Levels of Blood CD1c⁺ mDC1 and CD1c^{hi} mDC1 Subpopulation Reflect Disease Activity in Noninfectious Uveitis

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PURPOSE. Myeloid dendritic cells (mDCs) play an important role in autoimmune diseases. However, the role of blood CD1c⁺ myeloid dendritic cells 1 (mDC1s), the subset of human blood mDCs, is not well understood in noninfectious uveitis.

METHODS. Fresh peripheral blood samples from human noninfectious uveitis patients ($n = 32$) and healthy controls (HCs) ($n = 64$) were stained with FITC-Lineage 1 (Lin1), PERCP-HLADR, and PE-CD1c antibodies. The levels of mDC1 were quantified by using flow cytometric analysis. Longitudinal data from patients ($n = 16$) were analyzed to correlate the levels of mDC1 with disease activity.

RESULTS. Blood CD1c⁺ mDC1 and its subpopulation, CD1c^{hi} mDC1, were increased in uveitis patients compared with HCs. Longitudinal data demonstrated that both the CD1c⁺ mDC1 and CD1c^{hi} mDC1 subpopulation reflected a dynamic change in clinical uveitis activity: CD1c expression was increased in active uveitis but decreased when uveitis became inactive.

CONCLUSIONS. Given these observations, an alteration in blood CD1c⁺ mDC1 and the CD1c^{hi} mDC1 subpopulation could be a potential biomarker to monitor clinical uveitis activity within patients.

Keywords: CD1c⁺ mDC1, CD1c^{hi} mDC1 subpopulation, noninfectious uveitis, autoimmune disease

Dendritic cells (DCs) present antigens to T cells, thereby initiating adaptive immune responses to prevent the pathogen invading.¹ However, DCs also respond to self-antigens and present them to T cells, thereby inducing autoimmune diseases.^{2–4} Animal studies have demonstrated that injection of DCs pulsed with specific antigens induce autoimmune diseases, such as experimental autoimmune uveitis (EAU),⁵ experimental autoimmune myocarditis (EAM),⁶ experimental autoimmune encephalomyelitis.⁷ In addition, to initiate immune and autoimmune responses, DCs are also able to maintain immune tolerance. Tolerogenic DCs, generated by using short interfering RNA to knockdown the expression of co-stimulatory molecules on DCs, have been found to attenuate autoimmune arthritis.⁸ Similarly, DCs transfected with herpesvirus entry mediator are protected against EAM by the production of IL-10 from DCs.⁹

In humans, CD1c⁺ myeloid DC1 (mDC1), CD141⁺ mDC2, and CD303⁺ plasmacytoid DCs have been classified.^{10–12} The CD1c⁺ mDC1 is the major DC population among three types regarding their proportions. In peripheral blood, CD1c⁺ mDC1 produces a large amount of IL-10 and regulatory molecules indoleamine 2,3-dioxygenase in response to *Escherichia coli*, whereas CD141⁺ mDC2 fails to secrete cytokines.¹³ In intestinal lamina propria, CD1c⁺ mDC1 shows an activated phenotype at steady state compared with those from peripheral blood.¹⁴ However, CD1c⁺ mDC1 in noninfectious uveitis has not been reported.

Noninfectious uveitis (abbreviated here as uveitis) refers to a group of diseases characterized by intraocular inflammation. Increasing evidence supports the hypothesis that DCs play an important role in uveitis.^{15,16} Herein, we observed that the levels of blood CD1c⁺ mDC1 and its subpopulation CD1c^{hi} mDC1 were increased in uveitis patients. Longitudinal data showed the positive correlation between CD1c expression level on mDC1 and disease activity.

