Myeloid-Derived Suppressor Cells in Psoriasis Are an Expanded Population Exhibiting Diverse T-Cell–Suppressor Mechanisms

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Psoriasis vulgaris is an inflammatory skin disease caused by hyperactivated T cells regulated by positive and negative mechanisms; although the former have been much studied, the latter have not. We studied the regulatory mechanism mediated by myeloid-derived suppressor cells (MDSCs) and showed that MDSCs expanded in melanoma patients express dendritic cell-associated heparan sulfate proteoglycan-dependent integrin ligand, a critical mediator of T-cell suppressor function. We examined expansion of DC-HIL$^+$ MDSCs in psoriasis and characterized their functional properties. Frequency of DC-HIL$^+$ monocytic MDSCs (CD14$^+$HLA-DR$^{no/low}$) in blood and skin was markedly increased in psoriatic patients versus healthy control subjects, but there was no statistically significant relationship with disease severity (based on Psoriasis Area and Severity Index score). Blood DC-HIL$^+$ MDSC levels in untreated patients were significantly higher than in treated patients. Compared with melanoma-derived MDSCs, psoriatic MDSCs exhibited significantly reduced suppressor function and were less dependent on DC-HIL, but they were capable of inhibiting proliferation and IFN-γ and IL-17 responses of autologous T cells. Psoriatic MDSCs were functionally diverse among patients in their ability to suppress allogeneic T cells and in the use of either IL-17/arginase I or IFN-γ/inducible nitric oxide synthase axis as suppressor mechanisms. Thus, DC-HIL$^+$ MDSCs are expanded in psoriasis patients, and their mechanistic heterogeneity and relative functional deficiency may contribute to the development of psoriasis.

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INTRODUCTION

Psoriasis is a common immune-mediated, chronic inflammatory skin disease characterized by hyperproliferative keratinocytes (epidermal hyperplasia or acanthosis) and extensive infiltration of various leukocytes, including T cells, dendritic cells, macrophages, and neutrophils (Rivas Bejarano and Valdecantos, 2013). Among these leukocytes, T cells play a central role in development of these characteristic clinical features. In particular, hyperactivated T helper (Th) 1 and Th17 responses are frequently observed in the blood and skin of psoriasis patients and have been considered to be responsible for psoriatic dermatitis (Di Cesare et al., 2009; Lowes et al., 2014; Ma et al., 2008). However, the pathogenesis of psoriasis still remains ambiguous, particularly regarding mechanisms leading to persistence of T-cell hyperactivation.

T-cell activation is regulated by competing positive and negative co-regulatory signals delivered through interaction of co-regulatory receptors (expressed on T cells) and their ligands (on antigen-presenting cells and nonlymphoid cells) (Wang and Chen, 2004). The positive regulators (or co-stimulators) include CD28:CD80/CD86, CD40:CD40L, and OX40:OX40L paring receptors (Briones et al., 2011; Chatzigeorgiou et al., 2009; Ishii et al., 2010); the negative regulators (or co-inhibitors) include CTLA-4:CD80/CD86 and PD-1:PD-L1/PD-L2 (Egen et al., 2002; Francisco et al., 2010). In psoriatic patients, expression of co-stimulators is elevated significantly in hyperactivated T cells and other leukocytes compared with healthy control subjects (Ferenczi et al., 2000; Niu et al., 2015). Treatment of psoriatic patients or psoriatic skin grafts in severe combined immunodeficiency mice with co-stimulator–specific inhibitors (antibodies or chemicals) reduces acanthosis and lymphocyte skin infiltrates (Abrams et al., 1999; Raychaudhuri et al., 2008), indicating that the co-stimulators are critically involved in the development of psoriatic skin. Although T-cell hyperactivation is considered to be also due to dysregulated expression of or deficiency in the function of co-inhibitors, little is known about their contribution to pathogenesis.

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Abbreviations: HLA-DR, HLA-antigen D related; MDSC, myeloid-derived suppressor cell; NO, nitric oxide; PASI, Psoriasis Area and Severity Index; PBMC, peripheral blood mononuclear cell; SD-4, syndecan-4; Th, T helper; Treg, regulatory T cell

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Myeloid-derived suppressor cells (MDSCs) were originally identified by the $CD11b^{+}Gr1^{+}$ phenotype in tumor-bearing mice (Serafini et al., 2006), but in humans different surface markers are used, for example, $CD14^{+}HLA\text{-}DR^{no/low}$ and other phenotypes (Filipazzi et al., 2007), because of a lack of the Gr1 gene homologue. In healthy individuals, MDSCs consist of myeloid progenitors that differentiate into dendritic cells, granulocytes, and macrophages, so that MDSCs are a critical component in replenishing potent immune systems (Gabrilovich and Nagaraj, 2009). In healthy individuals, MDSCs are weakly immunosuppressive. By contrast, in cancer patients, MDSCs fail to differentiate, thereby proliferating and mobilizing from bone marrow to other organs, where they exert potent T-cell suppression (Frey, 2006; Youn and Gabrilovich, 2010). Recently, it was reported that expanded MDSC populations with suppressor function are also associated with inflammatory disorders, including alopecia areata (Marhaba et al., 2007; Singh et al., 2011), arthritis (Fujii et al., 2013), and infectious diseases such as mycobacterial infections (du Plessis et al., 2013), but their exact role in these conditions has been debated (Cripps and Gorham, 2011; Cuenca et al., 2011).

