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What is This?
Systemic Monocyte-Derived Dendritic Cells and Associated Th2 Skewing in Chronic Rhinosinusitis

Brendan P. O’Connell, MD¹, Rodney J. Schlosser, MD¹,², Jennifer L. Wentzel, MS¹, Whitney Nagel¹, and Jennifer K. Mulligan, PhD¹,²,³

Abstract

Introduction. Monocyte-derived dendritic cells (moDCs) are antigen-presenting cells capable of directing immune responses toward T-helper 1 (Th1) or T-helper 2 (Th2) phenotypes. The systemic profile of moDCs and their association with Th1/Th2 skewing in chronic rhinosinusitis (CRS) is unclear. The purpose of this study is to characterize circulating moDCs in controls, CRS without nasal polyps (CRSsNP), and CRS with nasal polyps (CRSwNP) and correlate moDCs with Th1/Th2 skewing, mucosal inflammation on computed tomography (CT), and quality of life (QoL).

Study Design. Cross-sectional study.

Setting. Tertiary care hospital.

Subjects. Blood was drawn from control (n = 12), CRSsNP (n = 18), and CRSwNP (n = 15) patients during endoscopic sinus surgery.

Methods. Peripheral blood moDCs were analyzed with flow cytometry for expression of HLA-DR, CD209, and CD14. Th1 and Th2 cells were identified by CXCR3 and CCR8 expression, respectively. Lund-Mackay CT scores were assigned by blinded graders. Sino-Nasal Outcome Test 22 (SNOT-22) surveys were completed by patients before surgery.

Results. CRSsNP and CRSwNP displayed elevations in systemic moDCs compared with controls. In CRSwNP, systemic Th2 skewing was observed and circulating CD4+ Th2 cells correlated with percent moDCs. MoDCs strongly correlated with higher Lund-Mackay CT scores in CRSsNP but not in CRSwNP. No relationship between moDCs and SNOT-22 scores was observed for either subset of CRS.

Conclusion. These data support that CRSwNP and CRSsNP display alterations in systemic immune profiles. CRSwNP is characterized by significant elevations in circulating moDCs, which is associated with systemic Th2-biased inflammation. Circulating moDCs are associated with mucosal inflammation on CT imaging in CRSsNP. No association between moDCs and QoL is evident in either CRS subset.

Keywords

chronic rhinosinusitis, nasal polyposis, dendritic cells, t-helper cells, Th2 inflammation

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Chronic rhinosinusitis (CRS) is a heterogeneous group of disorders characterized by inflammation of the sinus mucosa. While the etiology and pathogenesis of CRS remain controversial, recent research suggests that an abnormal host immune response to a variety of disease-modifying pathogens may underlie the chronic inflammatory state.¹ Chronic rhinosinusitis is commonly subdivided into patients with nasal polyps (CRSwNP) and those without polyps (CRSsNP) on the basis of clinical examination. CRSwNP is associated with a T-helper 2 (Th2)–biased local inflammatory infiltrate, whereas CRSsNP displays a mixed T-helper 1 (Th1) and Th2 immune phenotype.²,³ Heterogeneity exists within CRS subtypes with regard to the degree in which patients display Th1 or Th2 polarization. “Asian” polyps are primarily neutrophilic in cellular composition, while “North American or European” polyps are eosinophilic. This reinforces the notion that the immune infiltrate associated with CRSwNP is not the result of a uniform Th2 inflammatory cascade but rather is multifactorial.
and influenced by a variety of host and environmental factors.\textsuperscript{4}

Th2 airway inflammation has deleterious effects on host antimicrobial defense mechanisms. In mice, Th2 airway inflammation results in decreased bacterial clearance and suppressed levels of antimicrobial peptides.\textsuperscript{5} In humans, Th2 cytokines downregulate sinonasal epithelial cell expression of multiple antibacterial innate immunity genes in CRS\textsuperscript{wNP}.\textsuperscript{6} Th2 cytokines have also been shown to drive many of the physical symptoms commonly associated with CRS, including rhinorrhea and mucus production.\textsuperscript{7} Taken together, the local Th2 inflammatory milieu commonly associated with CRS\textsuperscript{wNP} likely contributes to the ongoing pathologic inflammation associated with this condition. It is unclear if patients with CRS\textsuperscript{wNP} display Th2-skewing systemically.

