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Current Opinion in Immunology

Myeloid derived-suppressor cells: their role in cancer and obesity

Suzanne Ostrand-Rosenberg[1,2]

Myeloid-derived suppressor cells (MDSC) are present in most individuals with cancer where they inhibit adaptive and innate antitumor immunity and are an obstacle to cancer immunotherapies. Chronic inflammation is characteristic of adipose tissue and is a risk factor for the onset and progression of cancer in obese individuals. Because MDSC accumulate in response to inflammation, it has been hypothesized that one of the mechanisms by which obesity promotes malignancy is through the induction of MDSC. This article reviews the data supporting this hypothesis, the role of leptin and fatty acid metabolism in the induction of MDSC, and the surprising finding that although MDSC promote tumor progression, they are protective against some of the metabolic dysfunction associated with obesity.

Addresses
[1] Department of Biological Sciences, University of Maryland Baltimore County (UMBC), 1000 Hilltop Circle, Baltimore, MD 21250, United States
[2] Department of Pathology and Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, United States

Corresponding author: Ostrand-Rosenberg, Suzanne (srosenbe@umbc.edu)

Current Opinion in Immunology 2018, **51**:68–75

This review comes from a themed issue on **Tumour immunology**

Edited by **Anahid Jewett**

https://doi.org/10.1016/j.coi.2018.03.007

Introduction

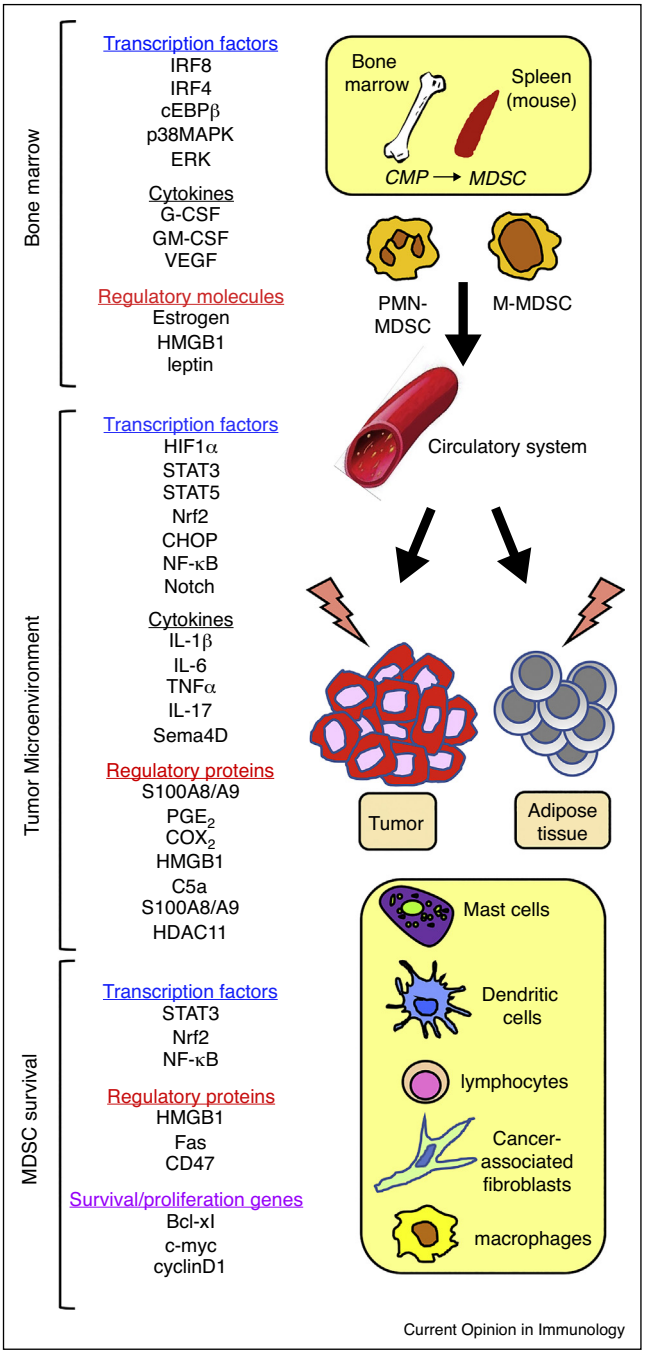
During the past approximately ten years myeloid-derived suppressor cells (MDSC) have been under intensive study because they are present in most cancer patients and are recognized as a significant obstacle to cancer immunotherapies. Chronic inflammation associated with solid tumors is the dominant driving force for the accumulation of tumor-induced MDSC, and led to the hypothesis that one of the mechanisms by which inflammation facilitates cancer progression is by the induction of MDSC which inhibit antitumor immunity [1]. Chronic inflammation is also associated with obesity, suggesting that MDSC may also be elevated in obese individuals. This article describes how obesity-driven MDSC protect against some of the metabolic dysfunction associated with obesity while simultaneously increasing the rate of tumor progression that is characteristic of obese cancer patients. Several recent review articles detail the induction, function, characterization, and nomenclature for MDSC [2,3,4••,5], so only a brief overview of MDSC characteristics and function will be presented here.

