity-associated MDSCs on cancer progression. However, the mechanisms by which this occurs have remained to be fully elucidated. This paper addresses the relevant role that MDSCs play in the immune system. There is evidence supporting the protumorigenic role of MDSCs in obese murine models and patients. Some authors have described the mechanisms of action of obesity-associated MDSCs and suggest different therapeutic approaches targeting MDSCs in obesity-related cancer. The protective role of obesity-associated MDSCs in maintaining immune homeostasis is also briefly mentioned in this paper.

2. MDSCs

MDSCs are IMCs developed during myelopoiesis by a variety of cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), IL-17 and TNF-α (10). In normal conditions, hematopoietic stem cells differentiate into common myeloid progenitors, which, in turn, differentiate into neutrophils, monocytes, dendritic cells (DCs) or macrophages. However, myelopoiesis is disrupted in pathological settings, thereby leading to abnormal development of mature myeloid cells. This leads to the accumulation of IMCs at specific sites, depending on the disease (11).

Two main MDSC subpopulations have been described in the literature, namely monocytic MDSCs (M-MDSCs) and granulocytic MDSCs (G-MDSCs). Both cell subsets were first identified in lymphoma BW-Sp3- and chicken ovalbumin-transfected EL-4 thymoma EG7-bearing mice as cell subfractions with different morphological, molecular and functional characteristics. MDSCs have been documented to resemble inflammatory monocytes (M-MDSCs) and immature neutrophil-like or low-density polymorphonuclear cells (G-MDSCs) (12). Characterization standards for MDSCs suggest defining mouse MDSCs as granulocytic marker 1 $(Gr1)^{+}CD11b^{+}$ cells expressing $Ly6C^{high}Ly6G^{-}$ (M-MDSCs) or $Ly6C^{low}Ly6G^{+}$ (G-MDSCs), whereas human MDSCs are $CD11b^{+}$human leukocyte antigen (HLA)-$DR^{low/-}$ cells that express $CD14^{+}CD15^{-}$ (M-MDSCs) or $CD14^{-}CD15^{+}$ (G-MDSCs), although G-MDSCs may also express CD66b (13). Other markers such as CD45 and CD33 have also been used to define human MDSCs (14,15). Of note, there is another MDSC subset known as 'early stage MDSCs', defined as immature Lin^{-}(CD3, CD14, CD15, CD19, CD56) HLA-$DR^{-}CD33^{+}$ MDSCs (13).

The main role of MDSCs is to suppress immune responses, particularly T-cell responses, and it has been extensively described in a variety of settings (16-19). Of note, M-MDSCs mainly express nitric oxide synthase 2, whereas G-MDSCs express high levels of arginase type 1 (ARG1) (20,21). This means that each MDSC subset may use different mechanisms and effector molecules to inhibit immune responses. MDSC activity in cancer is as follows (Fig. 1):

i) MDSCs promote both the loss of the T-cell receptor (TCR)ζ-chain and cell cycle arrest in T cells. MDSCs exert this effect by taking up L-arginine and L-cysteine, which are essential amino acids for T-cell proliferation and expansion;

ii) MDSCs release reactive oxygen species (ROS), such as hydrogen peroxide and peroxynitrite, to promote the loss of the TCRζ-chain;

iii) MDSCs downregulate T-cell migration to draining lymph nodes and induce apoptosis via disintegrin and metalloproteinase domain-containing protein 17/CD62L interaction and galectin 9/T-cell immunoglobulin and mucin domain-containing protein 3 interactions;

iv) MDSCs induce the development of M2 macrophages by releasing ARG1, IL-10 and transforming growth factor (TGF)-β;

v) MDSCs induce regulatory T cells (Tregs) by releasing ARG1, IL-10 and TFG-β and after CD40/CD40L and major histocompatibility complex class II/TCR interaction;

vi) MDSCs prevent DC migration by downregulating DC maturation and antigen uptake via IL-10 and nitric oxide;

vii) MDSCs inhibit the cytotoxic capacity of natural killer (NK) cells via TGF-β or indoleamine 2,3-dioxygenase;

viii) MDSCs promote angiogenesis via vascular endothelial growth factor, which, in turn, promotes Treg and MDSC proliferation.

3. Obesity-associated MDSCs in preclinical tumor models

As shown in Table I, there is a growing body of evidence of the effects of MDSCs that link obesity and cancer. It has been demonstrated that the monocyte chemoattractant protein-1 [best known as C-C motif chemokine ligand 2 (CCL2)] is secreted by adipocytes to induce the migration of myeloid cells into tissues (22). In addition, CCL2 governs the migration of MDSCs into the TME after binding C-C motif chemokine receptor 2 (CCR2) (23). It was reported that CCL2 promotes breast cancer (BC) by stimulating aromatase gene expression in mammary adipose tissue and activating the signaling pathways involved in cytochrome P450 19A1 transcription (24,25). In this sense, CCL2 has been associated with high concentrations of visceral adipose tissue, MDSC recruitment and cancer progression in both renal adenocarcinoma-bearing mice (26) and a murine model of triple-negative BC with high concentrations of adipose tissue (27). CCR2-expressing MDSCs have also been documented to be highly infiltrated in mice with obesity-related renal tumors (28,29).

