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Journal Title: American Journal of Cancer Research
Volume: Volume 3, Number 1
Publisher: e-Century Publishing | 2013, Pages 21-33
Type of Work: Article | Final Publisher PDF
Permanent URL: http://pid.emory.edu/ark:/25593/f576b

Final published version: http://www.ajcr.us/AJCR_V3N1.html

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Accessed November 27, 2018 1:09 AM EST
Obesity-driven inflammation and cancer risk: role of myeloid derived suppressor cells and alternately activated macrophages

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Received December 5, 2012; Accepted December 23, 2012; Epub January 18, 2013; Published January 25, 2013

Abstract: During carcinogenesis, tumors induce dysfunctional development of hematopoietic cells. Myeloid lineage cells, in the form of myeloid derived suppressor cells (MDSCs) and alternatively polarized M2 macrophages, influence almost all types of cancers by regulating diverse facets of immunosuppression, angiogenesis, cell proliferation, growth and metastasis. One-third of Americans are obese, and accumulating evidence suggests that obesity is a risk factor for various cancers. However, the relationship between these immune players and obesity are not well-described. In this review, we evaluate potential mechanisms through which different aspects of obesity, namely insulin resistance, increased estrogen, adiposity and low grade chronic inflammation from adipose tissue macrophages, may coalesce to promote MDSC induction and M2 macrophage polarization, thereby facilitating cancer development. Detailed understanding of the interplay between obesity and myeloid mediated immunosuppression may provide novel avenues for therapeutic targeting, with the goal to reduce the challenge obesity presents towards gains made in cancer outcomes.

Keywords: Obesity, inflammation, myeloid derived suppressor cells, alternately activated macrophage, cancer

Introduction

Despite significant advances in screening and therapeutics, cancer remains a major cause of mortality and morbidity worldwide. In the United States alone, 1 in 4 deaths are attributed to cancer, second only to cardiovascular-related deaths[^1]. Various indices such as obesity, smoking, metabolic syndrome and genetics are known to not only increase the risk of cancer, but also to complicate response to chemotherapy and radiation[^2]. In the past decade, the role of the immunosuppressive and cancer-promoting myelomonocytic compartment within the tumor environment has also received a great deal of attention[^3]. By mechanisms that are incompletely understood, cancer promotes the accumulation of a heterogeneous pool of bone marrow-derived immature, poorly differentiated myelomonocytic cells (monocytes, neutrophils, immature macrophages and dendritic cells), called myeloid derived suppressor cells (MDSCs)[[^3] ][^4]. These cells are marked by CD11b(+)Gr-1(+) expression, but do not express the mature macrophage marker F4/80. In addition, the tumor microenvironment preferentially polarizes monocytes and mature macrophages towards the so-called alternatively activated M2 phenotype[^5][^6]. Together, MDSCs and M2 macrophages foster an immunosuppressive environment by recruiting other immunosuppressive cells such as regulatory T cells[^7], targeting apoptosis of tumor-specific cytotoxic CD8 T cells[^8], promoting and facilitating metastasis[^9], while producing various chemokines, cytokines and angiogenic factors to support primary tumors[^10]. However, the interplay between these complex mechanisms of myeloid immunosuppression and the widely known cancer risk factors are not well delineated. It is imperative to appreciate and address all details of the mechanistic molecular underpinnings of these risk factors, so as to indentify new therapeutic
Obesity and cancer: role of myeloid cells

Recent data indicate that one-third of Americans are obese [11]. A body mass index (BMI) greater than 30 is associated with increased risk for a wide range of cancers including endometrial, esophageal, kidney, pancreatic and other gastrointestinal malignancies [12, 13] (Table 1). Obesity also increases cancer-related morbidity and mortality. The risk holds true across race, gender and different geographic groups [12]. Obesity may exert direct, organ-specific effects in certain cancers. For instance, in esophageal cancer, the increased risk may be secondary to increased reflux from obesity leading to chronic local inflammation, Barrett’s esophagus and subsequently adenocarcinoma [14]. In renal cancers, the risk may be secondary to increased risk of hypertension or genetic susceptibility such as VHL in obese individuals [15, 16]. The link between obesity and cancer is even broader in colon cancer, because the direct effect of low fiber diet, high caloric intake, energy balance and BMI are intricately connected and difficult to discriminate [17, 18]. It has also been proposed that obese patients suffer worse outcome because of delay in cancer detection [2, 19], and sub-optimal dosing of chemothera-
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Mechanisms of MDSC induction M2 macrophage polarization

