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Letter to the Editor

Immune system elements - a puzzle in CRS

Elementi del sistema immunitario - un puzzle nella rinosinusite cronica

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Dear Editor,

We read with great interest and appreciated the comments by Gelardi et al. to our paper entitled "The SWI/SNF complex in eosinophilic and non-eosinophilic chronic rhinosinusitis" [1]. In their Letter "Should the role of mast cells in chronic rhinosinusitis with nasal polyps be revaluated?", Gelardi et al. [2] pointed out a very important issue related to chronic rhinosinusitis (CRS), namely the role of mast cells (MCs) in chronic rhinosinusitis with nasal polyps (CRSwNP). Mast cells have been reported in the pathophysiology of diseases like asthma, allergy, skin diseases, gastrointestinal disorders and various malignancies as well as cardiovascular disease [1]. MCs associated with eosinophils play a complex role, sometimes distinct and sometimes complementary, depending on the context [2]. Interestingly, mast cells can present antigens and modulate T cell response [3], and tumour-associated mast cells have immunosuppressive function in the tumour microenvironment. Apart from the broad repertoire of diseases involving their action, MCs, when activated, may promote eosinophilic inflammation in chronic rhinosinusitis with nasal polyps. Thus, we fully agree with Gelardi et al. that scientific attention in CRS should be given to the role of MCs. We additionally postulate that the role of other immune cells like macrophages, NK, dendritic, and T and B cells [4] should be evaluated more carefully in CRS, although the current EPOS 2020 guidelines sub-classify CRS based on the eosinophil infiltration as non-eosinophilic (neCRS) or eosinophilic (eCRS) [5]. In our paper, we followed the classification and found a negative correlation between SWI/SNF subunit abundance in the epithelium and eosinophil count, thus supporting the role of SWI/SNF in eCRS [6]. We are, however, fully aware of the fact that our study represents only a part of a broader picture of changes characteristic for CRS.

It has been described that epithelial to mesenchymal transition (EMT) is associated with CRSwNP. Moreover, the Wnt signaling pathway is involved in nasal polyp pathogenesis via EMT [7]. SWI/SNF impairment, namely the loss of SMARCB1/INI1, a core SWI/SNF complex subunit, has been linked with activation of the Wnt signaling pathway [8]. The SWI/SNF complex is involved in epigenetic control of gene expression and plays an important role in the response of upper airway epithelial cells to infections. Deficiency of the SMARCA4/BRG1 central ATPase subunit disrupts function of the SWI/SNF complex and triggers a hybrid epithelial/mesenchymal state which may

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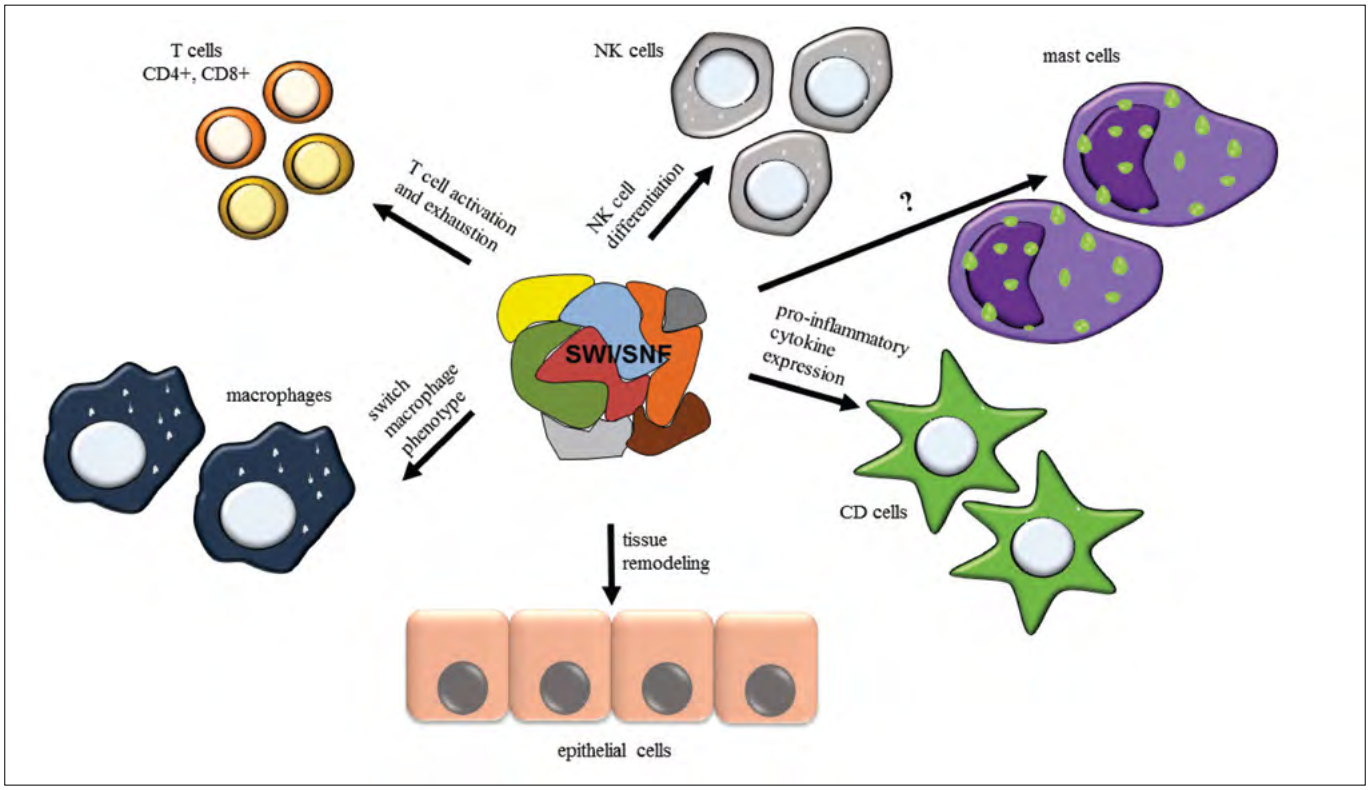

Figure 1. The role of SWI/SNF in immune cell function.

lead to tissue remodeling upon RSV infection [9]. The SWI/SNF complex is also involved in inflammation and immune response. Furthermore, we recently found that SWI/SNF chromatin remodeling complex plays a crucial role in $CD4^+$ T cell exhaustion mediated by cancer cells [10]. T cell exhaustion is well documented in chronic infections and leads to T cell dysfunction. Therefore, in view of our unpublished data and currently available knowledge, we postulate that in precision medicine of CRSwNP not only the role of eosinophils should be assessed, but also other types of immune cells need to be taken into the consideration.

In our opinion, the substantially broader picture of CRS will be constructed only if potential links between SWI/SNF alterations and the role of other immune cells will be evaluated. The extent of the SWI/SNF complex should likely be tested in both nasal epithelium and immune cells. Thus, in agreement with Gelardi et al. suggestions, we highlight the following potential directions which should be taken into consideration in further study of CRS: i) investigation of the extent of T cell exhaustion in CRS; ii) assessment of the role of mast cells and other immune cells in CRS-associated immune response and inflammation; iii) correlation of the SWI/SNF aberrations with epithelial cells and mucosa tissue remodeling observed in CRS. Last, but not least, since the SWI/SNF complex plays an important role in the eviction of the Polycomb Repressive Complex 2, another epigenetic machinery involved in the control of gene expression, evaluation of the potential role of EZH2 (central PRC2 subunit) in CRS seems to be vital because it may open the possibility of the use of epidrugs in CRSwNP treatment.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

All authors contributed equally.

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