MATERIALS AND METHODS

Study Population

Peripheral blood was obtained from patients with noninfectious uveitis ($n = 32$) attending the National Eye Institute, and from age- and sex-matched healthy controls (HCs) ($n = 64$) from the Blood Bank of the National Institutes of Health (NIH). The research followed the tenets of the Declaration of Helsinki. All protocols were approved by the NIH Institutional Review Board. Informed consent was obtained from all subjects before the study commenced. Disease activity recorded at each visit was categorized as “active,” “slightly active,” or “inactive.” This classification scheme was developed for reporting Systemic Immunosuppressive Therapy for Eye Diseases study results and was adopted to allow the investigator to assess activity based on multiple clinical

TABLE 1. Characteristics of Uveitis Patients and HCs

Parameter	Uveitis, <i>n</i> = 32	HCs, <i>n</i> = 64
Age, y, median (range)	45 (12–70)	48 (19–76)
Sex, <i>n</i> (%)		
Male	9 (28)	16 (25)
Female	23 (72)	48 (75)
Race, <i>n</i> (%)		
Caucasian	12 (38)	27 (42)
African American	10 (31)	20 (31)
Other	10 (31)	17 (27)
Anatomic type of uveitis, <i>n</i> (%)		NA
Anterior	4 (13)	
Intermediate	5 (16)	
Posterior	7 (21)	
Panuveitis	16 (50)	
Disease association, <i>n</i> (%)		NA
Sarcoidosis	11 (34)	
Idiopathic	9 (28)	
Birdshot chorioretinopathy	5 (16)	
Vogt-Koyanagi-Harada disease	4 (13)	
Behçet's disease	2 (6)	
Serpiginous choroidopathy	1 (3)	
Systemic immunosuppressive therapy, <i>n</i> (%)	25 (78)	NA
Active uveitis at time of sample, <i>n</i> (%)	9 (28)	NA

markers, beyond the Standardization of Uveitis Nomenclature criteria.^{17,18}

For example, the presence or absence of macula edema on optical coherence tomography (OCT) scanning may lead the reporting physician to describe the patient as active or quiet. If terms such as “active” were used in the medical record on the day blood was drawn for this study, then the patient was classified as “active”; if terms such as “quiet” were used, the patient was classified as “inactive.” The third category of “slightly active” could include patients with descriptions such as “trace cells” or “mild activity” or minor OCT cystic changes in the macula. The baseline demographic characteristics of patients and HCs are summarized in Table 1.

By examining blood DCs, we are interrogating the whole body's immune system; thus, we were concerned about systemic immunosuppressive therapy primarily and did not consider topical, local therapies. The presence or absence of systemic immunosuppressive therapy was thus documented; this could include corticosteroids, secondary immunomodulatory therapy, and biologic response modifiers.

Identification of CD1c⁺ mDC1 in Human Peripheral Blood

Blood CD1c⁺ mDC1s were identified by four-color staining performed on 200 μ L whole fresh peripheral blood using the following monoclonal antibodies: PE-CD1c (Miltenyi Biotec, Auburn, CA, USA); PERCP-HLADR (Miltenyi Biotec); and FITC-labeled mAbs against lineage markers CD3, CD14, CD16, CD19, CD20, and CD56 (BD Biosciences, San Jose, CA, USA). Cells that were not labeled with these lineage markers were designated as lineage 1 negative (Lin1[−]). Lineage 1-negative HLADR⁺ cells were total DCs and mDC1s were defined as Lin1[−]HLADR⁺CD1c⁺. Cells were measured on a FACSCalibur (BD Biosciences, Franklin Lakes, NJ, USA) and analyzed by FlowJo (Tree Star, Ashland, OR, USA).

Statistical Analysis

Data are presented as mean $\pm$ SD. The unpaired Student's *t*-test was used between uveitis and HC groups and paired Student's *t*-test was used for longitudinal data; *P* < 0.05 was considered significant. Analyses were accomplished using Prism 6 software (GraphPad Software, Inc., La Jolla, CA, USA).

RESULTS

The CD1c⁺ mDC1 Population Was Increased in Uveitis Patients

The percentage of CD1c⁺ mDC1 (of the total DC population) in uveitis was increased compared with that in HCs (*P* < 0.0025, Figs. 1A–F). The uveitis patient population included patients with ocular and systemic diseases, both active and quiescent disease and patients receiving systemic immunosuppression, as detailed in Table 1. To elucidate the effect of immunosuppressive treatment on the levels of CD1c⁺ mDC1, patients were divided into untreated and treated groups, and the analysis showed that treatment did not alter the levels of mDC1 significantly (Fig. 1G).