The transcriptional pathways leading to MDSC and M2 macrophage polarization are an area of current intense research due to their implication in cancer [21]. In brief, hematopoietic stem cells give rise to a clonogenic common myeloid progenitor cell, from which arises all myeloid lineage cells, including granulocytes, monocytes and myeloid dendritic cells through their respective precursor cells [22]. During cancer development, dysfunctional myelopoiesis arises, and some of these precursors are directed towards the myeloid derived suppressor cells category. Macrophages are instructed by their environmental cues to two major classes of polarization [23]. M1 macrophages are instructed by bacterial antigens such as lipopolysaccharide (LPS) and gamma interferon (IFNγ), and produce pro-inflammatory cytokines such as IL-12, IL-6, iNOS and TNF-α. These cells are required for robust clearance of tumors and bacterial infections. In contrast, M2 macrophages are generated by cell factors such as IL-4 and prostaglandins to mediate tissue repair and dampen inflammatory response through cytokines such as IL-10 and TGF-β [23]. Unfortunately, some of the effects of these cytokines promote tumor growth through angiogenesis, matrix degradation (which enables metastasis) and cell survival [23].

Monocytes and MDSCs may also differentiate preferentially towards the alternatively activated M2 macrophage phenotype [24, 25]. Among the transcriptional factors described include C/EBPα, C/EBPβ, PPARγ, NF-κβ, STAT-3, IRF-4, Jmjd3 and COX-2 (See Figure 1). The C/EBP (CCAAT/enhancer-binding protein) family is a group of transcription factors that can bind as a homodimer to promoters and enhancers involved in myelopoiesis, monocyte differentiation, and macrophage polarization as well as adipogenesis [26]. The peroxisome proliferator activated receptors (PPARs) are a family of nuclear receptor proteins that play essential role in regulation of genes responsible for metabolism of carbohydrates, lipids and fats, as well as cellular differentiation and development. Recent data suggest a key role of PPARγ in alternative macrophage polarization [27]. These various pathways provide therapeutic opportunities for eliminating immunosuppression during carcinogenesis. In addition, chemokines such as monocyte chemotactic protein 1 (MCP-1, or CCL-2) that recruit MDSCs, monocytes and M2 macrophages from the bone marrow to the tumor microenvironment are important avenues of therapy.

Insulin resistance, MDSCs and M2 macrophages

Insulin resistance secondary to obesity is a crucial component of mechanisms leading to can-

Table 1. Cancers with strong link to obesity

<table>
<thead>
<tr>
<th>Men</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal Adenocarcinoma</td>
<td>1.52 (1.33-1.74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.33 (1.04-1.70)</td>
<td>0.02</td>
</tr>
<tr>
<td>Colon</td>
<td>1.24 (1.20-1.28)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal</td>
<td>1.24 (1.15-1.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>1.17 (1.05-1.30)</td>
<td>0.004</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.11 (1.05-1.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rectum</td>
<td>1.09 (0.99-1.21)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial</td>
<td>1.59 (1.50-1.68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>1.59 (1.02-2.47)</td>
<td>0.04</td>
</tr>
<tr>
<td>Esophageal</td>
<td>1.51 (1.31-1.74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal</td>
<td>1.34 (1.25-1.43)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.17 (1.04-1.32)</td>
<td>0.01</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.14 (1.06-1.23)</td>
<td>0.001</td>
</tr>
<tr>
<td>Breast</td>
<td>1.12 (1.08-1.16)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Obesity and cancer: role of myeloid cells

