

Myeloid-derived suppressor cells, age and cancer

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We have recently discovered that the levels of circulating myeloid-derived suppressor cells, which are associated with an impaired T-cell proliferation and produce high amounts of reactive oxygen species, increase with age and are elevated in individuals in remission from cancer. Herein, potential mechanisms underpinning these observations are discussed.

Aging, like cancer, can be viewed as a chronic inflammatory condition. Although the causes of age-related inflammation are unknown, it is clear that aging is associated with a progressive increase in circulating cytokines as well as with changes in leukocyte numbers, phenotype, and function. Similarly, individuals exhibiting increased inflammation-associated parameters (as compared with average values for their age range) have an increased risk of developing chronic inflammatory diseases such as diabetes, dementia, and cancer.^{1,2} Although the underlying mechanisms have not yet been fully elucidated, the combination of increased inflammatory mediators and altered leukocyte phenotype ultimately impact diverse leukocyte functions such as glucose metabolism, pathogen-associated molecular pattern (PAMP) signaling, phagocytic capacity, and cytokine secretion.³

Parallels between the aging microenvironment and the tumor microenvironment are obvious but often overlooked. The latter is characterized by increased levels of pro-inflammatory cytokines but an overall immunosuppressive environment. In this setting, a combination of pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β), interferon γ (IFN γ), granulocyte macrophage colony-stimulating factor (GM-CSF), and perhaps other less well-characterized microenvironmental signals, results in an increased production of myeloid-derived suppressor cells (MDSCs) from the bone

marrow and accumulation in lymph nodes and within neoplastic lesions.⁴ Elevated levels of MDSCs result in the suppression of T-cell proliferation and activation and a net increase in the levels of pro-inflammatory mediators such as reactive oxygen species (ROS). The aging microenvironment is systemic and is characterized by increased levels of circulating pro-inflammatory mediators such as IL-1 β , IFN γ , and ROS,⁵ but decreased myeloid cell function and T-cell proliferative potential.⁶ Whether these age-related immunosuppressive alterations result from increased levels of MDSCs is not known. However, the number of MDSCs has recently shown to be increased in the blood, bone marrow, and lymphoid tissues of aged mice, possibly as a consequence of elevated levels of circulating cytokines.⁷

Since it was not known whether the aging microenvironment directly contributes to MDSC production and immunosuppression, we first assessed whether the frequency of MDSCs increases with age.⁵ We observed a statistically significant increase in the percentage of both CD33⁺HLA-DR⁻ (conventional) and CD33⁺HLA-DR⁻CD11b⁺CD15⁺ (CD15⁺) MDSCs among CD45⁺ cells in the elderly (median age = 87) or seniors (median age = 69) compared with adults (median age = 32). Consistent with previously published data, we found that at least some of the cytokines known to simulate the accumulation of MDSCs within tumors (e.g., IL-1 β , IL-6, and IFN γ) were

also increased with age. Because we were specifically interested in investigating a typical population of aging individuals, the only criterion for exclusion from our study was being on immunosuppressive medication. Accordingly, our cohort encompassed individuals with the normal constellation of age-associated comorbidities (e.g., cardiovascular diseases, dementia, diabetes, cancer). In particular, 23 out of 148 individuals were in remission from various malignancies including (but not limited to) breast, prostate, lung, skin, and colon cancers. We compared the circulating levels of conventional and CD15⁺ MDSCs of these individuals to those of cancer-free subjects and found a statistically significant increase in both MDSC populations ($P = 0.031$ and $P = 0.03$, for conventional and CD15⁺ MDSCs, respectively) among individuals with a history of cancer. Although increases in circulating MDSCs have been well documented in individuals with cancer,⁸ this was the first study to document elevations in MDSCs during remission.