The CD1c^{hi} mDC1 Subpopulation Was Increased in Uveitis Patients and Displayed a Mature Phenotype

The CD1c⁺ mDC1 subpopulation was grouped into CD1c^{hi} and CD1c^{lo} subpopulations based on their expression of CD1c. The CD1c^{hi} mDC1 subpopulation was increased in uveitis patients (*P* = 0.001, Figs. 2A, 2B) and the CD1c^{lo} mDC1 was decreased accordingly (data not shown). The HLADR is expressed on human mDCs and an important marker for DC maturation through its role initiating T-cell responses.¹⁹ We found HLADR expression was higher in the CD1c^{hi} mDC1 subpopulation compared with that in CD1c^{lo} mDC1 subpopulation (*P* = 0.0002, Fig. 2C). These data indicate that the increased CD1c^{hi} mDC1 subpopulation in uveitis patients exhibits a mature phenotype and has the capability to present more antigens to T cells, suggesting they are more pathogenic.

Increased CD1c⁺ mDC1 Reflected Uveitis Clinical Activity in Longitudinal Data

A total of 16 uveitis patients (ID: Pt1–Pt16) were enrolled in the longitudinal study. Table 2 shows details of the underlying diagnosis, clinical activity at the different time points, and whether the patients had a recent increase in systemic immunosuppression. Eleven uveitis patients (Pt1–Pt11) had blood samples taken at two different time points when their disease was classified as “active,” “slightly active,” or “inactive” uveitis, as described in the Methods section above. We found that 8 of 11 patients (except Pt1, Pt2, and Pt9) had an increased CD1c⁺ mDC1 population, at time points when their uveitis was classified as active or slightly active, compared with the population with inactive uveitis (Table 3). As negative controls, 10 blood samples at two different time points from five patients with sustained inactive disease status were measured (Pt12–Pt16). Statistical analysis showed that the levels of CD1c⁺ mDC1 did not significantly change at two time points in inactive patients (Table 4, *P* = 0.8). Figure 3C shows representative data from patient Pt3, who had high levels of CD1c⁺ mDC1 during active uveitis and low levels of CD1c⁺ mDC1 while inactive.

The three patients whose data deviated from this observational trend included patient Pt1, Pt2, and Pt9.

FIGURE 1. The CD1c⁺ mDC1 was increased in uveitis. (A) Total live cells were gated based on forward scatter (FSC) and side scatter (SSC) in *dot plot figures* of flow cytometry. (B) Total DCs were gated by their negative expression of Lin1 and positive expression of HLADR (Lin1⁻HLADR⁺). (C) Isotype control for CD1c is shown. (D, E) The proportion of blood CD1c⁺ mDC1 was analyzed in HCs and uveitis patients by flow cytometry. (F) Statistical analysis shows increased CD1c⁺ mDC1 in uveitis patients compared with HCs ($P < 0.0025$). (G) The levels of mDC1 were evaluated between untreated and treated groups ($P = 0.56$).

Patients 2 and 9 had similar levels of CD1c expression at both time points, this could be because the patients were described as slightly active at the first time point compared with inactive at the second. Patient 1's sample when inactive had a higher content of CD1c⁺ mDC1 than in the sample obtained during a period of activity; however, as detailed later, the CD1c^{hi} subpopulation followed the expected trend (Table 3).

Increased CD1c^{hi} mDC1 Subpopulation Was Correlated With Uveitis Activity in Longitudinal Data

In light of the observed increase in CD1c⁺ mDC1 in active patient samples, we further investigated specifically whether the CD1c^{hi} mDC1 subpopulation level mirrors this dynamic change in disease activity as well. Consistent with the shift in

CD1c⁺ mDC1 levels, the longitudinal data from 10 of 11 patients (Pt1–Pt11) showed that the CD1c^{hi} mDC1 subpopulation was increased in active uveitis and decreased in inactive uveitis (see Table 3). When the blood samples were drawn from uveitis patients (Pt12–Pt16) who kept inactive at both time points, the levels of CD1c^{hi} mDC1 were not significantly different. Figure 3D shows representative data from Pt3 with active and inactive uveitis at two time points.

