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## Role of interleukin-32 in chronic rhinosinusitis

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### Abstract

**Purpose of review**—IL-32 is a recently described proinflammatory cytokine and has been reported to be involved in inflammatory diseases. The purpose of this review is to discuss the role of IL-32 in chronic rhinosinusitis (CRS).

**Recent findings**—Two groups have recently reported data regarding the expression of IL-32 in CRS. IL-32 was induced by IFN- $\gamma$ , TNF- $\alpha$ , dsRNA, and incubation with Th1 cells in primary nasal epithelial cells. IL-32 may be elevated in epithelial cells from patients with CRS without nasal polyps. IL-32 was significantly elevated in whole sinonasal tissue samples of nasal polyps compared with control tissue. IL-32 mRNA expression positively correlated with mRNA for CD3 and macrophage mannose receptor in nasal polyp tissue. Immunohistochemical studies demonstrated localization of IL-32 in epithelium, CD3<sup>+</sup> and CD68<sup>+</sup> cells, suggesting that epithelial cells, T cells, and macrophages are the major IL-32-producing cells in CRS. Activation of these cell types may trigger IL-32-related inflammation in CRS.

**Summary**—Elevated levels of IL-32 may play a role in the pathogenesis of CRS through its role as a proinflammatory cytokine and as an endogenous enhancer of pathogen-dependent cytokine production.

### Keywords

chronic rhinosinusitis; epithelial cells; interleukin-32; macrophages; nasal polyps; T cells

## INTRODUCTION

Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disease of the nose and paranasal sinuses characterized by at least 12 weeks of two of the following symptoms: nasal obstruction, mucopurulent drainage, facial pain/pressure, and hyposmia/anosmia [1]. The diagnosis of CRS is made on the basis of clinical history and often objective documentation of inflammation via nasal endoscopy or computed tomography scan. CRS is commonly subclassified into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) on the basis of gross endoscopic appearance. Although substantial symptomatic overlap exists, nasal obstruction and smell loss predominate in CRSwNP,

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### Conflicts of interest

There are no conflicts of interest.

whereas mucopurulent drainage and facial pain/pressure predominate in CRSsNP. Similarly, the mechanisms of inflammation underlying these two forms of CRS also overlap, but CRSwNP in whites is classically characterized as a more Type 2 helper T (Th2) polarized disease with greater tissue eosinophilia than CRSsNP, which tends to exhibit more Type 1 helper T (Th1) features [2]. Thus, the pathogenesis of these clinical entities may be different. However, the mechanisms underlying the initiation and amplification of inflammation in CRS have not been identified. This review highlights the function of a new cytokine IL-32 and its possible role in inflammatory diseases with a focus on its expression and proposed mechanism in CRS.

## FUNCTION OF IL-32

IL-32 is a proinflammatory cytokine produced by T cells, natural killer (NK) cells, monocytes, endothelial cells, and epithelial cells [3,4]. It was initially named as NK cell transcript 4 that was identified in IL-2-stimulated NK cells [5]. The *IL-32* gene is located on human chromosome 16p13.3 and has six isoforms,  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ , and  $\zeta$  caused by alternative RNA splicing [4]. The receptor for IL-32 has not yet been discovered, although IL-32 has been shown to bind to proteinase 3 and integrins,  $\alpha V\beta 3$  and  $\alpha V\beta 6$  [4,6]. However, the role of proteinase 3 as a binding protein or in cleavage of the cytokine is unknown [4]. In addition, it is not known whether IL-32 can induce signaling via these integrins [6]. The discovery of receptors for IL-32 and investigation into the role of proteinase 3 and integrins in the function of IL-32 are urgently required. IL-32 has been shown to induce IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and chemokines by activating the signal pathways of nuclear factor- $\kappa$ B (NF- $\kappa$ B) and p38 mitogen-activated protein kinase [3]. IL-32 has also been shown to synergize with nucleotide-binding oligomerization domain (NOD)-like receptor ligands including muramyl dipeptide for the production of IL-1 $\beta$  and IL-6 [7]. Silencing of endogenous IL-32 has been shown to attenuate IL-1 $\beta$  or lipopolysaccharide (LPS)-dependent production of TNF- $\alpha$ , IL-6, and IL-8 in endothelial cells and monocytes [8,9]. IL-32 has also been shown to play a key role in apoptosis, induced by T cell receptor signaling and IFN- $\gamma$ , in T cells and keratinocytes [10,11]. Thus, IL-32 may be a multifunction protein, acting as a proinflammatory cytokine, an endogenous regulator of cytokine production, and an inducer of apoptosis.