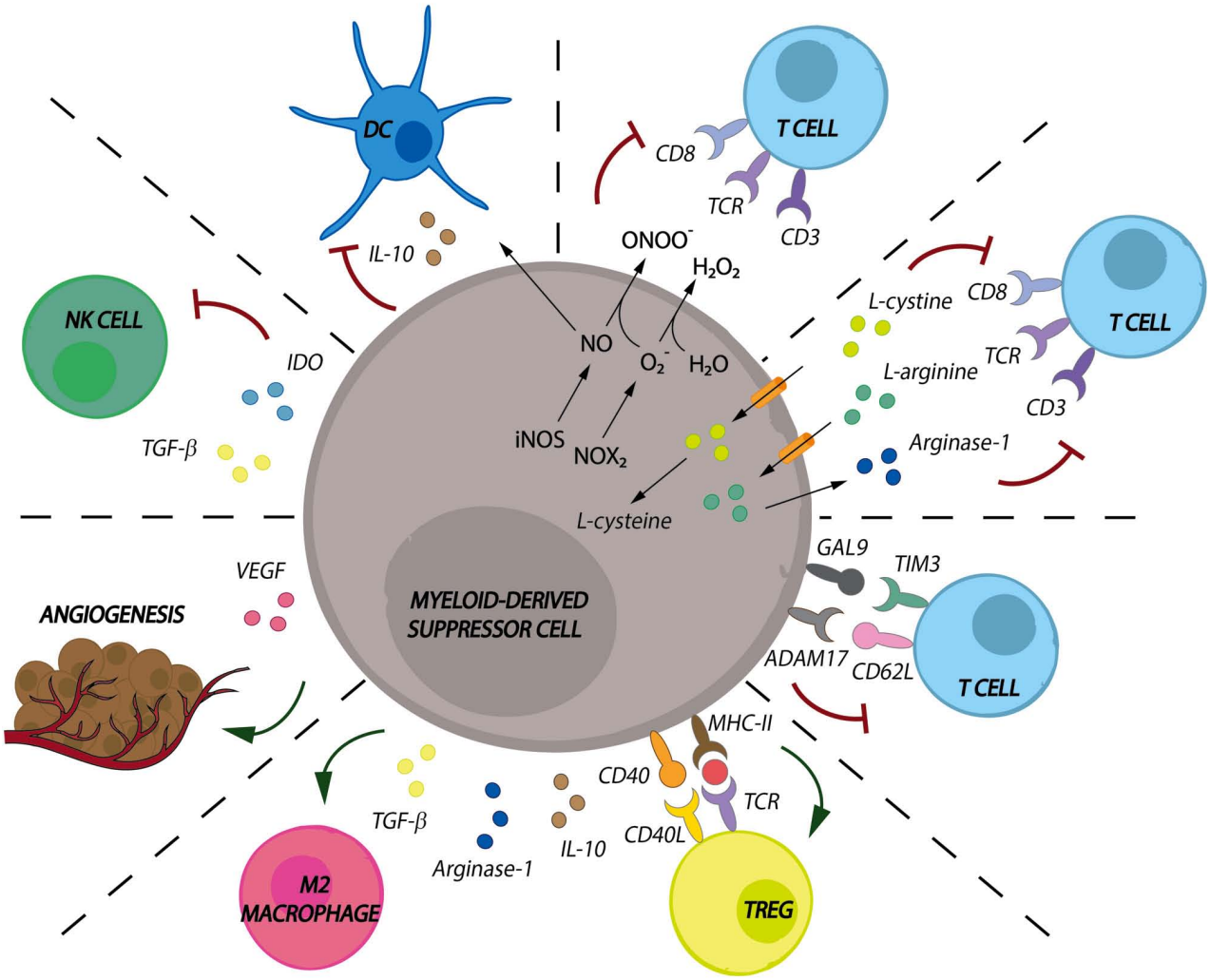

Figure 1. Immunosuppressive roles of MDSCs in the tumor-microenvironment. MDSCs exert potent suppressive effects not only by inhibiting T-cell responses, dendritic cell priming or NK-cell activity, but also promoting angiogenesis and the development of regulatory T cells or M2 macrophages. ADAM17, disintegrin and metalloproteinase domain-containing protein 17; DC, dendritic cell; GAL9, galectin 9; IDO, indoleamine 2,3-dyoxygenase; IL, interleukin; MHC, major histocompatibility complex; NK, natural killer; TCR, T-cell receptor; TGF, transforming growth factor; TIM3, T-cell immunoglobulin and mucin domain-containing protein 3; Treg, T-regulatory cell; VEGF, vascular endothelial growth factor; MDSC, myeloid-derived suppressor cell.