Insulin resistance leads to increased levels of circulating insulin, which in turn increases the bioactivity insulin growth factor (IGF-1), IGF-1 receptors, and insulin receptors (IR) in normal and cancerous cells. The multiple role of IGF-1 in cancers has received recent thorough review [28, 29]. In brief, IGF-1 induces vascular endothelial growth factor (VEGF) expression in tumor cells, thereby inducing angiogenesis [30]. IGF-1 also induces CD147, a transmembrane protein whose expression on tumor cells equally leads to angiogenesis and increased glycolysis (required for energy metabolism) in tumor cells [31, 32]. Furthermore IGF-1 signaling activates beta catenin, a key regulator of epithelial mesenchymal transition, and potentiates other cell growth stimulants. Both insulin and IGF-1 signaling through IGF-1R and IR mediate angiogenesis, cell differentiation and cell proliferation, thereby promoting cancer burden [33, 34]. Accordingly, individuals with elevated IGF-1 have increased risk of several malignancies, including bladder, colorectal, endometrial, lung and prostate cancer [35-38]. Indeed, elevated IGF-1 has been implicated in the increased susceptibility to cancer in patients with acromegaly [39].

Further investigations by other groups have recently revealed that in addition to the mechanism of direct stimulation of angiogenesis, insulin resistance may inadvertently promote carcinogenesis through MDSCs and M2 macrophages. An exciting observation has been described in the laboratory of Dr Qi et al, whose group showed that MDSC and M2 macrophage induction may be a physiological response to promote insulin sensitivity [40]. The obese (ob/ob) mouse has remained a standard model to understand the interconnection of genetics and diet in obesity [41]. They present with hypercholesterolemia, increased IGF-1 and increased adiposity [42, 43]. Xia et al showed that these mice have profound accumulation of MDSC and M2 macrophage as they are fed a high fat diet. It appears that increased accumulation of MDSCs and M2 macrophages was associated with increased response to insulin. In fact, adoptive transfer of MDSCs into mice fed high fat diet improved the response of the recipient mice to insulin [40]. In contrast, depletion of these cells increased their susceptibility to obesity and further worsened their insulin insensitivity. Yin et al have also described the ability of MDSCs to delay onset of diabetes and insulin resistance [44].

Although mechanisms by which MDSCs enhance insulin sensitivity are unknown, there are insights into to how upregulated IGF-1 in the setting of insulin resistance may lead to the accumulation of MDSCs and M2 macrophages. During acute skeletal muscle injury, monocytes are recruited by way of the CC chemokine ligand 2 (CCL2) to facilitate repair of damaged muscle tissue. These recruited monocytes differentiate towards the alternatively activated M2 phenotype, which is required for resolution of inflammation and muscle repair [45]. Interestingly, Lu et al have recently provided evidence that upregulation of local IGF-1 is necessary for the polarization of these recruited myeloid cells towards the M2 phenotype [46, 47]. In fact, the potent M2 response essential for limiting overt acute tissue damage during experimental helminth infection is not only dependent on IL-10, but also on IGF-1 [48]. Altogether, these data suggest that not only does insulin resistance induce physiological response for MDSC and M2 macrophage expansion, but that insulin may also modulate direct gene transcriptional control of these cells. Further work is required to determine the mechanisms by which IGF-1 drives monocyte differentiation. These data suggest that pharmacologic enhancement of insulin sensitivity in obese individuals may preemptively hinder the development of MDSCs which inadvertently contribute to immune escape of cancer cells from an effective host response.