The contribution of dendritic cells (DCs) to CRS has been a focus of recent research, as they are potent antigen-presenting cells capable of initiating antigen-specific T-helper cell responses. Dendritic cells play a critical role in the polarization of immune responses toward either Th1 or Th2 bias.\textsuperscript{8} Studies have demonstrated that DCs are increased in the sinonasal mucosa of patients with CRS, supporting the notion that DCs are integral to the development and persistence of inflammation in CRS.\textsuperscript{9-11}

Alterations in DCs are also observed systemically in CRS; however, the circulating DC profile remains incompletely understood, and further investigation into systemic DC subsets is warranted.\textsuperscript{9,12} Dendritic cells in circulation can mature locally at the site of inflammation and then enter the circulation en route to lymphoid tissue or may be recruited from systemic circulation to augment a local immune response. Monocyte-derived DCs (moDCs) represent a distinct DC subset found at low levels in steady-state conditions and are upregulated in the presence of inflammation. Monocyte-derived DCs are fully capable of presenting antigen and priming immune responses to the same extent as conventional DCs.\textsuperscript{13} Monocytes possess the capacity to differentiate into moDCs in vivo and can be identified in human peripheral blood by staining for cell-surface markers HLA-DR, CD209, and CD14.\textsuperscript{14}

In these studies, we sought to investigate systemic levels of moDCs in CRS\textsuperscript{wNP} and CRS\textsuperscript{sNP} for a number of reasons. Monocyte-derived DCs are highly susceptible to the influence of inflammatory factors and can influence the initiation of Th1 and Th2 responses.\textsuperscript{15-17} In lower airway animal models, moDCs have been implicated in Th2 cell-mediated inflammation. Specifically, in lung tissue of mice, moDCs are capable of initiating and maintaining robust Th2 immune responses.\textsuperscript{17} Similarly, human moDCs accumulate in mediastinal lymph nodes after house dust mite allergen exposure and subsequently present antigen to T cells, thus generating Th2 effector responses.\textsuperscript{18} Monocytes are also roughly 20 times more abundant than other DC subsets in blood and marrow, and thus mobilization of this vast reservoir to generate moDCs potentially has considerable clinical implications.\textsuperscript{19} The principal aims of this study were to characterize the presence of moDCs in CRS peripheral blood and to correlate systemic moDC profiles with Th1/Th2 skewing, objective measures of radiographic disease severity, and CRS-specific quality of life (QoL).

**Methods**

**Subjects**

The Medical University of South Carolina Institutional Review Board granted approval prior to the study. Informed consent was obtained from all participants. Patients undergoing endoscopic sinus surgery as part of their standard care for CRS, tumor removal, or cerebrospinal fluid (CSF) leak repair were asked to donate blood for research. Patients were divided into 3 groups: control (n = 12), CRSsNP (n = 18), and CRS\textsuperscript{wNP} (n = 15). Control patients were undergoing resection of non–hormone-secreting pituitary tumors or repair of CSF leak and had no evidence of inflammatory sinus disease. Patients with CRS were classified into CRSsNP and CRS\textsuperscript{wNP} subgroups in accordance with EPOS 2012.\textsuperscript{20} Atopic status within the CRS\textsuperscript{wNP} group was determined by a positive skin prick or ImmunoCAP Specific IgE blood testing (Viracor-IBT Laboratories, Lee’s Summit, Missouri) obtained as part of the patient’s standard of care. Exclusion criteria included the use of immunomodulatory agents; oral steroids in the preceding month; immunologic, renal, gastrointestinal, endocrine, or skeletal disorders (rheumatoid arthritis, immunodeficiency, cystic fibrosis, ciliary dyskinesia, malabsorption, etc); and pregnancy.