Similarly, the macrophage inflammatory protein-1 γ (best known as CCL9) is upregulated in murine models with obesity (30) and is considered another important agent in the recruitment of MDSCs in the TME (31). CCL9 may induce $CD11b^{+}Gr1^{+}$ MDSC expansion after binding CCR1 (particularly in G-MDSCs from spleen and bone marrow) in oral squamous cell carcinoma (OSCC)-bearing mice after treatment with a high-fat diet (HFD). This diet boosted the immunosuppressive effects of MDSCs via intracellular fatty acid uptake (32).

In, thymus-expressed chemokine (best known as CCL25), together with GM-CSF, S100A8 and S100A9 (both upregulated by IL5 and IL-6), were indicated to be involved in MDSC recruitment and expansion in peripheral blood, the bone marrow and tumor tissue from obese ovarian cancer-bearing mice (33). The key role of IL-6 has also been demonstrated in a pancreatic cancer mouse model with HFD-induced obesity. The HFD led to G-MDSC and M-MDSC expansion, tumor growth and proliferation, and failure of T-cell responses (34).

MDSCs also accumulated in the TME of E0771 and Py8119 BC-bearing mice using an HFD via the growth-regulated α protein [C-X-C motif chemokine ligand 1 (CXCL1)]/CXCR2 signaling pathway. This axis was associated with the body mass index (BMI) and poor survival (35). Adipose tissue from obese patients with prostate cancer also mobilized IL-8 [known as CXCL8 and an important chemoattractant for MDSCs (36)] to recruit adipose stromal cells into the TME and induce tumor growth and progression. Of note, CXCL1 silencing *in vivo* promoted CD11b+Gr1+ MDSC depletion in obese and lean mice (37).

4. Obesity-associated MDSCs in cancer patients

It has been estimated that excess adipose tissue increases the risk of human cancer by 20%. The underlying mechanisms that link cancer to obesity need to be completely understood for adequate treatments to be developed (38). For these reasons, most of the studies focus on the long-term effectiveness of treatments (39) instead of the impact of immunosuppressive

Table I. Impact of obesity-associated MDSCs in preclinical tumor models.

Type of cancer	Country	Murine model	Effects on MDSCs	(Refs.)
Breast	USA	BALB/c mice with 4T1 tumors	CCL2, which recruits MDSCs into the TME, was secreted by tumor-associated adipocytes, facilitating tumor progression. MDSC levels were higher in cancer-bearing mice, but a plasmid DNA encoding CCL2 trap reduced MDSCs within the TME.	(27)
Breast	USA	C57BL/6 mice with E0771 tumors	Fas ligand-expressing G-MDSCs were promoted in obese cancer-bearing mice via the CXCL1/CXCR2 axis.	(35)
Breast	USA	BALB/c and C57BL/6 mice with 4T1 tumors	MDSCs increased tumor progression in mice on an HFD compared to those on an LFD. Obesity and MDSC levels were associated with shorter overall survival and a significant elevated number of metastatic cells in the liver.	(78)
Breast	USA	C57BL/6J mice with E0771-luc tumors	Obesity induced by an HFD increased tumor progression and MDSC levels in mice compared to those fed an LFD. Anti-PD1 inhibitor achieved both tumor regression and reduction of MDSCs.	(118)
Ovary	China	C57BL/6J, BALB/c and OB/OB mice with ID8-Luc tumors	Obesity increased the proportion of circulating MDSCs in obese mice compared to normal-weight mice. Obesity also promoted the expression of S100A8 and S100A9 by upregulating IL-6, promoting an increase of MDSCs, as well as tumor evasion and metastasis.	(33)
Pancreatic	USA	C57BL/6 and BALB/c mice with Panc.02 tumors	Adiposity was positively correlated with MDSCs and tumor growth. MDSCs inhibited effector T-cell responses, increased tumor growth and decreased survival in obese tumor-bearing mice.	(34)
Prostate	USA	C57BL/6 mice with RM1 tumors	G-MDSCs were decreased by two-fold in tumors upon CXCL1 silencing in both lean and obese mice.	(37)
Renal	USA	BALB/c mice with Renca tumors	Obesity not only induced early MDSC accumulation and intratumoral proinflammatory mediators, but also reduced the percentage of responder mice to immunotherapy. Specifically, IL-1β positively correlated with tumor size and tumor-infiltrating MDSCs.	(26)
Renal	USA	BALB/c mice with Renca tumors	MDSC levels were higher in tumor-bearing mice treated with an HFD compared to their lean counterparts. After treatment, MDSC levels frequently persisted, probably because MDSCs were developed during obesity, independently of the tumor status.	(28)
Renal	USA	BALB/c mice with Renca tumors	Tumor-bearing mice fed an HFD had more tumor $CCR2^+$ MDSCs than those fed an LFD. In obese mice, tumors had high levels of CCL2, but arginase levels remained unchanged.	(29)

LFD, low-fat diet; HFD, high-fat diet; TME, tumor microenvironment; G-MDSC, granulocytic myeloid-derived suppressor cell; CCL, C-C motif chemokine ligand; CCR, C-C motif chemokine receptor; PD-1, programmed cell death 1.

cells on obesity-related cancer. Only two studies analyzed MDSC-like cell populations in obese cancer patients (Table II).