One pharmacotherapy that improves insulin sensitivity and has found recent implication in cancer is metformin. It is a guanide based anti-diabetic agent that works by activating AMP-activated protein kinase (AMPK), an enzyme which plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats [49, 50]. Metformin suppresses hepatic gluconeogenesis and is the mainstay therapy for type 2 diabetes particularly in obese patients [51]. Interestingly, a series of studies have shown that diabetic patients on metformin have a reduced risk of cancers such as breast, pancreatic and ovarian cancer [52-54]. The effects are probably not due to anti-diabetic mechanisms, because
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Other similar agents do not reduce- and may even increase-risk for pancreatic and other cancers [52, 55]. The mechanisms of the anti-cancer effect of metformin remain largely unknown, but anti-proliferative effects on several cancer lines have been demonstrated in vitro, with AMPK signaling the proposed primary pathway [56-58]. However, the doses required to achieve this in vitro effect were several folds higher than those used in the clinical setting. Furthermore, recent work by Bonani et al revealed equivalent proliferative index between breast cancer surgical tissues of control and metformin-treated patients, suggesting possible alternative tumor cell-independent mechanisms [59]. In addition, several AMPK-independent effects have been described, raising questions as to the true mechanism mediating the effect of metformin [60-62]. Importantly, recent work by different groups revealed reduced macrophage infiltration and cytokine production within tumors after metformin treatment in vivo and in vitro [54, 63]. Further work is needed to unravel the likely complex mechanisms by which metformin affects cancer development. In that effort, the potential role of metformin via IGF-1 in modulating the myeloid-cell inflammatory response through MDSC and M2 macrophages should be closely explored.

Estrogen, MDSCs and M2 macrophages

Obesity is associated with increased estrogen production through conversion of androgens in adipocytes by aromatase [64, 65]. The role of estradiol, the predominant circulating estrogen, in breast, endometrial and other hormone responsive cancers is well known and thoroughly described elsewhere [66-68]. Increasing new evidence also indicates an interesting association between estradiol and myeloid cell differentiation and polarization. Estradiol may drive differentiation of myelomonocytic cells from the bone marrow towards ineffective antigen presenting cells. This is thought to be mediated by the increased activation of the interferon response factor -4 (IRF4) [69], which collaborates with the jmdj3 axis as a potent pathway in differentiation of myeloid cells towards the M2 phenotype [70]. Estrogen is an important growth factor for bone marrow stimulation of myelomonocytic cell production, such that estrogen excess results in hematopoietic dysfunction and inability to produce mature dendritic cells from the bone marrow [71-73]. Thus, estrogen excess in obese individuals may be another mechanism by which immunosuppression is promoted through MDSCs and M2 macrophages. Estrogen antagonism with agents such as tamoxifen and raloxifene may improve hormone-responsive cancer survival. Recently, the role of these selective estrogen receptor modulators (SERMs) in suppressing the inflammatory response and decreasing the recruitment of monocytes has been described [74, 75]. It is noteworthy that IRF-4 pathway involved in macrophage polarization is also implicated in adipocyte handling of lipids [76]. Furthermore, estrogen also increases the function of CD4+CD25+ regulatory T cells, another immunosuppressive cell type associated with immune evasion by cancer cells [77, 78].

Chronic inflammation, MDSCs and M2 macrophages

Clinically, obese patients have an increased circulating pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β and IL-12 [79]. The levels of these cytokines may correlate with BMI [80]. The importance of these cytokines is underscored in animal models, where their deficiency leads to improved response to insulin and reduced obesity [81, 82]. Furthermore, pharmacologic or genetic inhibition of these cytokines also improves severity of some obesity-induced cancers [83, 84]. The source of these cytokines may be from the adipocytes themselves or recruited bone-marrow derived monocytes [85], although the relative contribution from these sources are unclear.