## ROLE OF IL-32 IN HOST DEFENSE

IL-32 plays a role in host defense against infectious organisms such as mycobacteria and viruses. IL-32 was induced in monocytes and macrophages by *Mycobacterium tuberculosis* [12]. Mycobacteria induced production of IL-18 in monocytes occurred in a caspase-1-dependent manner, which, thereby, induced the production of IFN- $\gamma$  from lymphocytes. IFN- $\gamma$  then induced the production of IL-32 in monocytes [12]. These suggest that the induction of IL-32 by *M. tuberculosis* in monocytes requires interaction with lymphocytes [12]. Bai *et al.* [13] reported increased expression of IL-32 in airway epithelial cells and alveolar macrophages from lung biopsies of patients infected with *M. avium*. They found that infected cells produced IL-32 in a NF- $\kappa$ B-dependent manner. Importantly, they found that exogenous IL-32 inhibited the growth of intracellular *Mycobacterium avium*, and silencing of endogenous IL-32 increased the intracellular burden of *M. avium* in airway epithelial cells and macrophages [13]. This antimycobacterial effect of IL-32 was, in part, mediated by increased apoptosis of infected cells. Accordingly, several groups have reported a potential antiviral function for IL-32. Smith *et al.* [14] demonstrated increased expression of IL-32 in gut and lymphatic tissue of HIV-1-infected patients. IL-32 has also been shown to be increased in the sera of HIV-infected patients [15]. Nold *et al.* [16] reported that silencing of endogenous IL-32 in peripheral blood mononuclear cells (PBMCs) enhanced the infection of HIV, whereas recombinant IL-32 suppressed HIV via a type I IFN-

dependent mechanism, suggesting that IL-32 was a potential natural inhibitor of HIV infection [16]. In contrast, Smith *et al.* [14] reported that IL-32 induced expression of immunosuppressive molecules, including indoleamine 2, 3-dioxygenase and Ig-like transcript 4 (ILT4) in PBMCs, and might impair host defense and support HIV replication. Further investigation is still required regarding the role of IL-32 in HIV infection. IL-32 expression has been shown to be elevated in hepatitis B and C infection and acts as a proinflammatory cytokine [17,18]. Thus, IL-32 may play a role in liver inflammation and fibrosis. IL-32 has also been demonstrated to be elevated in the sera of patients with H1N1 influenza A [19]. Recombinant IL-32 inhibited replication of influenza A [20]. Overall, most studies suggest that IL-32 may play a role in innate immunity to viruses. Although IL-32 is known to control type 1 IFN production, activation of the PKR pathway, and IFN-independent and PKR-independent antiviral mechanisms [16,19,20,21], it is still not clear whether these mechanisms are virus-dependent, infected cell type-dependent, or both.

## ROLE OF IL-32 IN DISEASE STATES

IL-32 has been reported to be involved in the pathogenesis of many disorders, including inflammatory, infectious, malignant, and allergic diseases. IL-32 expression has been shown to be elevated in patients with rheumatoid arthritis (RA) compared with patients with osteoarthritis [22]. Additionally, the magnitude of IL-32 expression correlated with the severity of RA symptoms. In human synovial fibroblasts, TNF- $\alpha$  was a potent inducer of IL-32 mRNA expression and overexpression of IL-32 stabilized mRNA transcripts for TNF- $\alpha$ , IL-1 $\beta$ , and IL-8. Furthermore, synovial knee biopsies from patients with RA showed a significant decrease in IL-32 expression after initiation of anti-TNF- $\alpha$  treatment [23]. Joosten *et al.* [24] demonstrated that injection of human IL-32 into the joints of naive mice produced joint swelling and an influx of inflammatory cells with subsequent cartilage damage. In contrast, IL-32-related joint swelling and influx of inflammatory cells were significantly reduced in TNF- $\alpha$ -deficient mice in this model [24]. These results suggest that there is an amplification loop between IL-32 and TNF- $\alpha$  in disease states. IL-32 has been shown to be overexpressed in inflammatory bowel disease (IBD) and a similar amplified inflammatory response between IL-32 and TNF- $\alpha$  may play a role in the pathogenesis of IBD [25].