Peng *et al* (32) demonstrated that CD33+ cell expression in obese patients with OSCC was significantly correlated with local adipocyte levels and negatively associated with overall survival and progression-free survival. CD33 is a surface cell marker that has been widely used to identify MDSCs in obesity (40) and in different types of cancer (9,41,42). However, CD33 may not be appropriate to differentiate MDSCs from other myeloid cells such as DCs or macrophages

Table II. Impact of obesity-associated MDSCs in cancer patients.

Type of cancer	Country	Groups	Results	(Refs.)
Kidney	USA	Group 1: Obese patients with kidney cancer; Group 2: Healthy donors	TANs from Group 1 were phenotypically and metabolically different from neutrophils of Group 2. TANs resembled MDSCs due to the high expression of specific markers, such as CD45, CD15 and arginase-1, and low expression of other markers, such as HLA-DR. Obesity and adipose tissues were significantly associated with TANs, arginase 1 and disease progression.	(43)
OSCC	China	Group 1: Obese patients with OSCC; Group 2: Non-obese patients with OSCC	Expression of CD33, a marker of human MDSCs, was significantly correlated with local adipocyte levels in Group 1. Both CD33 expression and high adipocyte levels were associated with poor overall survival and progression-free survival in Group 1.	(32)

TAN, tumor-associated neutrophil; OSCC, oral squamous cell carcinoma; HLA, human leukocyte antigen; MDSC, myeloid-derived suppressor cell.

in tissues (13). However, Peng *et al* (32) demonstrated that CD33+ cells were increased in cancer patients with obesity, similar to $CD11b^{+}Gr1^{+}$ MDSCs in a cancer murine model treated with an HFD.

In patients with renal cancer with obesity, Margaroli *et al* (43) found that blood immature-like neutrophils acquired an immunosuppressive phenotype (resembling MDSCs) upon migration to the tumor site. Of note, immature-like neutrophils, which were highly expressed in neutrophil elastase and programmed cell death-ligand 1 (PD-L1), along with ARG1 levels, were significantly associated with adipose tissue distribution and disease progression. In line with these results, MDSCs have been proven to express high levels of PD-L1 (44). In addition, arginase has been reported to induce MDSCs in obesity and obesity-related diseases (45), including cancer (46). Also, neutrophil elastase, which facilitates tumor-cell intravasation and metastasis (47), can be released by CD33+ MDSCs in human cancer (48).

Of note, obesity is an independent risk factor for the development of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)-related hepatocellular carcinomas (HCC) (49). MDSCs, together with T cells and tumor-associated macrophages, are highly infiltrated in patients with NAFLD-/NASH-related HCC (50). Certain mechanisms have been suggested to explain the activation and recruitment of MDSCs in these diseases. For instance, it has been shown that the release of IL-13 could activate MDSCs to promote tumor progression (51). MDSCs expressing PD-L1 and inducible T-cell co-stimulator have been suggested to interact with exhausted programmed cell death 1 $(PD\text{-}1)^{+}CD8^{+}$ T cells to induce immunosuppression in these patients (50). The m6A reader protein YTH N6-methyladenosine RNA binding protein F1 promoted the signaling axis between the enhancer of zeste homolog 2 protein and IL-6 to recruit MDSCs; as a result, CD8 T-mediated immune responses were inhibited (52). In a mouse model, it has been demonstrated that $CD11b^{+}$ $Ly6C^{Int}Ly6G^{+}$ MDSCs, but not M-MDSCs, can be recruited into the liver TME by hepatic cyclin-dependent kinase 20 (also known as CCRK) signaling through mTORC1-dependent G-CSF expression (53). In this case, $CD11b^{+}$ $Ly6C^{Int}Ly6G^{+}$ MDSCs positively correlated with tumor weight. Also, the administration of anti-Ly6G antibody significantly suppressed CCRK-induced MDSCs and reduced liver-related HCC tumorigenicity (53).

5. Mechanism of action of MDSCs in obesity-related cancer

Based on experimental evidence from obese cancer murine models and obese patients with cancer, the milieu produced by chronic inflammation during obesity is likely to increase MDSC recruitment and expansion. This environment promotes cancer development and increases cancer risk, as shown in Fig. 2.

Chronic inflammation occurs when the immune system is under permanent, non-resolving stimulation, which can lead to the development of several health conditions, including obesity (54). During this prolonged process, leukocytes and plasma proteins are continually recruited into affected tissues to promote vascularization and phagocytosis via proinflammatory signaling (55,56). Chronic inflammation also induces lymphocyte and macrophage recruitment (57-59).

