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Expanding the List of Dysregulated Immunosuppressive Cells in Psoriasis

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Traditionally, myeloid-derived suppressor cells (MDSC) have been studied in regard to their increased numbers of circulating cells in cancer patients. Recent research efforts have also increased awareness of MDSC in non-malignant inflammatory diseases, including asthma, inflammatory bowel disease, and arthritis. Psoriasis can now be added to the growing list of inflammatory disorders with an MDSC component. Cao et al. report increased numbers of monocytic myeloid-derived suppressor cells (Mo-MDSC) in psoriasis patients and examine the implication of dysregulated Mo-MDSC function. Cao et al. describe psoriatic Mo-MDSC that produce increased IL-23, IL-1b, and CCL4 cytokines compared to Mo-MDSC from healthy controls. These results complement previous research demonstrating psoriatic Mo-MDSC are unable to suppress autologous and heterologous CD8 T-cell proliferations, display decreased expression levels of PD-1 as well as PD-L1, and fail to produce effective immuno-competent regulatory T cells (Tregs). Cao et al. also identify the unique expression of the surface protein DC-HIL on psoriatic Mo-MDSC. The expanded population of DC-HIL$^+$ Mo-MDSC in psoriasis patients, however, display inferior suppressive capabilities compared to DC-HIL$^+$ Mo-MDSC found in melanoma patients, suggesting contextual signaling as a potential contributing factor to Mo-MDSC function.

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Myeloid-derived suppressor cells (MDSCs) have been studied with respect to their increased numbers in patients with cancer. Recent research efforts have also led to an awareness of MDSCs in nonmalignant inflammatory diseases, including asthma, inflammatory bowel disease, and arthritis. Psoriasis can now be added to this growing list of inflammatory disorders recognized as having an MDSC component. Cao et al. (2016) report increased numbers of monocytic MDSCs (Mo-MDSC) in patients with psoriasis, and they examine the implications of dysregulated Mo-MDSC function. They have described psoriatic Mo-MDSCs that produce increased amounts of IL-23, IL-1β, and C-C motif chemokine ligand 4 (CCL4) cytokines compared with Mo-MDSC from healthy control subjects. These results complement previous research (Soler et al., 2016) showing that psoriatic Mo-MDSCs are unable to suppress autologous and heterologous CD8 T-cell proliferation, that they display decreased expression levels of programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1), and that they fail to produce effective immunocompetent regulatory T cells. Cao et al. also report unique expression of the surface protein dendritic cell-associated heparan sulfate proteoglycan-dependent integrin ligand on psoriatic Mo-MDSCs. The expanded population of DC-HIL$^+$ Mo-MDSCs in patients with psoriasis, however, displays inferior suppressive capabilities compared with DC-HIL$^+$ Mo-MDSCs found in melanoma patients, suggesting contextual signaling as a potential contributing factor to Mo-MDSC function.

Psoriasis is a common immune-mediated inflammatory skin disease affecting 2–3% of the North American population. A growing consensus of basic and applied research points toward a major role for chronic activation of T cells as the major factor sustaining the disease over time. Thanks to intensive research efforts and key scientific breakthroughs over the last several years, it has been possible to identify rather precisely how the disease might be initiated (Nestle et al., 2005) and sustained (Cheuk et al., 2014; Clark, 2015). The identification of T-helper 17 cells, in particular, as the main effector cells in sustaining the disease has created an unprecedented expansion of biologic treatments specifically targeting IL-17, with promising clinical results (Langley et al., 2014). However, limited effort has been directed toward understanding the dysregulated immunosuppressive side of this disease, such as the immune mechanisms that fail to control effector cell expansion and execute its remission in the first place (Sugiyama et al., 2005). In this respect, our recent work (Soler et al., 2016) and that of Cao et al. (2016) has attempted to address this undercharacterized area of immunologic responses in psoriasis.

In two independent sets of scientific experiments, our data and that of Cao et al. (2016) have reached similar conclusions, indicating that there are increased numbers of circulating MDSCs in patients with psoriasis. Conventionally, MDSCs have been studied with respect to their increased numbers in patients with cancer (Talmadge and Gabrilovich, 2013). Recently, however, a growing body of evidence points to a major role for MDSCs in nonmalignant inflammatory diseases, including asthma, inflammatory bowel disease, and arthritis (Fujii et al., 2013; Ostanin and Bhattacharya, 2013; Zhang et al., 2013). Human MDSCs are currently characterized as two distinct cell types: granulocytic (G-MDSC) or monocytic (Mo-MDSC), based on expression of CD14 (negative or positive, respectively)

