**Name of Journal:** *World Journal of Otorhinolaryngology*

**Manuscript NO:** 40319

**Manuscript Type:** EDITORIAL

**CX3CR1 receptor as a potential therapeutic target in chronic rhinosinusitis and allergic rhinitis**

El-Shazly A. CX3CR1 in CRS and AR

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**Author contributions:** El-Shazly A contributed to the manuscript.

**Conflict-of-interest** **statement:** No potential conflicts of interest relevant to this article were reported.

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**Manuscript source:** Invited manuscript

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**Telephone:** +32-4-3662111

**Received:** June 15, 2018

**Peer-review started:** June 15, 2018

**First decision:** August 9, 2018

**Revised:** January 23, 2019

**Accepted:** March 15, 2019

**Article in press:** March 16, 2019

**Published online:** April 27, 2019

**Abstract**

Chronic rhinosinusitis and allergic rhinitis are chronic inflammatory diseases that affect the mucous membrane of the nose and paranasal sinuses. These diseases are characterized by recruitment of inflammatory cells to the upper airway. For this to take place a complex interaction between inflammatory cells and the cytokines/chemokines (ligand) liberated at the site of inflammation is involved in a process termed chemotaxis or directed cell migration against concentration gradient of the ligand. This entails signal transduction through the cell surface receptor resulting in cellular functional response and directed migration. In this editorial the novel role of CX3CR1 receptor in the immunopathology of chronic inflammation of the nose and paranasal sinuses will be explored with its potential role as therapeutic target in chronic nasal inflammation.

**Key words**: Nasal Inflammation; CX3CR1 receptor; Chronic rhinosinusitis; Allergic rhinitis; Therapeutic modalities

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**Core tip:** In this editorial, we explore the role of CX3CR1 as therapeutic target in diseases, characterized by recruitment of inflammatory such as chronic rhinosinusitis and allergic rhinitis. Both diseases are chronic inflammatory diseases that affect the mucous membrane of the nose and paranasal sinuses. In this editorial, the novel role of CX3CR1 receptor in the immunopathology of chronic inflammation of the nose and paranasal sinuses will be explored with its potential role as therapeutic target in chronic nasal inflammation.

El-Shazly A. CX3CR1 receptor as a potential therapeutic target in chronic rhinosinusitis and allergic rhinitis. *World J Otorhinolaryngol* 2019; 8(1): 1-3

**URL:** https://www.wjgnet.com/2218-6247/full/v8/i1/1.htm

**DOI:** https://dx.doi.org/10.5319/wjo.v8.i1.1

**INTRODUCTION**

Chronic rhinosinusitis (CRS) is a disease characterized by chronic inflammation of the mucous membrane lining the nose and paranasal sinuses. The immunological response of CRS is biased towards TH1 immunological response and its cytokine profile. On the other hand, allergic rhinitis (AR) is another form of chronic inflammation of the mucous membrane of the nose. It is broadly classified as seasonal (intermittent) or perennial (persistent). Here the immunological response is biased towards TH2 and its cytokine profile. However, both diseases; CRS and AR, may coexists especially in poorly controlled AR that is complicated by sinuses. Both diseases demonstrate leukocytes infiltration at the mucosal level. This entails a complex interaction between the ligand (chemokine or cytokine) and its specific receptor in the cell surface resulting into specific signal transduction and hence chemotaxis or infiltration of the inflamed tissue by inflammatory leukocytes.

CX3CR1 is the receptor for its ligand CX3CL1 or fractalkine and also for eotaxin 3[1,2] that is involved in adhesion and migration of leukocytes[3]. CX3CR1 is expressed by lymphocytes, natural killer (NK) cells and monocytes. It is recently shown to be also expressed by human neutrophils in CRS and CRS associated with airways allergy[4]. This further highlights the importance of this receptor in recruiting important types of inflammatory cells to the inflamed nose in CRS and/or AR. In the lower airway, CX3CR1 receptor signaling promotes TH2 survival in the inflamed lungs[5] and promotes asthma inflammation.

CX3CR1 seems to be significantly upgraded in allergy of the airways. It was shown that allergen challenge upregulates the function of CX3CR1 in peripheral blood NK cells in AR patients and that NK cell infiltrated the epithelial layers of nasal tissue only in patients with CRS with allergy[2]. Likewise, infiltrating neutrophils to the sub-epithelial layer of nasal mucosa showed maximum expression of CX3CR1 in CRS patients with combined airway allergy; AR and asthma[4]. Interestingly, CX3CL1 or fractalkine was also shown to be expressed by inflammatory cells infiltrating the inflamed nasal tissue in CRS with AR. A maximum expression of fractalkine was seen in CRS patients with combined airway allergy; AR and asthma[2].

Although there are only few reports in the literature reporting on this novel receptor role in the nasal inflammation, it is clear from the existing evidences that CX3CL1/CX3CR1 axis in CRS and AR, play a pivotal role in promoting the chronicity of inflammation in CRS and AR patients, through inflammatory cells recruitment. It is interesting the predominance towards TH2 immunological response for the NK cells and neutrophils in this scenario. This makes this receptor a novel target for CRS with associated combined airways allergy. Therefore, it is mandatory to further explore the signaling of CX3CR1 in CRS and AR. Further studies are required to explore the role of this very important receptor in the pathophysiology of CRS and AR.

While Anti FKN (E6011; KANAb001) is under continuous evolution and evaluation as pharmacological target for CXCL1/CX3CR1 axis in rheumatoid arthritis patients[6], the author believes a similar approach in blocking CX3CR1 would be a promising therapeutic modality in treating inflammation seen in CRS and AR, especially the recalcitrant CRS and severe AR. Blocking of this receptor can attenuate the inflammatory cells influx in the epithelial and sub-epithelial layers of the nasal mucosa of NK cells and neutrophils, respectively.

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**P-Reviewer:** Ciuman RR, Coskun A **S-Editor:** Cui LJ **L-Editor: A E-Editor: Zhang YL**

**Specialty type:** Otorhinolaryngology

**Country of origin:** Belgium

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0