**Analysis of Circulating Immune Cells**

Peripheral blood was collected intraoperatively and used as the source of peripheral blood mononuclear cells (PBMCs); this technique has been described.\textsuperscript{21} The PBMCs were thawed, washed twice, and resuspended in FACS buffer (phosphate-buffered saline [PBS], pH 7.4, with 0.1% DNAse). FcgII/III receptors were blocked with Human FC Block (eBioscience, San Diego, California) and 10% bovine serum albumin (BSA) for 5 minutes.

The PBMCs were stained with the following antibodies at concentrations recommended by the manufacturer: anti–HLA-DR PE and anti–CCR3 PE from R&D Systems (Minneapolis, Minnesota), rat IgG1 APC isotype control from eBioscience, and anti–CD209 APC, anti–CD14 PE-Cy7, anti–CD4 PE-Cy7, anti–CXCR3 APC, mouse IgG1 PE isotype control, mouse IgG2a PE-Cy7 isotype control, and mouse IgG1 APC-Cy7 isotype control from BD Biosciences (Franklin Lakes, New Jersey). The cells were then incubated on ice, in the dark for 30 minutes. Fixable PE-Cy5–conjugated 7AAD was added for the last 5 minutes of incubation. Cells were washed twice in FACS buffer, resuspended, and analyzed immediately.

Eight-parameter flow cytometric analysis was performed using a Guava 8HT flow cytometer (Millipore, Billerica, Massachusetts). Twenty thousand events were acquired for each well. Cell viability was determined by 7AAD staining, which is only permeable to cells with a disrupted membrane; 7AAD-positive cells were excluded from analysis. Matched isotype control subtraction was performed on all
samples; samples were excluded from analysis if isotype staining was greater than test-antibody staining.

Antigen-presenting cells were characterized by high expression of HLA-DR antigen-presenting molecules. Monocyte-derived DCs were identified by concomitant cell surface expression of HLA-DR, CD209, and CD14.14 Th1 and Th2 cells were isolated by expression of CXCR3 and CCR8, respectively.22-24 CD4 and CD8 staining was employed to increase the specificity of isolating T-helper cells, as CXCR3 can be found on human airway epithelial cells and CCR8 can be expressed on inflammatory macrophages.25-27

**Computed Tomography Scoring**

Radiographic disease severity was assessed using the Lund-Mackay staging system.28 This metric has high interobserver reliability and has been endorsed by the Task Force on Rhinosinusitis for outcome research.29,30 Each group of sinuses was judged on cross-sectional computed tomography (CT) imaging to be completely clear (0 points), partially opacified (1 point), or completely opacified (2 points); an additional 0 or 2 points were assigned based on patency of the osteomeatal complex bilaterally. This yields a numeric score from 0 to 24. The CT scores were assigned by 2 blinded graders and then averaged to yield a mean score for each patient.

**SNOT-22**

Sino-Nasal Outcome Test 22 (SNOT-22) surveys were completed by patients prior to surgery. The SNOT-22 is designed to capture CRS-specific QoL and has been validated as a reliable clinical outcome measure for patients with CRS. It has high internal consistency, has highly correlated test-retest scores, and is considered by many to be the best available tool for CRS-specific QoL assessment.31

**Statistical Analysis**

Data were analyzed using GraphPad Prism 6.0 (GraphPad Software, La Jolla, California). Nominal data were analyzed using a Fisher exact test. For continuous variables, values were determined to follow a normal distribution using a D’Agostino and Pearson omnibus normality test. For normally distributed data, one-way analysis of variance (ANOVA) followed by a Tukey multiple-comparison test was performed. For nonparametric data, the Kruskal-Wallis test followed by Dunn’s multiple-comparison test was performed. Correlations for parametric and nonparametric data were examined using a Pearson or Spearman correlation analysis, respectively. P values <.05 were considered significant.