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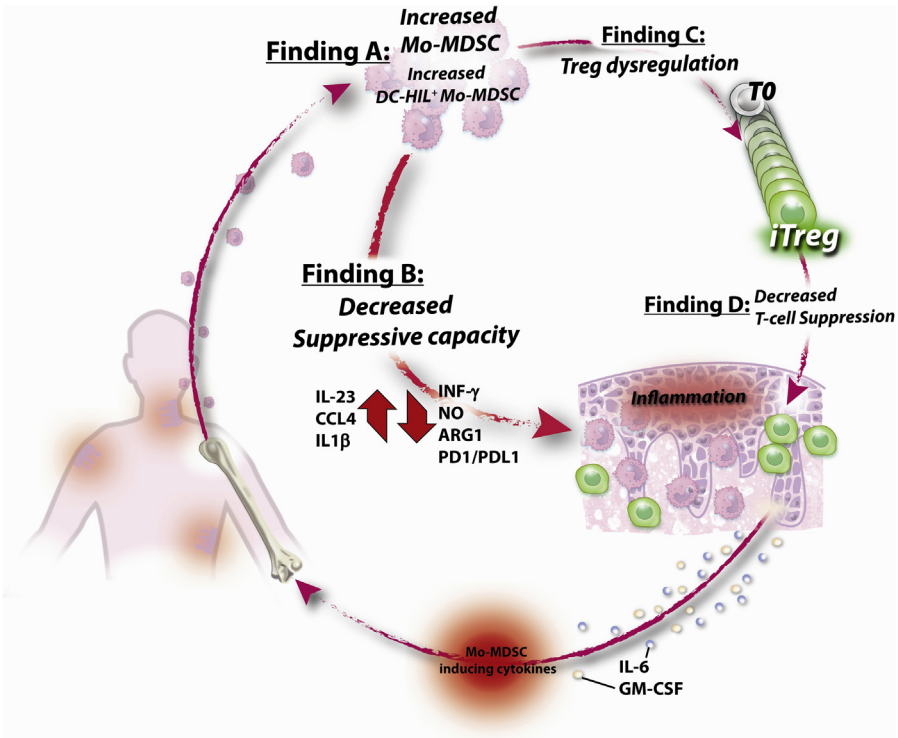

Figure 1. Dysregulated immunosuppressive loop in psoriasis. Mo-MDSCs are increased in the peripheral blood of patients with psoriasis; despite increased numbers of Mo-MDSCs, a decrease in their suppressive capacity is reported. Several Mo-MDSC suppressive mechanisms appear to be affected, that is, reduced induction of INF-γ in co-culture with T cells and reduced secretion of nitric oxide, arginase 1, and expression of PD1/PDL1 on Mo-MDSCs. In addition, psoriatic Mo-MDSCs lack the ability to induce competent Tregs. Stimulatory cytokines IL-6 and GM-CSF, known to promote Mo-MDSC expansion, are also shown. Illustrated by David C. Soler. ARG-1, arginase 1; CCL4, C-C motif chemokine ligand 4; DC-HIL, dendritic cell-associated heparan sulfate proteoglycan-dependent integrin ligand; iTreg, immunocompetent regulatory T cells; GM-SCF, granulocyte-macrophage colony-stimulating factor; Mo-MDSC, monocytic myeloid-derived suppressor cells; NO, nitric oxide; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; T0, naive T helper; Treg, regulatory T cell.

with comarkers, including $CD15^+$, $CD33^+$, $CD11b^+$, DC-HIL^+, and lack of expression of $HLA\text{-}DR^{(neg)}$. The reported increase in circulating Mo-MDSCs in cancer has been hypothesized to occur because of decreased differentiation of immature myeloid cells after release from the bone marrow (Talmadge and Gabrilovich, 2013). The current work of Cao et al. focused on the expansion of Mo-MDSCs in psoriasis, although Ariizumi and colleagues (Turrentine et al., 2014) have previously enumerated these cells in patients with melanoma (Chung et al., 2014). In patients with cancer, once the MDSC numbers increase in peripheral blood, the MDSCs are thought to accumulate at local tumor sites, where they provide an immunosuppressive milieu (e.g., increased arginase 1 and inducible nitric oxide synthase [iNOS]), which then inhibits effective immune response and permits growth of the tumor (Talmadge and Gabrilovich, 2013). The presence of MDSCs is generally regarded as a bad prognostic sign in cancer (Wu et al., 2015).