Adipose tissue has been traditionally known for its capacity to store energy, but it is currently considered a *bona fide* immune organ due to its interactions with the immune system (60). Obesity may increase the risk of different conditions and diseases such as cancer, cardiovascular disease, type 2 diabetes, hypertension, dyslipidemia and reproductive disorders (2-5). These effects are induced by the release of a variety of proinflammatory mediators, including TNF-α, IFN, IL-1β, IL-6, leptin, resistin, CCL2, CXCL5 and prostaglandin E2, during adipocyte hypertrophy and hyperplasia [extensively reviewed in (61,62)]. Similarly, chronic inflammation can

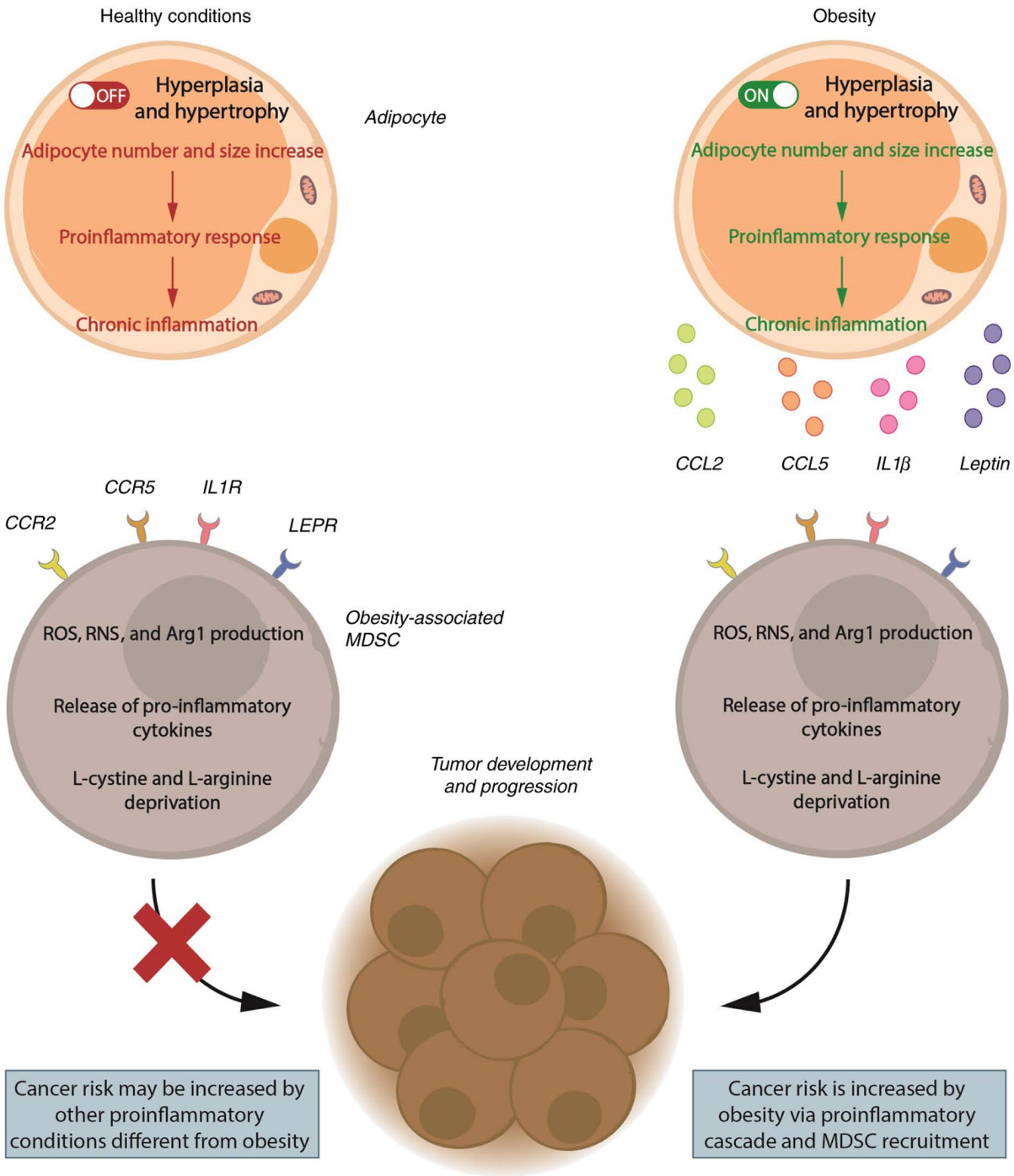

Figure 2. Obesity-associated MDSCs increase cancer risk and promote tumor development and progression via proinflammatory mediators. In healthy conditions, the 'hyperplasia and hypertrophy machinery' of adipose tissue is turned off; as a result, adipocytes do not release proinflammatory molecules to activate and recruit MDSCs. In contrast, obesity promotes chronic, low-grade inflammation characterized by hyperplasia and hypertrophy and induces a proinflammatory cascade (e.g., cytokines, chemokines and leptin); these proinflammatory mediators can activate, recruit and expand MDSCs in the tumor microenvironment, thereby enhancing tumor development and progression. Arg1, arginase type 1; CCL, C-C motif chemokine ligand; CCR, C-C motif chemokine receptor; IL, interleukin; LEPR, leptin receptor; MDSC, myeloid-derived suppressor cell; RNS, reactive nitrogen species; ROS, reactive oxygen species.