We discovered a co-inhibitory pathway comprising the DC-HIL receptor on inflammatory antigen-presenting cells and its paired receptor syndecan-4 (SD-4) on effector/memory T cells (Chung, Dougherty, et al., 2007a; Chung, Sato, et al., 2007b). Using mouse models, we showed the DC-HIL/SD-4 pathway to be a potent regulator of T cell-mediated immune responses in contact hypersensitivity, graft-versus-host disease, experimental autoimmune encephalomyelitis, and melanoma (Chung, Tamura, Cruz, et al., 2014; Chung et al., 2013). Recently, we found that an expanded MDSC population in melanoma patients expressed DC-HIL, and this expression positively correlated with melanoma stage progression; DC-HIL is a critical mediator of MDSC suppressor function (Turrentine et al., 2014). Thus, DC-HIL may serve as a marker of the immunosuppressive capacity of MDSCs.

To explore the possible contributions of MDSC-mediated suppression to psoriasis development, we examined the expansion of $DC\text{-}HIL^{+}$ MDSCs in psoriatic patients, its correlation with disease severity, and its functional properties. Data were interpreted compared with those of MDSCs from melanoma patients and healthy control subjects. Although exhibiting some similarities with their melanoma counterparts, psoriatic MDSCs had a reduced ability to suppress activation of autologous T cells and exhibited heterogeneous suppressive mechanisms among patients. Their functional deficiency and mechanistic diversity indicate an array of impaired immunosuppression that may contribute to the autoreactivity in chronic psoriasis patients.

RESULTS

Psoriasis induces expansion of $DC\text{-}HIL^{+}$ monocytic MDSCs

Because some inflammatory diseases can induce MDSC expansion as strongly as in cancer patients and because immunosuppressive MDSCs induced in melanoma patients express DC-HIL, we examined expansion of MDSCs and their DC-HIL expression in the blood of psoriatic patients versus that of healthy control subjects. We recruited patients (n = 49) and age-/sex-matched healthy donors (n = 21); demographics are summarized in Table 1. At the time of blood draw, 19 patients were untreated, and 30 were treated with various regimens (topical steroids, topical vitamin D analogues, topical calcineurin inhibitors, and/or narrow-band UVB). Blood samples were assayed by flow cytometry for frequency (%) of $CD14^{+}HLA\text{-}DR^{no/low}$ monocytic MDSCs, total peripheral blood mononuclear cells (PBMCs), and DC-HIL expression on the MDSCs (Figure 1a). These MDSCs were also $CD15^{neg}CD33^{+}CD11b^{+}$ (see Supplementary Figure S1 online). MDSC levels were significantly elevated in psoriatic patients, albeit with considerably high variation, compared with heathy control subjects (median = 6.1%, range = 0.2−11.7% vs. median = 0.4%, range = 0.1−2.7%, respectively; $P < 0.0001$) (Figure 1b). Although MDSCs in healthy control subjects expressed DC-HIL at 8.8% (range = 1−26%, mean fluorescence intensity = 5.7 ± 5.38), most psoriatic MDSCs expressed DC-HIL (median = 81.5%, range = 2.8−100%, mean fluorescence intensity = 81 ± 93; $P < 0.0001$) (Figure 1c). Using these data, we calculated the percentage of $DC\text{-}HIL^{+}$ MDSCs in total PBMCs and found the population to be expanded significantly in psoriatic blood (median = 4.2%, range = 0−11% vs. median = 0.1%, range = 0.01−0.27%, respectively; $P < 0.0001$, Figure 1d). This level was higher than in metastatic melanoma patients (mean ± standard deviation = 2.6% ± 0.6%) (Turrentine et al., 2014). The T-cell ligand SD-4 of DC-HIL was also up-regulated in $CD4^{+}$ and $CD8^{+}$ T cells of psoriatic patients (see Supplementary Figure S2 online). Thus, $DC\text{-}HIL^{+}$ monocytic MDSCs were markedly proliferated in the blood of psoriatic patients.

Table 1. Demographics of psoriasis patients and healthy control subjects

Characteristic	Psoriasis Patients	Healthy Control Subjects
Number of analyzed patients	49	21
Age in years, mean ± SD	52 ± 12	53 ± 13
Sex, n	22 men, 27 women	11 men, 10 women
Race/ethnicity, n	21 white, 16 Hispanic, 7 Asian, 3 Middle Eastern, 2 African American	11 white, 2 Hispanic, 8 Asian
Treatments, n (%)[1]		N/A
None	19 (39)	
Topical steroids	29 (90)	
Topical vitamin D analogue	6 (18)	
Topical calcineurin inhibitors	3 (9)	
NBUVB	12 (37)	
Psoriasis type, n (%)		N/A
Plaque	49 (100)[2]	
PASI score, median (range)	6.1 (0.4−45)	N/A

Abbreviations: N/A, not applicable; NBUVB, narrow-band UVB light therapy; PASI, Psoriasis Area and Severity Index.
[1]Some patients were treated with multiple therapies.
[2]One patient (out of 49) had concurrent palmoplantar psoriasis.