

## Editorial



# Does Inflammatory Endotype Change in Patients With Chronic Rhinosinusitis?

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Chronic rhinosinusitis (CRS) shows remarkable heterogeneity and it clinically classified into 2 phenotypes based on nasal endoscopic findings, chronic rhinosinusitis with nasal polyps (CRSwNP) or chronic rhinosinusitis without nasal polyps (CRSSNP).<sup>1</sup> In Western studies, these clinical phenotypes reflect that CRSSNP showed a predominance of type 1 inflammation, whereas CRSwNP is well known to be characterized by type 2 inflammation and eosinophilia compared to CRSSNP or control sinus mucosa.<sup>2-4</sup> However, to date, it is well-known that the inflammation in CRSwNP varies based on race and regional differences.<sup>5,6</sup> Increasing evidences revealed that mixed inflammatory patterns are found in Asian patients with CRSwNP and the ratio of eosinophilic versus non-eosinophilic NP is usually detected similarly in these countries.<sup>7,10</sup> Moreover, recent a multi-national study described that Th1/Th2/Th17 cytokine profile is diverse in terms of the immunologic endotypes among CRS subjects in Europe, China, Japan, and Australia.<sup>11</sup> Furthermore, one cluster study with phenotype-free approach identified that CRS patients have 10 distinct inflammatory endotypes,<sup>12</sup> and the other cluster study described that each cluster had distinct inflammatory endotype and its related prognosis.<sup>13</sup> It implies that the characteristics of each endotype in CRS may have a serial continuum of immunologic profile. However, no studies have yet been reported on whether CRSSNP evolves into CRSwNP with a long duration of illness, or whether 2 diseases occur independently in patients. Because, in order to solve these problems, it is essential to design a long-term cohort study. Unfortunately, there are many hurdles to design a cohort study, regarding cost, time, and ethics.

In the current issue of *Allergy, Asthma and Immunology Research*, Kim et al.<sup>14</sup> described signature cytokines of nasal tissues in subtypes of CRS. This study is the first to compare the profile of 28 different immunologic markers (T cell-associated cytokines and chemokines, pro-inflammatory mediators, adhesion molecule, and remodeling markers) according to the clinical phenotypes (CRSSNP and CRSwNP) and histologic subtypes (eosinophilic and non-eosinophilic) of CRSwNP. In addition, in this study, authors hypothesized that the paired comparison of immunologic profile between nasal tissues from uncinate process mucosa (UP) and nasal polyp (NP), within same patients might provide some clues on the transition from CRSSNP to CRSwNP in an individual patient. Because UP is one of the most common origin sites of NP development. In this study, authors described that eosinophilic CRSwNP showed higher levels of Th2 cytokines than controls, whereas non-eosinophilic

CRSwNP significantly related to Th1/Th2/Th17 cytokines compared to controls. In addition, the signature inflammatory markers, which were at the highest level among all the groups, of non-eosinophilic CRSwNP is interleukin (IL)-17A, IL-1 $\beta$  (markers for Th17), matrix metalloproteinase (MMP)-9 (a marker for neutrophil), whereas IL-5, C-C motif chemokine ligand (CCL)-11, monocyte chemoattractant protein (MCP)-4 (markers for Th2), and vascular cell adhesion molecule (VCAM)-1 were signature inflammatory markers in eosinophilic CRSwNP. Interestingly, although 2 groups showed different signature inflammatory profiles, non-eosinophilic and eosinophilic CRSwNP patients showed common changes of several immunologic profiles on the paired comparison between UP and NP. It indicates that the increased Th2 immune response from UP to NP tissues on both CRSwNP endotype. Additionally, on performed the principal component analysis (PCA) in different CRS groups, the PCA2 component, which indicated a relative Th2 profile, can help to discriminate among the different subgroups of CRS (CRSsNP-UP vs. CRSwNP-UP vs. non-eosinophilic CRSwNP-NP vs. eosinophilic CRSwNP-NP). These findings mean that there is a continuum among subtypes of CRS based on Th2 inflammatory mediators.

As you know that, in the human study, it is very difficult to prove the mechanism for the evolution of nasal polypogenesis. This is because the CRS patient must be monitored for several years and the immunologic changes must be verified by continuous testing until the nasal polyp develops. This study used UP tissues where NP occurs commonly, as internal controls, then, compared the changes between UP and NP, within the same patient. Thus, although this is a cross-sectional study, these comparisons may tell us what the key protein is while nasal mucosa changes to NP. Moreover, our unpublished data show that the symptom duration in patients with non-eosinophilic CRSwNP has a positive correlation with IL-5 ( $r = 0.5658$ ,  $P = 0.0223$ ), CCL-11 ( $r = 0.5694$ ,  $P = 0.0213$ ), and IL-10 ( $r = 0.5201$ ,  $P = 0.0389$ ). These results suggest immunologic endotype may change according to the disease duration which can give a clue about CRS evolution.

In summary, the increase of Th2 cytokines in NP compared to UP was shown irrespective of subtypes of CRSwNP, whereas signature cytokines were distinct in each nasal tissue in subtypes of CRS. Carefully, we suggest that non-eosinophilic CRSwNP showed increased Th2 immune response according to the prolonged disease duration, implying the likelihood of non-eosinophilic CRSwNP being changed into eosinophilic.

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