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Opinion Article
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Fractalkine and Nasal Inflammation

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Chemokines that attract inflammatory cells play a critical role in promoting nasal inflammation and the development of nasal polyps. CX3CL1 that belongs to CX3C chemokine family is expressed as a membrane bound form and under suitable conditions CX3CL1 is cleaved to its soluble form that has been reported to be higher in the plasma of patients with allergic rhinitis (AR) [1]. The specific receptor for CX3CL1 is the CX3CR1 that is expressed on monocytes, NK cells, T cells and mast cells, mediating adhesion and migration of these leukocytes [2-4]. Moreover, segmental allergen challenge up-regulates the function of CX3CR1 in peripheral blood CD4 T cells [4].

It is surprisingly that only few reports have studied this important pro-inflammatory axis in the upper airway. Danielsen et al. [5] reported CX3CL1 protein detection in nasal polyps. In another study on the gene expression of CX3CL1/CX3CR1, the authors isolated the total RNAs from the nasal mucosa of 20 allergic rhinitis patients to study the cDNA of chemokines and their receptors. They found that CX3CL1/CX3CR1 among other chemokines and their receptors that play important roles in T_{H2} response, were upregulated in the nasal mucosa of AR patients [6]. We also showed that allergen challenge up-regulates the function of CX3CR1 in peripheral blood NK cells and that NK cell infiltrated the epithelial layers of nasal tissue only in chronic rhinosinusitis with allergy (ACRS) patients and not in the chronic rhinosinusitis without allergy (NACRS) patients or controls [7]. This migration could be mediated by CX3CL1, since fractalkine was able to induce NK cytoskeleton changes and F-actin reorganization as well as chemotaxis in microchemotaxis chambers [7].

This interesting predominance of CX3CL1/CX3CR1 towards T_{H2} immunological response in the inflamed nose alerted us to further study fractalkine expression by inflammatory cells infiltrating the inflamed nasal tissue in allergic and non-allergic inflammation. After obtaining the approval of our hospital ethics committee, a total of 28 nasal biopsies from patients operated for CRS by endoscopic sinus surgery, were studied by immunohistochemistry. A total of 28 subjects participated in the study. Out of those, 23 were subjected to endoscopic sinus surgery and their nasal biopsies were obtained by trimming of the middle turbinate as a part of the surgical procedure. As control group, biopsies from the inferior turbinate of patients undergoing partial turbinectomy and did not suffer from either CRS or allergy were obtained (n=5). The 23 patients with CRS were divided into 2 groups: group 1 is 11 patients with NACRS (patients who had no history of allergy and was proven negative to prick skin tests and allergosorbant test (RAST)) while group 2 is 12 patients with ACRS (patients with long history of poorly controlled AR with positive skin tests and RAST to aeroallergens and in whom nasal tissue swelling resulted into obstruction of the ostiomeatal complex and the development of CRS). Interestingly as seen in Figure 1A, the highest percentage of inflammatory cells infiltrating the inflamed nasal tissue and expressing fractalkine was seen in the ACRS group. Further, subdividing the ACRS group into two groups; one with AR only (n=6) and the other with AR and asthma (n=6), we witness maximum expression in the latter group (Figure 1B). This result further highlights the importance of fractalkine chemokine in allergic inflammation of the nose and its maximum expression in the combined airways allergy.

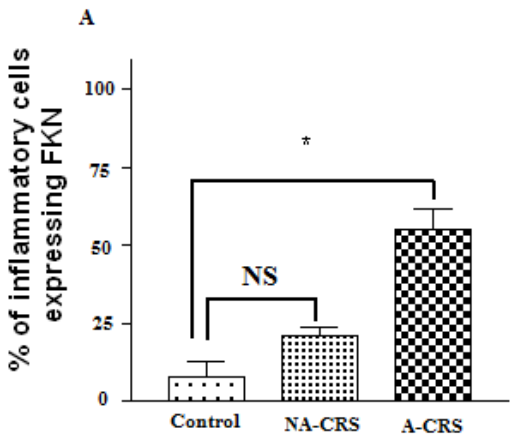

Figure 1A: Formalin-fixed paraffin embedded nasal specimens sections were deparaffinized in xylene, rehydrated in graded alcohols and washer in distilled water. To uncover antigenic sites, antigen retrieval was performed by heating the 4 µm-thick tissue sections in citrate buffer (pH6) for 11 min at 121°c (pressure cooking). The sections were incubated 1 h with antibody directed against fractalkine. The number of infiltrating cells, stained with the anti-fractalkine antibody was counted by an investigator who was blinded to the source of each sample, in 20 adjacent high power fields per sample (10 fields within the epithelium and 10 fields within the stroma). Control N=5, NACRS N=11, ACRS N=12. Asterisk indicates $p<0.05$ by paired t-text. Y axis indicates the total number of inflammatory cells irrespective to their phenotype, infiltrating the nasal tissue in different types of CRS. X axis indicates 1=control subjects, 2=Patients with CRS without allergy and 3=patients with CRS and airways allergy.

It is the author's opinion that further studies need to focus in CX3CL1/CX3CR1 axis in upper airway allergic inflammation. Studies exploring gene regulation of fractalkine and its receptor by different inflammatory cells in response to different T_{H2} cytokines is mandatory, to further understand the novel role CX3CL1/CX3CRI in allergic

inflammation. Therapeutic modalities targeting CX3CL1/CX3CR1 would be an interesting way of attenuating upper airway inflammation. An anti-fractalkine mAb (E6011) has been recently shown to be safe and effective in phase 1/2 study clinical trial in rheumatoid arthritis patients [8]. This may provide a therapeutic implication in the severe forms of AR and ACRS with or without concurrent asthma and may be a valuable addition to the current existing antibody therapy against IgE and IL-5.

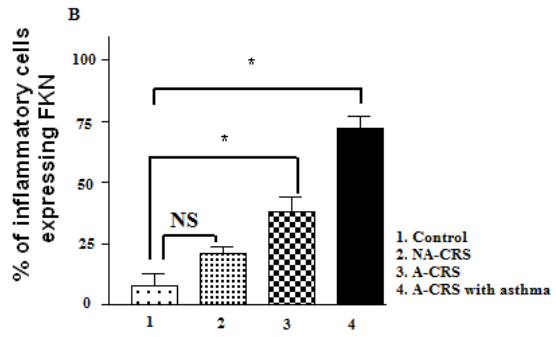

Figure 1B: Y axis indicates the total number of inflammatory cells irrespective to their phenotype, infiltrating the nasal tissue in different types of CRS. X axis indicates 1=control subjects, 2=Patients with CRS without allergy, 3=patients with CRS and AR only and 4=patients with CRS and combined airway allergy; AR and asthma).

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