Focusing specifically on the Mo-MDSC subtype of MDSCs in psoriasis, both Cao et al. (2016) and Soler et al. (2016) have described an increase in Mo-MDSCs in the peripheral blood of patients with psoriasis (Figure 1, Finding A). To address this counterintuitive initial finding—increased immunosuppressive cells, yet sustained chronic inflammation—Cao et al. examined the function of psoriatic Mo-MDSCs, and they have reported a decrease in nitric oxide and arginase (ARG-1) production in the psoriatic Mo-MDSC, whereas co-cultured T cells secrete lower amounts of INF-γ (Figure 1, Finding B). Cao et al. described psoriatic Mo-MDSCs that produce increased amounts of IL-23, IL-1β, and CCL4 cytokines compared with Mo-MDSCs from healthy control subjects. These results complement those of Soler et al., which show psoriatic Mo-MDSCs to be unable to suppress autologous and heterologous CD8 T-cell proliferation, to display decreased expression levels of PD-1 and PD-L1, and to fail to produce effective immunocompetent regulatory T cells (Figure 1, Findings C and D). Cao et al. also identified unique expression of surface protein DC-HIL on psoriatic Mo-MDSCs. The expanded population of DC-HIL^+ Mo-MDSCs in psoriasis patients (Figure 1, Finding A), however, displays lower suppressive capabilities compared with DC-HIL^+ Mo-MDSCs found in melanoma patients, suggesting contextual signaling as a potential contributing factor to MDSC function. Finally, both reports identify Mo-MDSCs in psoriatic skin, although whether they are increased or decreased in number in skin has not been addressed conclusively.

These results introduce an additional myeloid cell type potentially regulating immune responses in psoriasis. Given the known ability of MDSCs to differentiate further into dendritic cells, macrophages, and neutrophils, the increase found in psoriasis opens several new avenues of research. Can second-generation biologics be developed that target MDSCs in psoriasis? Would it be possible to reverse psoriatic MDSC—T-cell immunosuppressive relationships and restore the balance of suppressor-to-effector cell ratios in psoriasis? Elucidation of these questions may inform the development of next-generation cellular targets in treating psoriasis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Mechanisms of Melanoma Promotion by Ultraviolet Radiation

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The mutagenic properties of ultraviolet radiation drive the initiation of melanoma. Induction of matrix metalloproteinases in melanoma cells by long-wave UVA radiation, possibly via a Warburg-like effect, promotes melanoma invasiveness. This is one of several mechanisms by which ultraviolet radiation also promotes further growth of previously established melanomas.

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In 1924, Otto Warburg observed that most cancer cells have higher glucose uptake than their normal counterparts (Otto, 2016). With only a small fraction of this glucose being used for oxidative phosphorylation in mitochondria, cancer cells rely on cytoplasmic high-rate anaerobic glycolysis for energy, with production of lactic acid, even when oxygen tensions are high. Today, this observation carries his name (the *Warburg effect*), and it has entered routine clinical application in positron emission tomography, where the increased glucose uptake by cancer cells is used for clinical tumor imaging. Although Warburg thought that the high-rate glycolysis in cancer cells would be the cause of cancer, today these metabolic changes are mostly considered secondary to other cellular changes occurring during malignant transformation. Several possible explanations have been put forward to explain this profound alteration of cellular energy metabolism in cancer and how it may help cancer cells to survive and thrive, including, for example, adaptation to low-oxygen environments, prevention of mitochondria-derived apoptotic signals, provision of glycolysis-derived metabolites as critical components for rapid cell proliferation, among others (Asgari et al., 2015).

Kamenisch et al. (2016) describe effects of longwave ultraviolet radiation (UVA) on the metabolism of several different melanoma cell lines, effects that are consistent with an accentuation of the Warburg effect. Because they did not study metabolism in normal melanocytes, it remains uncertain how much the melanoma cells they studied already had Warburg effect-like metabolism at baseline. Nevertheless, after repetitive exposures to low doses of UVA, they observed increased glycolysis and lactate production. These effects are, in part, mediated by UVA-induced oxidative stress and reactive oxygen species (ROS), because they were at least to some degree abrogated in the presence of Trolox (Sigma Aldrich, Germany), an analog of vitamin E and a quencher of ROS. These effects were also not reversible immediately after cessation of UVA exposure but, rather, persisted for at least 5 days after the last exposure.

It would be interesting to know whether exposure to shortwave ultraviolet radiation (i.e., UVB) had a similar effect on melanoma cells. Given that UVB induces much less oxidative stress than UVA, it is conceivable that the induction of high-glycolysis metabolism is a unique effect of UVA. However, because ROS quenching only partially abrogated the UVA effects, other mechanisms may be at play as well and, thus, also activated by UVB.

The reported metabolic changes per se do not render melanoma cells more dangerous. However, Kamenisch et al. (2016) have shown that the UVA-induced, Warburg effect-like changes in melanoma cell metabolism are associated with an up-regulation of several matrix metalloproteinases (MMPs) and increased invasiveness. Because these effects could also be elicited by lactic acid alone, they concluded that the UVA-induced metabolic changes with increased lactic acid promotes melanoma invasion.

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