DISCUSSION

We set out to investigate the proportion of human blood CD1c⁺ mDC1 in noninfectious uveitis patients to further elucidate the significance of DCs. The CD1c⁺ mDC1s are increased in uveitis patients compared with HCs. Within CD1c⁺ mDC1, the CD1c^{hi} mDC1 subpopulation is further increased in patients, also expressing higher HLADR compared

FIGURE 2. The CD1c^{hi} mDC1 subpopulation was increased in uveitis patients. (A) The representative *dot plot* figures show the CD1c^{hi} mDC1 subpopulation derived by the expression level of CD1c on the gate of CD1c⁺ mDC1 population in uveitis patients and HCs. (B) The statistical data analysis show that the CD1c^{hi} mDC1 subpopulation was increased in uveitis patients compared with HCs ($P = 0.001$). (C) Expression of HLADR was higher on the CD1c^{hi} mDC1 subpopulation than that on the CD1c^{lo} mDC1 subpopulation ($P = 0.0002$).

with the complementary subpopulation of CD1c^{lo} mDC1. Interestingly, the proportions of CD1c⁺ mDC1 and the CD1c^{hi} mDC1 subpopulation appear to reflect disease activity in uveitis patients throughout the longitudinal data.

Noninfectious uveitis has an unclear etiology, with multiple different systemic and ocular diseases producing similar end-point inflammatory activity.¹⁷ Managing uveitis clinically is challenging, with patients often requiring multiple medications with extensive side-effect profiles for long periods. Once clinical activity is controlled, the dose of medications, such as corticosteroids, will be tapered over time, leading to the risk of uveitis recurrence. It is vital to identify uveitis recurrence quickly, ideally before the patient is symptomatic, something current laboratory biomarkers cannot achieve.

Several animal studies have shown that the DCs found in the EAU model display a mature phenotype, and depletion of DCs causes decreased activation of IL-17⁺ interphotoreceptor retinoid binding protein-specific T cells.²⁰ In humans, a previous study has shown that CD11c⁺ mDCs are increased in the peripheral blood of uveitis patients compared with healthy donors.²¹ In our data, the proportion of CD1c⁺ mDC1 cells was increased in the blood of uveitis patients. Our findings support the idea that the alteration of blood DCs reflects the disease activity in uveitis, suggesting the measurement of DCs could be a useful biomarker both for the presence of an autoimmune disease and also the level of activity.

We have identified two subpopulations of CD1c⁺ mDC1, classified as CD1c^{hi} and CD1c^{lo} mDC1 subpopulations based on their expression levels of CD1c. However, no study has yet to demonstrate their function and proportional change within autoimmune uveitis and other autoimmune diseases. From our study, CD1c^{hi} mDC1s are significantly increased in uveitis patients compared with healthy donors. Using flow cytometry, the CD1c^{hi} mDC1 subpopulation exhibits higher HLADR expression compared with the CD1c^{lo} mDC1 subpopulation. The HLADR is a marker for DC maturation, given that the function of HLADR is to present antigens to T cells to stimulate T-cell immune responses.¹⁹ The suggested hypothesis is that autoimmune uveitis patients have an increased CD1c^{hi} mDC1 subpopulation; these are additional maturation marker for DCs. A previous study has demonstrated the activation of CD1c⁺ mDC1 in rheumatoid arthritis,²² supporting our idea that CD1c⁺ mDC1 is activated in autoimmune diseases.

A limitation of this study is the low patient numbers for which we have longitudinal data. More samples are required to make further, robust conclusions, and to calculate the specificity and sensitivity of this method. Additional exploration to characterize the mechanism and function of CD1c⁺ mDC1 is also required for our ongoing study.