The role of IL-32 in diseases of the upper and lower airways including asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, and CRS is also an area of active investigation. IL-32 was shown to be induced by IFN- $\gamma$ , TNF- $\alpha$ , dsRNA, and rhinovirus in normal human bronchial epithelial (NHBE) cells [26,27]. In these studies, IL-32 appeared to act as an intracellular protein in airway epithelium because it was not secreted. Silencing of IL-32 in NHBE cells enhanced the production of vascular endothelial growth factor and platelet-derived growth factor, and supernatants from these experiments enhanced angiogenesis in human umbilical vein endothelial cells [26]. Thus, IL-32 may play a role as an endogenous controller of the production of proangiogenic factors in airway epithelial cells. It should be considered that IL-32 may be an important inhibitor of airway remodeling by the reduction of angiogenesis in asthmatics. Although airway epithelial cells did not secrete IL-32, Meyer *et al.* [26] found that IL-32 was elevated in the serum of patients with asthma. This indicates that other cell types might contribute to the elevation of IL-32 in the serum of asthmatics. Importantly, released IL-32 can act as a proinflammatory cytokine [3,28]. Therefore, whether IL-32 plays a protective role to inhibit airway remodeling or has a pathogenic role in asthma still requires further investigation.

IL-32 has been shown to be elevated in lung biopsies of smokers with COPD, particularly in alveolar macrophages, the alveolar wall, and bronchial epithelium. IL-32 expression was positively correlated with CD8<sup>+</sup> cells and TNF- $\alpha$ , and negatively correlated with FEV1 [29].

Kudo *et al.* [30] demonstrated that IFN- $\gamma$ -dependent IL-32 induction in human bronchial epithelial cells was significantly enhanced by oxidative stress, which occurs during COPD exacerbations. These results suggest that there is a previously unrecognized interaction between IL-32 and oxidative stress for the induction of COPD exacerbations. IL-32 was also found to be elevated in the nasal mucosa of patients with allergic rhinitis [31]. The levels of IL-32 in nasal mucosa correlated with levels of IL-1 $\beta$ , IL-18, and Granulocyte macrophage colony-stimulating factor (GM-CSF). IL-32 was detected in eosinophils in nasal mucosa, and GM-CSF enhanced the production of IL-32 in a human eosinophilic leukemia cell line. In animal models of allergic rhinitis, pretreatment with IL-32 prior to allergen challenge resulted in increased levels of IgE and the inflammatory cytokines IL-1 $\beta$ , IL-4, IL-6, IL-18, and TNF- $\alpha$  [31]. These results indicate that IL-32 may be involved in the pathogenesis of Th2-related inflammation in allergic rhinitis.

The role of IL-32 in cancer and cancer therapy is currently being studied. Marcondes *et al.* [32] showed that IL-32 was remarkably reduced in the bone marrow of patients with chronic myelomonocytic leukemia and was elevated in patients with myelodysplastic syndrome. Sorrentino and Di Carlo [33] showed that IL-32 expression was lacking in the majority of squamous cell carcinomas and their precursor lesions, but strongly upregulated in most adenocarcinomas. IL-32 was identified as a marker for clinical response to IL-2 therapy in melanoma, as determined by gene array profiling in fine needle aspirates of melanoma lesions [34]. IL-32 has been reported to promote tumor suppression through the induction of apoptosis and augmentation of cell-mediated cytotoxicity to cancer cells [32,35–37]. IL-32 induced apoptosis of cancer cells by the induction of proapoptotic molecules including caspase-3 and bax and the reduction of antiapoptotic molecules including bcl-2 [36]. Oh *et al.* [36] reported that apoptotic effects of IL-32 were associated with inhibition of the NF- $\kappa$ B and STAT3 pathways in colon cancer cells, although they did not show a direct link between apoptotic genes and these transcription factors. In addition, IL-32 enhanced cytotoxic effects of CD8<sup>+</sup> cytotoxic T cells and natural killer cells on cancer cells [32,35–37]. These results clearly show that IL-32 has been implicated to have a role in cancer.