Despite the limitation of a small sample size, these data raise interesting questions. First, which came first, cancer or the elevation in MDSCs? Perhaps individuals with high levels of MDSCs have a tolerogenic microenvironment that supports tumor growth, and hence are at increased risk for developing cancer (Fig. 1). Large population based studies are needed to determine whether this is indeed the case. Second, as it is well documented that aging is associated with

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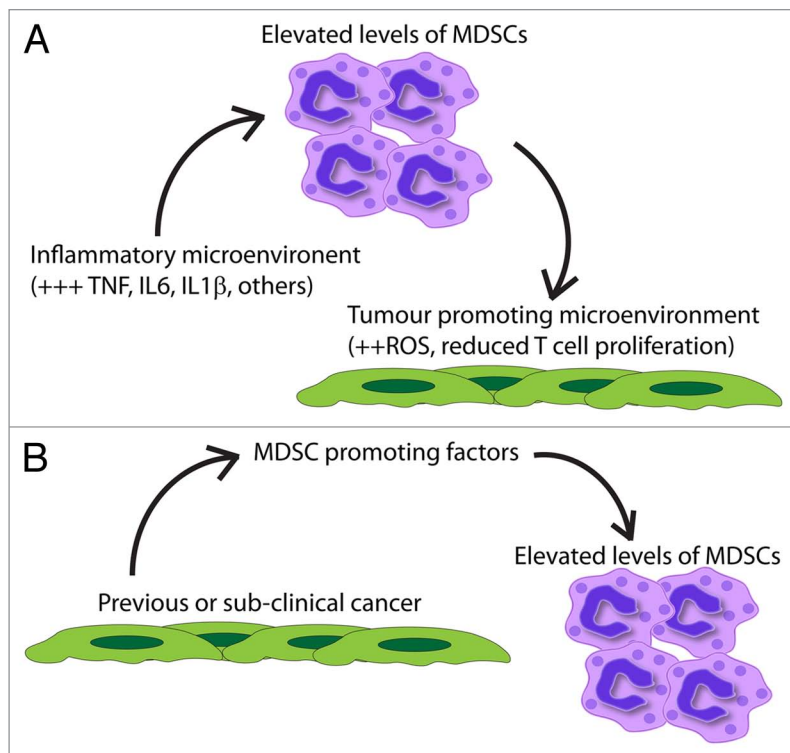


Figure 1. Possible explanations for the elevated levels of myeloid-derived suppressor cells associated with age or previous history of cancer. **(A)** The increased levels of inflammatory cytokines that accompany age may create a myeloid-derived suppressor cell (MDSC)-promoting microenvironment. Individuals with high levels of MDSCs may be predisposed to developing cancer owing to the tumor-promoting effects of MDSCs (e.g., the inhibition of T-cell proliferation and functions). **(B)** Individuals with a history of cancer or bearing a subclinical tumor may continuously produce factors that promote the development of MDSCs, whose levels remain permanently elevated.

changes in the development and output of myeloid cells, could patients with a history of cancer undergo permanent changes in myeloid cell production? If so, could this contribute to their increased risk of developing seemingly unrelated cancers or other chronic inflammatory conditions? We and others have observed a decrease in circulating monocytes with age, which is consistent with alterations in myelopoiesis. Of note, preclinical studies in mice have found that the number of MDSCs decreases along with therapy and at remission. Thus, although the subjects of our study were currently in remission, elevated levels of MDSCs might actually suggest that these individuals are at risk for disease recurrence. Longitudinal studies are required to test these hypotheses.

Irrespective of the possible link between a lifetime history of cancer and elevated levels of MDSCs, the observation that MDSCs accumulate with age is important. For example, in addition

to their well-described ability to reduce T-cell responses, MDSCs have been demonstrated to impair the efficiency of dendritic cell-based immunotherapies.⁹ With a few exceptions,¹⁰ preclinical experiments on anticancer therapy employ young mice (6–8 wk of age in mice is probably the equivalent to 14–18 y in humans), and hence are intrinsically unsuitable to take into account changes of the aging microenvironment that will have to be overcome for these treatments to be effective in the patient population for which they are primarily intended. In addition, it is well known that age, which is often considered to be a chronic inflammatory condition, is a risk factor for additional chronic inflammatory conditions such as cancer, and that individuals with more than one chronic inflammatory condition are at increased risk for developing others. The mechanisms behind these associations are beginning to be understood, but age-associated changes in MDSCs may be

a critical component to the inflammatory and immunosuppressive microenvironment that occurs with age.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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