predispose to cancer development, tumor cell dissemination and metastasis (7,8) by promoting mutagenic DNA damage via ROS or reactive nitrogen species production (63). The resulting epigenetic alterations, such as DNA methylation or microRNA dysregulation (64), increase oxidative stress and mediate molecular pathways, including NF-κB or signal transducer and activator of transcription (STAT)3 signaling (65). These epigenetic alterations also induce the release of proinflammatory cytokines (e.g., TNF-α, IL-1β, IL-6 and IL-17) (66).

As mentioned above, cancer and obesity both create similar chronic inflammatory environments. In a cancer-related environment, MDSCs are recruited (67), thus leading to tumor growth, resistance to cancer therapies and poor outcomes (11,68,69). In obese patients, MDSCs are recruited (70) partly through the migration of inhibitory

factor-related protein (MRP)-8 (best known as S100A8) and MRP-14 (S100A9), which regulate MDSC-mediated immunosuppression (40,71). Of note, lipid and fatty acid metabolisms have been associated with the modulation of MDSC activity (72). Adeshakin *et al* (73) reported that fatty acid transport protein 2 (FATP2) confers a protumorigenic environment. This effect is exerted by FATP2 by regulating MDSC and ROS activity and inducing the accumulation of lipids via the upregulation of arachidonic acid metabolism (73). Furthermore, the proto-oncogene serine/threonine-protein kinase Pim-1 has been reported to strongly correlate with fatty acid oxidation, and its targeting resulted in MDSC depletion from the TME (74).

6. Obesity-associated MDSCs as a protective factor in immune homeostasis

Although low levels of circulating MDSCs are found in healthy individuals, these cells play a major role (see section on MDSCs) in maintaining immune homeostasis. Thus, MDSCs limit the hyperactivation of pro-inflammatory cells and reduce tissue damage (75). In obesity conditions, maintaining immune homeostasis is crucial to avoid or prevent adipose tissue dysfunction (76). Obesity is associated with metabolic disorders such as diabetes, which is characterized by high glucose levels resulting from the inability of insulin to suppress hepatic glucose production (77). The role of MDSCs in these settings is scarcely known. To date, only a couple of studies have demonstrated the protective role of MDSCs in obesity-driven metabolic disorders. Xia *et al* (70) demonstrated that Gr-1+CD11b+ MDSCs are highly expressed in the peripheral tissue of obese mice. This high expression protected mice from inflammation and improved insulin sensitivity and glucose tolerance (70). The authors suggested that MDSCs from obese mice induced not only the apoptosis of cytotoxic CD8+ T cells, but also the polarization of M1 macrophages into their M2 phenotype, thereby exerting insulin-sensitizing effects (70). Similarly, Clements *et al* (78) reported that MDSCs from obese mice reduced inflammation and had protective effects against metabolic disorders. In parallel, MDSCs increased fat accumulation and the risk of tumor progression and metastasis (78).

7. Obesity-associated MDSCs and cancer: The potential role of leptin

Leptin is a non-glycosylated hormone consisting of 167 amino acids that has been described in leptin-deficient (ob/ob) and leptin receptor (LEPR)-deficient (db/db) mice (79,80) as the product of the 'obese gene' (81). Leptin has pleiotropic effects, and it is not only expressed in adipose tissue, which is considered the main source of leptin, but also in a variety of tissues such as the brain, kidney, liver and skeletal muscle (82). Leptin can also bind different LEPRs [extensively reviewed in (83)] to transduce activation signals into cells through the Janus kinase 2/STAT3, MAPK/ERK1/2 and/or PI3K/AKT signaling pathways (84).

In normal conditions, leptin expression is regulated to restore physiological functions and homeostasis. This hormone has a critical role during chronic inflammation (85) in different settings, such as obesity (86), fertility (87) and pregnancy (88), and when interacting with immune cells via proinflammatory mediators (89,90). Closely related to the role of obesity in cancer, leptin has also been suggested to be involved in all stages of tumorigenesis. Specifically, leptin binds LEPRs to induce a variety of processes, including systemic inflammation, promoting cancer stem cell phenotypes, epithelial-mesenchymal transition, antiapoptotic proteins, hypoxia and angiogenic factors. As a result, leptin enhances cancer cell survival, proliferation and migration, and inhibits T-cell responses (91-96). Hence, leptin correlates with cancer risk and poor survival rates in numerous types of cancer, including breast (97), esophageal (98) and colorectal cancer (99).