MDSC are a heterogeneous population of immature myeloid cells that arise in the bone marrow (and in the spleen of mice) from the common myeloid progenitor (CMP) and migrate through the circulatory system to solid tumors. The two subsets of MDSC, monocytic and polymorphonuclear/granulocytic (M-MDSC and PMN-MDSC), suppress adaptive and innate immunity using a variety of mechanisms including inhibition of T cell activation, anergizing activated T cells, inhibition of NK cell cytotoxicity, polarization of macrophages towards a tumor-promoting phenotype, and perturbation of immune cell trafficking. Multiple redundant pro-inflammatory mediators drive MDSC accumulation, suppressive potency, and survival by regulating various transcription factors, and a diversity of immune and non-immune host cells produce factors that contribute to the accumulation of MDSC and/or are modified as a result of MDSC development (see Figure 1). Most of the knowledge of MDSC biology is derived from studies of tumor-induced MDSC from mice and humans. As described in the following sections, since chronic low grade inflammation is also present in adipose tissue, many of the conditions that drive tumor-induced MDSC also drive MDSC accumulation and function in obese individuals.

Obesity is a risk factor for cancer onset and a driver of tumor progression

Abundant epidemiological data demonstrate that obesity not only increases the risk of cancer but also increases the progression of established cancers [6]. A 2003 study concluded that overall, obese men and women have a 1.5–1.6-fold increase in the risk of dying from cancer [7•]. Obesity is not an 'equal opportunity' risk for all organ sites, however, since obese men have a 4.5-fold risk and 2.6-fold risk of dying from liver and pancreatic cancer, respectively, while obese women have a 4.8 and 5.3-fold risk of dying from kidney and gastrointestinal (GI) cancers, respectively [8,9]. Therefore, although there is an overall propensity of obesity to facilitate cancer onset and progression, there are also organ and tissue-specific, as well as sex-related factors involved. Despite the differences in obesity-driven conditions that lead to increased

Figure 1



MDSC development, accumulation, suppressive activity, and survival are regulated by a complex network of transcription factors, cytokines, and non-cytokine immune regulatory factors produced by tumor cells and host cells. MDSC originate from the common myeloid progenitor (CMP) cell in the bone marrow (also in the spleen of mice) during myelopoiesis. There are two subtypes of MDSC: mononuclear (M-MDSC) and polymorphonuclear or granulocytice MDSC (PMN-MDSC). Tumor cells and/or host cells in the periphery produce cytokines and other factors that drive MDSC differentiation. From the bone marrow (and spleen of mice), MDSC circulate in the blood and home to sites of inflammation and to solid tumors. Within an inflammatory milieu such as the tumor microenvironment, a variety of factors promote MDSC suppressive activity. The survival of MDSC is facilitated by some of the same conditions and mediators that regulate MDSC accumulation, as well as genes that limit apoptosis. A variety of cells including tumor cells, adipocytes, macrophages, mast cells, dendritic cells, and cancer-associated fibroblasts produce molecules that regulate MDSC.

cancer risk, obesity-driven systemic and/or local inflammation appear to be a unifying condition that facilitates cancer onset and progression [10,11•,12,13].

The chronic inflammatory environment of adipose tissue is similar to the inflammatory conditions that drive cancer-associated MDSC

Obese individuals typically have elevated levels of IL-6, TNFα, and prostaglandin E2 (PGE2) in their blood. These molecules are produced by adipose cells as well as by macrophages that invade adipose tissue. Elevation of these pro-inflammatory mediators is at least partially due to the adipokine leptin, which is over-expressed in obese individuals and an inducer of IL-1β, TNFα, and IL-6. IL-1β, the product of cellular inflammasomes [14] and TNFα, in turn, induce leptin, thereby creating a feed-back loop that sustains the inflammatory environment (reviewed in [13]). Since leptin lacks inflammatory activity in IL-1β-deficient mice, inflammasomes are probably key regulators of the pro-inflammatory adipose tissue environment [15]. Prevalence of this inflammatory milieu is particularly evident in breast tissue of obese women, but also occurs in intestinal epithelial cells of obese mice [16], in liver cells in non-alcoholic fatty liver disease [17], as well as in other organs of both humans and mice.

The pro-inflammatory mediators IL-6 [18], IL-1β [19–21], TNFα [22], and PGE2 [23,24] are major inducers of the differentiation, accumulation, and potency of tumor-induced MDSC. Since the same constellation of molecules are present in adipose tissue [25], it has been hypothesized that the pro-inflammatory environment of adipose tissue may support the induction and accumulation of MDSC [26•,27••].

Immune suppressive MDSC are elevated in obese individuals

The first indication that obesity increased the levels of MDSC came from studies with genetically obese mice and with mice maintained on a high fat diet (HFD). *ob/ob* mice on a C57BL/6 background are genetically obese because they are deficient for the leptin gene. Leptin is a 16 kDa protein encoded by the *ob* gene and is predominantly produced by adipose cells. It regulates body mass by serving as an appetite inhibitor. The Leptin receptor (Ob-R) has multiple forms; however, leptin regulates appetite by binding to the long form of the Ob-R on cells in the hypothalamus [28]. By 28 weeks of age, *ob/ob*