**Results**

**Patient Characteristics**

The PBMCs were collected from a total of 45 patients (Table 1). The groups did not differ significantly concerning age, sex, or race. Comparisons between atopic and nonatopic patients were limited by the high number of patients with unknown allergy status in control (n = 12) and CRSsNP (n = 14) groups. Patients with CRSwNP had higher Lund-Mackay CT scores than patients with CRSsNP (P < .0001). There was no difference in SNOT-22 scores between CRSsNP and CRSwNP groups (P = .53).

**Circulating moDCs in CRS**

Differences in circulating moDCs between CRS subtypes was observed (P = .0003). Multiple comparison analysis was then performed. Compared with controls, patients with CRSwNP and CRSsNP had an increased percentage of circulating moDCs (P = .002 and P = .006, respectively) (Figure 1). No difference was noted between CRSwNP and CRSsNP (P = .34). Figure 2 shows representative flow cytometry data.

**Systemic Th1/Th2 Skewing in CRS**

Next we sought to analyze systemic Th1 and Th2 skewing in control, CRSsNP, and CRSwNP PBMCs. The percentage of circulating CD4+ Th1 and Th2 cells was quantified. In 1 CRSsNP sample, isotype staining exceeded true antibody staining for CD4+CXCR3+ cells and was therefore excluded from analysis. No difference in circulating CD4+ Th1 cells (Figure 3A) was observed (P = .12). However, the number of CD4+ Th2 cells in circulation differed significantly among CRS subtypes (P = .006). Multiple comparison analysis was then performed and demonstrated that CRSwNP was characterized by higher numbers of CD4+

<table>
<thead>
<tr>
<th>Table 1. Characteristics of patients and control group.</th>
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<td>Characteristic</td>
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<tr>
<td>Age, mean ± SD (range), y</td>
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<tr>
<td>Sex, M/F, No.</td>
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<td>Race, white/African American/Asian, No.</td>
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<td>No. of atopic/nonatopic patients (unknown)</td>
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<td>Lund-Mackay CT score, mean ± SD (range)</td>
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<td>SNOT-22 score, mean ± SD (range)</td>
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Abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; NA, not applicable; SNOT-22, Sino-Nasal Outcome Test 22.

*P < .0001.
Th2 cells (Figure 3B) than controls ($P = .006$). Th2 cells did not differ significantly between other subgroups.

CD8+ Th1 and Th2 cells were also quantified. No difference in circulating CD8+ Th1 cells was observed with ANOVA ($P = .18$) (Figure 3C). Differences in circulating CD8+ Th2 cells were observed with ANOVA ($P = .03$). Patients with CRSwNP displayed increased numbers of circulating CD8+ Th2 cells compared with controls ($P = .03$) (Figure 3D). Differences between other subgroups were not significant.

Given that CRSwNP patients demonstrated higher circulating Th2 cells and higher Lund-Mackay CT scores than patients with CRSsNP, the relationship between Lund-Mackay CT score and Th2 cells was examined.
with CRS, the percentage of circulating CD4\(^+\) or CD8\(^+\) Th2 cells did not correlate with Lund-Mackay CT score (data not shown).

The ratio of CD4\(^+\) Th2/Th1 cells was then calculated and differences between patient groups were evident \((P = .0005)\). As shown in Figure 4, an increased CD4\(^+\) Th2/Th1 cell ratio was observed in patients with CRSwNP compared with controls and those with CRSsNP \((P = .0004 \text{ and } P = .04, \text{ respectively})\). In CRSsNP, the ratio of both CD4\(^+\) Th2/Th1 cells was higher than that observed in controls; however, differences between these groups were not significant \((P = .31)\).

**Relationship between Circulating moDCs and CD4\(^+\) Th2 Cells in CRS**

In all patients with CRS (Figure 5A), a direct correlation was observed between percentage of circulating moDCs and CD4\(^+\) Th2 cells \((R = 0.53, P = .002)\). Given that higher percentages of both these immune cells were observed in CRSsNP compared with CRSsNP, subgroup analysis based on CRS disease state was then performed. No relationship between circulating moDCs and CD4\(^+\) Th2 cells was observed within the CRSsNP group \((R = 0.46, P = .06)\) (Figure 5B). However, as shown in Figure 5C, a direct relationship between circulating moDCs and CD4\(^+\) Th2 cells was evident in CRSwNP \((R = 0.63, P = .01)\).