The mechanisms by which obesity-associated chronic inflammation induces M2 macrophages and MDSCs are arguably stepwise. In general, the initial pro-inflammatory cytokine milieu induced by obesity may actually bear the trademark of the broadly anti-cancer, classically activated M1 macrophage features [86, 87]. However, it is still important to note that some of these cytokines can have dual, complex pro-tumor contributions as well. For example, IL-1β is capable of inducing MDSC function [88], while at the same time, directly stimulating angiogenesis and metastasis [89, 90]. In addition, TNFα is capable of supporting tumor growth through NF-kβ while at the same time increasing insulin resistance [115]. However, it
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is the long-standing chronic inflammation that may precipitate the induction of MDSCs and M2 macrophages by the following mechanism. In several well-described models of inflammation, MDSCs are induced in an attempt to curtail overt responses [3]. For example, chronic inflammation in the setting of viruses, complete freud's adjuvant and other infections induces accumulation of MDSCs [91, 92]. It is therefore conceivable that in a similar paradigm, obesity-related low-grade chronic inflammation may stimulate the deployment of immature myelomonocytic cells from the bone marrow, which eventually accumulate as MDSCs and M2 macrophages [93]. Fujikawa et al have attributed this subsequent M1 to M2 switch in recruited adipose tissue macrophage to IL-10 [94]. Thus, a possible scenario is set where the initial pro-inflammatory state created in early obesity induces adipogenesis and insulin resistance. This in turn leads to accumulation of MDSC in an attempt to curtail overt inflammation and improve insulin sensitivity (Figure 2).

The importance of the myeloid compartment of the chronic grade inflammation has been bolstered by recent work in which regulation of the alternative activation of bone marrow derived monocytes was sufficient to curtail inflammation secondary to high fat diet, and thereby protect mice from diabetes and the complicated sequelae. In brief, Dr Friedman's group have shown that genetic deletion of C/EBPβ specifically in the myeloid compartment successfully abrogate obesity, inflammation, insulin insensitivity [95]. As one might predict, C/EBPβ is a key regulator of alternative activation of macrophages, myeloid derived suppressor cells, and cancer [26, 96, 97].

**Adiposity, MDSCs and M2 macrophages**

Adiposity is associated with recruitment of macrophages that initiate chronic inflammation. In fact, the amount of visceral fat accumulation is a good measure of recruited adipose tissue macrophages [98]. It is important to recognize that increased lipid bioavailability is an excellent resource for cellular proliferation, growth and development. Any of these processes may be usurped by cancer cells to facilitate tumor growth. One such candidate is the fatty

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**Figure 2.** Schematic of stepwise effect of chronic inflammation and MDSC and M2 macrophages in the setting of obesity. In normal (non-obese) state, few macrophages are associated with fat cells in adipose tissues, with minimal inflammation. During early obesity, more macrophages are recruited. These cells produce pro-inflammatory cytokines, in a M1 macrophage inflammatory response pattern. As obesity progresses, insulin resistance develops. A physiologic as well as immune response to this chronic insulin resistance and chronic inflammation is the induction of the M2 macrophage response.

**Normal homeostasis**

- Cytokines:
  - TNF
  - IL-6
  - IL-1

- Transcriptional Factors:
  - NF-κβ

**Early Adiposity**

- Cytokines:
  - ↑↑↑ TNF
  - ↑↑ IL-6
  - ↑↑ ↑ IL-1

- Transcriptional Factors:
  - NF-κβ

**Late Adiposity**

- Cytokines:
  - ↑ TNF
  - ↑ IL-4
  - ↑↑ IL-10
  - ↑ Arginase
  - ↑ TGF-β
  - ↑ PPAR-γ
  - ↑ C/EBPβ
  - ↑ NF-κβ

**Adipocyte**

**Macrophage**

**MDSCs**
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Acid synthase (FASN). It is key to lipogenesis in obesity [99], and has received great deal of attention recently in carcinogenesis [100-102]. However, FASN via the COX-2 pathway, may induce MDSC accumulation as well as M2 macrophage differentiation [103]. Indeed, targeting FASN has become an attractive anti-cancer target [104].