In conclusion, we have identified that CD1c⁺ mDC1s and their subpopulation CD1c^{hi} mDC1 are associated with the presence of uveitis and appear to correlate with disease activity over time, raising the possibility that this could be a

TABLE 2. Clinical Characteristics of Patients Who Were Involved in the Longitudinal Study

ID	Disease Association	Time Point	Activity	Systemic Immunosuppression	Increased Immunosuppression Previous 3 Mo
Pt1	Idiopathic panuveitis	1	Active	Yes	No
		2	Inactive		
Pt2	Behçet's disease	1	Slightly active	Yes	Yes
		2	Inactive		
Pt3	Idiopathic panuveitis	1	Active	Yes	No
		2	Inactive		
Pt4	Sarcoidosis	1	Slightly active	Yes	No
		2	Inactive		
Pt5	Birdshot chorioretinopathy	1	Inactive	Yes	No
		2	Active		
Pt6	Idiopathic intermediate uveitis	1	Inactive	Yes	No
		2	Active		
Pt7	Idiopathic anterior uveitis	1	Inactive	Yes	No
		2	Slightly active		
Pt8	Birdshot chorioretinopathy	1	Slightly active	Yes	No
		2	Inactive		
Pt9	Sarcoidosis	1	Inactive	Yes	No
		2	Slightly active		
Pt10	Sarcoidosis	1	Inactive	Yes	No
		2	Slightly active		
Pt11	Birdshot chorioretinopathy	1	Inactive	Yes	No
		2	Active		
Pt12	Birdshot chorioretinopathy	1	Inactive	Yes	No
		2	Inactive		
Pt13	Sarcoidosis	1	Inactive	Yes	No
		2	Inactive		
Pt14	Birdshot chorioretinopathy	1	Inactive	Yes	No
		2	Inactive		
Pt15	Sarcoidosis	1	Inactive	Yes	No
		2	Inactive		
Pt16	Sarcoidosis	1	Inactive	Yes	No
		2	Inactive		

TABLE 3. Longitudinal Data of CD1c⁺ mDC1 and the CD1c^{hi} mDC1 Subpopulation Levels in Active and Inactive Uveitis Patients

ID	CD1c ⁺ , % of Total DCs		CD1c ^{hi} , % of CD1c ⁺ mDC1	
	Active/ Slightly Active	Inactive	Active/ Slightly Active	Inactive
Pt1	69	81	83	69
Pt2	86	86	56	40
Pt3	71	44	53	29
Pt4	69	63	57	33
Pt5	79	58	43	25
Pt6	89	21	65	55
Pt7	87	50	54	47
Pt8	87	82	56	50
Pt9	56	55	68	52
Pt10	69	57	57	62
Pt11	86	58	47	25
Mean	77	60	58	44
SD	11	19	11	15
P value	0.03*		0.0004*	

* Paired Student's *t*-test was used.**TABLE 4.** Longitudinal Data of CD1c⁺ mDC1 and the CD1c^{hi} mDC1 Subpopulation Levels in Inactive Uveitis Patients With Two Time Points

ID	CD1c ⁺ , % of total DCs		CD1c ^{hi} , % of CD1c ⁺ mDC1	
	First	Second	First	Second
Pt12	81	78	65	70
Pt13	57	63	62	33
Pt14	68	65	73	77
Pt15	77	68	43	41
Pt16	82	95	11	17
Mean	73	74	51	48
SD	11	13	25	25
P value	0.8*		0.7*	

* Paired Student's *t*-test was used.

useful biomarker in noninfectious autoimmune uveitis, even other autoimmune diseases.

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FIGURE 3. Dynamic changes in the CD1c⁺ mDC1 and the CD1c^{hi} mDC1 subpopulation in the longitudinal data of uveitis patients. The figure shows the representative Pt3 with active and inactive uveitis at two different time points. The proportions of CD1c⁺ mDC1 and the CD1c^{hi} mDC1 subpopulation demonstrated the observed correlation with disease activity. The flow cytometric analysis was first gated on live cells (A), the second gate was Lin1[−]HLADR⁺ total DCs (B), the third gate was CD1c⁺ mDC1 (C), and the fourth gate was the CD1c^{hi} mDC1 subpopulation (D).

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