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Figure 3. The percentage of circulating C4\(^+\)Th1 cells (A), CD4\(^+\)Th2 cells (B), CD8\(^+\)Th1 cells (C), and CD8\(^+\)Th2 cells (D). Dots represent individual patients. The line is the mean and error bars represent the standard error of the mean for each patient group.

Figure 4. The ratio of circulating CD4\(^+\) Th2/Th1 cells in controls, chronic rhinosinusitis without nasal polyps (CRSsNP), and chronic rhinosinusitis with nasal polyps (CRSsNP). The line is the mean and error bars represent the standard deviation for each patient group.
Clinical Correlations

Last, we sought to determine if percentages of circulating moDCs were related to CRS-specific measures of disease severity. Twenty-one patients with CRS had CT scans available for review. With regard to disease burden on CT imaging, systemic moDCs strongly correlated with higher Lund-Mackay CT scores in CRSsNP but not CRSwNP patients (R = 0.78, P = .005 and R = −0.24, P = .50) (Figure 6). Twenty-three patients had completed SNOT-22 surveys. No relationship between circulating moDC and SNOT-22 scores was observed in CRS as a whole (R = 0.15, P = .47), CRSsNP (R = −0.15, P = .47), or CRSwNP subgroups (R = 0.31, P = .34) (data not shown).

Discussion

While an increasing body of literature supports the notion that DC numbers may be altered in CRS, the role of DCs in Th1/Th2 skewing and their relationship to disease severity remain unknown. In light of the unified airway theory and the fact that patients with asthma display an increase in peripheral blood DCs, we hypothesized that patients with CRS display elevations in circulating DCs, in particular the moDC subset. In these studies, we showed that CRSwNP patients display a large increase in the percentage of circulating moDCs, which corresponds with an increased presence of circulating Th2 cells.

Although the systemic nature of CRS is not fully understood, alterations in peripheral blood immune cells and inflammatory cytokines in CRS have previously been reported. Our group demonstrated an upregulation of mature, circulating CD209+ and CD86+ cells in CRSwNP and CRSsNP compared with controls. Kirsch et al investigated systemic changes in myeloid (mDC) and plasmacytoid (pDC) DCs in CRS and found that the mDC/pDC ratio was higher in CRSsNP than in controls and CRSwNP. This study was limited by the fact that only the mDC1, but not mDC2 subset, was included in their overall quantification of mDCs. The study of DC subsets, using well-described cell-surface markers, is of critical importance, as specific DC subsets preferentially induce Th1 or Th2 differentiation of naive T cells.

Figure 5. Spearman correlation analysis between circulating monocyte-derived dendritic cells (moDCs) and CD4+ Th2 cells in chronic rhinosinusitis (CRS) (A), chronic rhinosinusitis without nasal polyps (CRSsNP) (B), and chronic rhinosinusitis with nasal polyps (CRSwNP) (C).
In this study, we found a strong correlation between elevated numbers of systemic moDCs and Th2 cells in CRSwNP. Patients with CRSsNP displayed moDC levels and a Th2/Th1 ratio between that of control and CRSwNP. Our results support the findings of Kirsche et al., who demonstrated a higher Th2/Th1 ratio in CRSwNP compared with CRSsNP. Similarly, other studies have shown that peripheral eosinophilia, a downstream marker of Th2 inflammation, is increased in CRSwNP. Further mechanistic studies are needed to determine the exact nature of the relationship between circulating moDCs and Th2 inflammation. While a causal link between the two is possible, factors not studied here such as the nature of the microbial stimuli and circulating microenvironment-derived inflammatory signals likely contribute to Th2 polarization as well.