Activation of other concomitant transcriptional programs in adipocytes and monocytes may also result in M2 polarization. As mentioned earlier, PPARs are a family of nuclear receptor proteins that regulate metabolism of carbohydrates and lipids. Overall, PPARγ activation may confer anti-cancer effect via apoptosis, growth arrest, and reciprocal downregulation of tumor cell IGF signaling. Accordingly, PPARγ agonists have emerged as a potential therapeutic target in a number of malignancies, while remaining mainstay therapy for diabetes and insulin resistance. However, activation of both adipocyte PPARδ and PPARγ can induce differentiation of macrophages towards the alternately activated M2 phenotype [27, 105]. Thus, adipogenesis requires upregulation of PPAR, which is an important transcription factor for alternate activation of macrophages and cancer development [106]. Interestingly, PPARγ agonist also may have cancer risks, particularly bladder cancer [107]. It is perhaps the untoward polarization of macrophages to the M2 phenotype that raises the risk of these drugs to cancer, as well as the disappointing results of these agents in clinical trials [108]. Thus, the details of these complex mechanisms must be investigated in order to harness the potential benefit of PPAR agonists. The PPAR example illustrates that the mere presence of excess adiposity may result in associated macrophages acting as bystanders that differentiate into M2 macrophages, while the excess availability of lipids themselves can drive cellular differentiation and growth. Whether adiposity alone is sufficient to drive carcinogenesis remains to be proven.

Conclusion

The obesity epidemic imposes an increasing burden on global health [109]. Accumulating evidence indicates that obesity represents a risk factor for various cancers and threatens to undercut the gains in the therapeutic advances made towards improving prognosis and survival in cancer-related morbidity and mortality.
Obesity increases circulating estrogen, insulin, IGF, and cause chronic low-grade inflammation. These diverse pathways directly or indirectly converge to induce accumulation of myeloid derived suppressor cells, while programming macrophages to the alternatively activated M2 phenotype (Figure 3). MDSCs and M2 macrophages are a major source of immunosuppression that allows for tumor-escape from effective anti-cancer responses. The induction and preferential tilting of macrophages towards the M2 phenotype may be a primary physiologic and metabolic response to insulin insensitivity, as well as a secondary consequence of an immune process to control overt, chronic, low grade inflammation. In any event, these processes may be inadvertently modulated by tumor cells to promote angiogenesis, metastasis and overall poor outcome.

The link between myeloid cells and obesity in cancer provides several avenues for therapeutic targeting. One approach is to reduce the recruitment of myeloid cells within the tumor microenvironment, so as to starve tumor cells from MDSCs and M2 macrophages which provide pro-tumor milieu. CCL2 is a chemokine responsible for recruitment of monocytes and macrophages from the bone marrow into the tumor microenvironment. Targeting CCL2 and CCL2 receptors is currently a promising mechanism in breast cancer therapy, and will likely be found to be critical in several other cancers as well [110-112]. Theoretically, CCL2 inhibitors could be used as combination therapy with other chemotherapeutic regimens that influence different aspects of carcinogenesis.

Another area of potential therapeutic targeting is the use of anti-inflammatory agents to reduce the low grade chronic inflammation that leads to the insulin insensitivity and subsequent physiologic response of MDSC and M2 macrophage induction. Some of these anti-inflammatory therapies are already in use for cardiovascular disease prevention in obese individuals. The use of aspirin is currently under trial for use against certain cancers, and is showing some promise [110, 113].

Finally, mechanisms that lead to signaling in adipose tissue that influence macrophage polarization are another attractive area of anti-cancer therapeutics. PPAR agonists have already been described above, with the caveat of potential pro-cancer risk because of their capacity to promote M2 macrophage polarization. COX-2 signaling promotes M2 macrophage differentiation, and is currently a target for chemoprevention in colorectal, pancreatic and other malignancies. This effect of COX-2 partly explains the rationale for the potential therapeutic use of aspirin in cancer prevention [114]. Upregulation of fatty acid synthase (FASN) in adipogenesis also links COX-2 pathway to MDSCs induction. FASN is also a new therapeutic target for colon cancers. Indeed, all the factors involved in macrophage polarization (outlined in Figure 3) are worthy of active research, with the hope to identify effective therapeutic advances against cancer. To this end, detailed mechanistic understanding of the role of obesity in MDSC and M2 biology could translate into novel, potentially convergent targets that may be exploited. Beyond pharmacotherapy, the effect of weight loss on macrophages and MDSCs may also merit investigation. Findings from these studies could help encourage weight loss in the general population, and inexpensively improve health outcomes in our society where cancer and cardiovascular disease account for the majority of deaths.

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