Inflammation in Chronic Rhinosinusitis and Nasal Polyposis

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• Eosinophils • Neutrophils • Immune regulation

All definitions of chronic rhinosinusitis (CRS) seem to agree on one aspect of the disease: that it involves inflammation. Unfortunately, how united the definitions are on inflammation, so varied the symptoms that develop from this inflammation when patients have to be considered to suffer from CRS. Despite the variety of symptoms, guidelines on CRS classify all sinus diseases as belonging to a single group, albeit that for clinical and basic research purposes the disease can be differentiated into groups depending on the presence or absence of nasal polyps.[1–4] Given the limited medical and surgical treatment options, a single collective is perhaps understandable, but in the long run probably not desirable.

This article focuses on current understanding of the cellular makeup of the inflammatory influx in CRS in relation to the different expression forms of CRS. The first part highlights an ongoing discussion about the role of eosinophils in the pathogenesis of CRS and offsets their presence to neutrophils. This distinction has become relevant in the concept of 2 types of CRS that could be characterized by either eosinophils or neutrophils. The second part focuses on a relatively new aspect, the role of dendritic cells and T lymphocytes in the pathogenesis of CRS. Special interest has recently been given to different subtypes of immune responses (Th1 versus Th2), and a new subtype of T lymphocytes (Th17) that is characterized by the production of interleukin (IL)-17. The final part again steps away from the detailed description of the cellular influx, and discusses specific issues that are important for the interpretation of all the cellular data currently available in the literature.

EOSINOPHILS VERSUS NEUTROPHILS

Probably the most evident misunderstanding in the chronic rhinosinusitis field is that CRS is a pure eosinophilic disease. When the group of CRS patients is considered as

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a whole it is clear that, despite CRS patients displaying different levels of eosinophils, the median values of CRS patients is higher than those of control groups.[5–7] This fact might have triggered the idea that eosinophilia would be present in all individuals, and might also have triggered lines of research that would substantiate the role of the eosinophilia, by focusing solely on related markers (RANTES, Eotaxin, IL-5, eosinophil cationic protein).[8–11] The importance of eosinophils was further strengthened by the introduction of the fungal hypothesis as the sole cause of CRS. In this hypothesis, toxic mediators secreted by eosinophils play an essential role in the elimination of the fungi infection and, as an unwanted side effect, in local tissue destruction and CRS-related symptoms.[12,13] However, the latter hypothesis was dealt a blow when placebo-controlled studies could not show any relevant effectiveness of an antifungal treatment in the alleviation of CRS symptoms or on relevant mediators.[14–17] The former counter-argument that not all CRS patients have eosinophilia is more complex, as the activation state of eosinophils should also be considered, and this cannot be deduced from eosinophil numbers only.[12,18]

Stronger arguments that eosinophils are not the end-all of CRS pathogenesis comes from several directions. Polyps found associated with cystic fibrosis[19,20] and polyps found in the Asian population[21] display hardly any eosinophilia, but are in contrast relatively neutrophilic. Both cystic fibrosis and Asian polyps are indistinguishable macroscopically from regular CRS polyps, showing that at least eosinophilia is not required for polyp formation. This finding is also suggested indirectly by the results of a new treatment option for CRS using anti–IL-5 antibodies.[22] This method is most effective in individuals with increased levels of IL-5, suggestive of an alternative pathogenesis mechanism that is independent of IL-5 and, as a potential consequence, eosinophilia. Upregulation of IL-8, a neutrophil chemokine, has been reported too, but has never been a main focus of research.[23–25] The authors recently were able to independently corroborate these observations at the protein level, showing tissue levels of IL-8 to be more than 5-fold higher in nasal polyps than turbinates from healthy controls.[26]

In a sense the discovery of neutrophils in CRS seems to mirror their discovery in asthma. Whereas asthma was once considered a purely eosinophilic disease, it is now clear that neutrophils are prevalent in difficult-to-treat, nonallergic asthma. For cystic fibrosis polyps this parallel could hold true as they are neutrophilic and, due to the high recurrence levels, should be considered difficult to treat. However, whether the same would hold true for the Asian polyps is not clear.

DENDRITIC CELLS AND T LYMPHOCYTES

In a classic view on the regulation of immune responses, peripheral dendritic cells survey local airway mucosa for potential threats. When such threats have breached the physical epithelial barrier, direct uptake of the pathogen or indirect uptake of an infected tissue cell leads to the initiation of the appropriate immune response. Essential in this process is that the locally activated dendritic cells travel to the corresponding draining lymph node, where they activate naïve T lymphocytes. In the case of a bacterial or viral infection this would result in the formation of the T helper 1 (Th1) subtype; in the case of a parasitic infection this would result in the activation of the T helper 2 (Th2) subtype. These responses are not the only ones possible. In addition to the classic Th1 or Th2 response, a Th17 or T-regulatory response has been identified, with even more responses suspected to exist.[27]

In this light it would seem easy to conceive a role for dendritic cells found in CRS or nasal polyposis (NP) in the initiation or control of a local immune reaction.