Leptin levels have been documented to be increased in cancer-bearing mice treated with an HFD. Similar conclusions have been drawn from cancer patients with obesity (26,34). Specifically, Koprivčić *et al* (100) demonstrated that women with malignant breast tumors exhibited significantly higher leptin levels (22.24±22.58 ng/ml), as compared to those with benign tumors (11.21±9.46 ng/ml). In addition, patients with triple-negative breast tumors (the most aggressive type of BC) showed higher leptin concentrations (36.11±17.95 ng/ml) than patients with other breast tumor subtypes (100). Lower concentrations of leptin have also been reported in invasive BC and breast carcinoma *in situ* (10.4±7.0 and 8.7±5.3 ng/ml, respectively), particularly in postmenopausal women. Of note, leptin concentrations were still higher in these patients, as compared to healthy donors (8.4±5.3 ng/ml) (101). Another study comparing leptin levels in patients with prostate cancer and a healthy cohort revealed serum leptin levels of 14.18 and 1.63 ng/ml, respectively (102). Of note, Tong *et al* (103) did not find any relationship between serum leptin levels and lung cancer; however, the authors found a significant association between leptin expression in tissue and lung cancer. In the same way, LEPR has been reported to be overexpressed in cancer tissue, as compared with normal mucosa (104).

In line with the previous results, leptin has been suggested to be involved in the induction and accumulation of MDSCs (78). Apart from circulating pro-inflammatory cytokines, adipose tissue also releases other pro-inflammatory mediators such as leptin. This adipokine, in turn, may partially elevate the concentration of those cytokines. Therefore, leptin is involved in a feedback loop that may induce the inflammatory milieu typically found in a variety of cancers (105,106). The pro-inflammatory mediators elevated by leptin are also inducers of both, MDSC differentiation and accumulation in the TME (107-109).

8. Therapeutic approaches to target MDSCs in obesity-related cancers

Based on previous studies, a high BMI increases the risk of cancer (110), as demonstrated in endometrial cancer (from 2.5- to 7.1-fold), esophageal adenocarcinoma (4.8-fold), colon, gastric, liver, gallbladder, kidney and pancreatic cancer (from 1.5- to 1.8-fold) or multiple myeloma (from 1.2- to 1.5-fold) (111). However, there are no specific recommendations for the management of obese patients with cancer because

obesity may i) influence treatment selection; ii) increase treatment-related toxicity; and iii) promote surgical complications, including infections and perioperative mortality. A decade ago, guidelines recommended estimating chemotherapy doses in obese patients based on their body weight (112). Doses of immunotherapy and targeted therapies have also recently been recommended to be calculated as a function of patients' body weight (113). In this regard, MDSC-targeted therapies may be a promising approach to improve clinical response in obese patients with cancer. The main strategies for MDSC targeting include: i) MDSC depletion; ii) inhibition of MDSC-mediated immunosuppression; iii) blocking MDSC recruitment; and iv) promoting the differentiation of MDSCs into granulocytes, monocytes and dendritic cells (114).

MDSC depletion in mice is commonly induced using antibodies against Gr1, which is located on the surface of murine MDSCs (13). In cancer-bearing mice with diet-induced obesity, different anti-Gr1 therapies have been shown to reduce MDSC expression in the TME (32,34,35,78). Chemotherapeutic agents have also been used to deplete MDSCs (115); however, according to the American Society of Clinical Oncology guidelines, evidence remains limited regarding the toxicity and efficacy of chemotherapy in obese cancer patients (113). This is probably due to the dysregulation of pharmacokinetics and metabolism (116). Consequently, there are no studies reporting the effects of chemotherapy on MDSCs in obese patients with cancer.

The inhibition of MDSC-mediated immunosuppression and the blocking of MDSC recruitment are the most widely used strategies in cancer immunotherapy. In this strategy, the immune checkpoint PD-1/anti-PD-L1 axis is blocked in one of the treatment groups. Anti-PD-1 treatments have shown promising survival rates in obese patients with renal cell carcinoma (26); therefore, it could be a therapeutic approach to reduce MDSC concentrations and improve T-cell responses (117,118). Also, the IL-6 inhibitor LMT28 has been demonstrated to reduce ovarian tumor growth in murine models of obesity and may also be a potential therapy for obese patients with cancer (33). IL-6 is a crucial regulator of MDSC activity and a target for cancer immunotherapy (108). Chemokine-targeted therapies are also useful to deplete the TME of MDSCs. In this sense, $CCR2^+$ MDSCs have been found in high proportion in renal cancer murine models treated with an HFD (29). CCR2 binds CCL2, which is secreted by adipose tissue to promote MDSC recruitment. These findings suggest that the CCR2/CCL2 signaling pathway may be a pivotal target for MDSC depletion (27). Similarly, anti-CXCR1 and anti-CXCR2 have been successfully used in patients with prostate cancer with obesity due to it having an involvement in the CXCR1/CXCL1 and CXCR2/CXCL8 axis; however, levels of MDSCs were not measured in this study (37). By contrast, SX-682, a CXCR1 and CXCR2 inhibitor, has been demonstrated to abrogate tumor trafficking of MDSCs in head and neck cancer murine models (119); thus, SX-682 may be another potential therapeutic approach to inhibit MDSC-mediated immunosuppression.