Although our results demonstrate that peripheral moDCs are increased in CRSwNP and to a lesser degree in CRSsNP, the origin of these circulating immune cells remains unknown. Dendritic cells migrate between body compartments via the bloodstream; therefore, it follows that they should be detectable in blood. One possible explanation for the observed pathologic elevations of moDC in CRS is that they mature from monocytes in the local sinonasal tissue and spill over into circulation during migration to lymph nodes. An alternative explanation is that monocytes differentiate into moDCs in blood and are subsequently recruited to local sites of inflammation. Our group has previously demonstrated increased expression of sinonasal CCL2 and CCL20, chemokines that are widely recognized to be important in DC recruitment. This finding supports the notion that sinonasal mucosa has the capacity to recruit DCs from peripheral circulation. This question highlights the need for further studies aimed at gaining a better understanding of DC migration in CRS from the sinonasal tissue to the blood or vice versa. Such information will be essential for therapeutic manipulation of DC trafficking as a means to improve pathologically elevated immune responses in clinical settings.

Prior studies have demonstrated a correlation between peripheral immune alterations, most of which focused on eosinophilia, and objective measures of disease severity in CRS. We sought to assess the clinical relevance of our findings and determine if elevations in circulating moDCs could serve as a biomarker for sinonasal QoL as measured by the SNOT-22 instrument, or local disease severity assessed with Lund-Mackay CT scoring. We found that circulating moDCs correlated directly with higher Lund-Mackay CT scores in CRSsNP but not CRSwNP. There was no correlation between moDCs and SNOT-22 scores in either CRS subtype. There are a number of possible explanations for these findings. Computed tomography scores reflect local inflammation and, therefore, may not correlate with all systemic immune parameters. In addition, current CT staging systems may not be sensitive enough to detect changes within certain subtypes of CRS, such as those with nasal polyps, which tend to cluster toward the higher end of the scoring scale. Similarly, the SNOT-22 is made up of a variety of local, disease-specific items, as well as some systemic symptoms, and such instruments may not correlate with systemic immune cell profiles.

This study is limited in that we did not examine sinonasal levels of moDCs and, therefore, could not determine if a relationship exists between local and circulating moDCs. Given the retrospective nature of the study, CT imaging and SNOT-22 scores were not available for all patients. In addition, all patients enrolled had severe enough disease to require surgical intervention. As such, our results are representative of systemic immunologic changes in the subset of patients with CRS who failed medical management and required surgical intervention and may not be indicative of changes observed within the entire CRS cohort.

Another limitation of this study was our inability to assess the impact of atopic status on systemic alterations in moDC numbers. Given the low number of atopic CRSsNP patients (n = 3) and nonatopic CRSwNP patients (n = 2), allergy status matched comparisons between groups could not be made. As shown in Table 1, most patients (11/15) in the CRSwNP group were atopic. These data corroborate reported percentages of patients with CRSwNP who have documented allergen sensitivity. Because allergy testing is...
not the current standard of care in CRSsNP patients, atopic status was unknown for a large cohort of patients within this group. It is possible that the large number of atopic patients within the CRSwNP group biased the reported results. The impact of systemic allergy on changes at the cellular level in patients with CRSwNP remains incompletely understood and warrants further investigation.9,10,21

Conclusion
In conclusion, the results of this study support the concept that CRSwNP and CRSsNP display alterations in systemic immune profiles. Specifically, circulating moDCs are significantly higher in CRSwNP than in controls, and levels of circulating moDCs correlate with Th2 cells in blood in both CRSwNP and CRSsNP. Circulating moDCs are associated with mucosal inflammation on CT imaging in CRSsNP, but no association between moDC and QoL as measured by SNOT-22 was evident in either CRSsNP or CRSwNP.

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Author Contributions
Brendan P. O’Connell, designed study, collected data, analyzed data, wrote article; Rodney J. Schlosser, designed study, collected data, revised article; Jennifer L. Wentzel, collected data, revised article; Whitney Nagel, collected data, revised article; Jennifer K. Mulligan, designed study, analyzed data, revised article.

Disclosures
Competing interests: Rodney J. Schlosser was a consultant for BrainLAB, Olympus, Sunovion, and United Allergy and received grant support from NeilMed, ArthroCare, Medtronic, and Intersect.

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