MDSC differentiation into mature non-suppressive cells has also been tested. For instance, cytosine-phosphate-guanosine oligodeoxynucleotides (CPG-ODNs) can stimulate plasmacytoid dendritic cells to produce IFN-α and, in turn, promote MDSC maturation *in vitro* (120). CPG-ODNs have been proven to improve the efficacy of adenovirus 5 carrying the TNF-related apoptosis-inducing ligand (Ad5-TRAIL/CpG) in obesity-related renal cell carcinoma (28). In this sense, TRAIL was demonstrated to potently induce tumor-cell apoptosis and the activation of tumor-specific cytotoxic T cells (121); furthermore, the addition of Ad5-TRAIL/CpG prolonged TRAIL production (122). Of note, TRAIL receptors can be considered potential targets to selectively inhibit MDSCs without them affecting mature myeloid or lymphoid cells (123,124).

Other therapeutic approaches to induce MDSC differentiation into mature cells in cancer patients include STAT3 inhibition (125) and the use of all-trans retinoic acid (ATRA) (126) or vitamin D3 (127). Of these, only STAT3 inhibitors have been successfully used in cancer mouse models of obesity (128,129). However, the impact of this therapy on MDSCs remains to be evaluated. ATRA therapy may be optimal to prevent obesity-related metabolic syndrome (130), although its role in obesity-related cancer has not yet been tested. Conversely, the clinical applications of vitamin D in obese patients remain controversial because of the confounding factors and limitations reported in numerous studies (131). Hence, the use of vitamin D still cannot be recommended for obese patients with cancer, despite the promising results achieved in the depletion of tumor MDSCs.

9. Conclusions and future perspectives

Based on the evidence provided by preclinical and clinical studies, obesity may be potentially associated with carcinogenesis. The chronic inflammatory environment promoted by obesity leads to MDSC recruitment, which has a key role in cancer development and progression.

MDSC depletion in obesity-related tumors has been successfully evaluated and associated with improved survival rates and lower tumor progression. However, most of the results have been obtained in murine models. It is worth mentioning that Gr1 inhibitors can only be tested in murine models, since Gr1 is a typical marker of mouse MDSCs. Therefore, its translation into clinical practice must be further investigated. Specific treatments for oncological patients may include anti-PD-1, anti-IL-6, anti-CCL2, anti-CXCR1, anti-CXCR2 and Ad5-TRAIL/CpG. However, there are a variety of MDSC-targeted options that still need to be tested, such as ATRA, vitamin D or STAT3 inhibitors, anti-CCR5, anti-VEGFR and chemotherapeutic agents (114).

Special emphasis has been placed on the role of obesity as a protective factor in tumorigenesis (the so-called 'obesity paradox') (132,133), which has been documented in a variety of tumors, including lymphomas (134,135); acute myeloid leukemia (136); hepatocellular cancer (137); colorectal cancer (138,139); renal cell carcinoma (140-143); lung cancer (144-146); or melanoma (147-149). In this sense, certain studies have demonstrated the inhibitory effects of leptin *in vitro* (150,151). Evidence has also been provided of an inverse relationship with cancer risk and a positive association with improved outcomes (151,152), which has been termed the 'leptin paradox' (96).

The reasons for the positive association between high amounts of adipose tissue and improved response to cancer

immunotherapies remain unknown (153). These phenomena could be explained by the fact that BMI estimation does not only consider adipose tissue but also protective muscle mass; consequently, the BMI should be dismissed as a tool for measuring adiposity (154). Finding optimal parameters may be difficult, since there are many variables that hinder the accurate measurement of adiposity, such as sex, ethnicity, age and pathophysiological group (155).

Cancer immunosuppression driven by obesity-associated MDSCs seems clear, but further research is needed, particularly in cancer patients. There are still various gaps of knowledge, including i) the mechanisms involved in the relationship between obesity, cancer and MDSCs; ii) the mechanisms by which obesity or leptin exert protective effects in certain types of cancer and the role of MDSCs in these settings; and iii) the efficacy and safety of other MDSC-targeted therapies.

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Authors' contributions

CJC, CGG, FSJ, TVG, RFC, APP, CG, MLSL, DJGD, LHP and NPC contributed to the literature search. CJC and CGG wrote the manuscript draft. LdlCM and VSM were involved in the conceptualization of the study. All authors contributed to the revision of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

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