The role of IL-32 in other disease states is also an area of active investigation. Meyer *et al.* [10] demonstrated that IL-32 was expressed in lesional skin of patients with atopic dermatitis, whereas it was present in neither normal skin nor lesional skin of patients with psoriasis. They also found that keratinocytes were the major source of IL-32, and IL-32 was involved in keratinocyte apoptosis [10]. Because keratinocyte apoptosis plays an important role in the pathogenesis of atopic dermatitis, IL-32 may contribute to the pathogenesis of atopic dermatitis. IL-32 has been shown to be elevated in the sera of patients with myasthenia gravis [38] and in artery biopsy samples from patients with giant cell arteritis [39]. Interestingly, IL-32 expression in periodontal tissue was lower in patients with periodontitis compared with healthy controls [40].

## EXPRESSION AND PROPOSED ROLE OF IL-32 IN CHRONIC RHINOSINUSITIS

Recently, two articles studying the expression of IL-32 in CRS have been published [27■■, 41■■]. Both studies showed the regulation of IL-32 expression in primary nasal epithelial cells by inflammatory cytokines [27■■,41■■]. Messenger RNA for IL-32 was significantly upregulated by stimulation with TNF- $\alpha$ , IFN- $\gamma$ , dsRNA (a TLR3 ligand), and incubation with Th1 cells in nasal epithelial cells. Furthermore, TNF- $\alpha$  and dsRNA synergistically enhanced IFN- $\gamma$ -dependent IL-32 expression in epithelial cells. In contrast, the expression of mRNA for IL-32 was not affected by IL-1 $\beta$ , IL-4, IL-13, IL-17A, IFN- $\beta$ , peptidoglycan (a TLR2 ligand), or LPS (a TLR4 ligand). IL-32 protein was detected in cell lysates of stimulated cells, but was not detected in supernatants indicating that IL-32 is not secreted

under these conditions and may act as an endogenous regulator in epithelial cells. Importantly, both groups showed almost identical in-vitro results regarding the regulation of IL-32 in airway epithelial cells, suggesting that this is highly reproducible [27■,41■].

In clinical samples, Keswani *et al.* [27■] examined the expression of IL-32 in epithelial scrapings. They found that IL-32 mRNA was elevated in epithelial cells from CRSsNP compared with CRSwNP and controls. Because CRSsNP is known to have a tendency toward Th1 inflammation, overexpression of IL-32 in the epithelium of CRSsNP may be induced by a Th1 environment. Both groups studied the expression of IL-32 in sinonasal tissue samples. Keswani *et al.* [27■] determined that IL-32 mRNA was significantly increased in nasal polyp tissue from patients with CRSwNP compared with uncinat tissue from CRSwNP, CRSsNP, and healthy controls. Soyka *et al.* [41■] also demonstrated that IL-32 mRNA was significantly increased in nasal polyps from CRSwNP compared with control tissues. In contrast to the findings by Keswani *et al.*, Soyka *et al.* [41■] found that there was no difference in IL-32 expression between CRSsNP and nasal polyps. This discrepancy may be due to localized differences in sinonasal tissue samples. Keswani *et al.* [27■] used nasal polyps and uncinat tissue from controls, CRSsNP, and CRSwNP. In contrast, Soyka *et al.* [41■] utilized sinus biopsies from septoplasties and turbinoplasties as controls, comparing these to affected areas of maxillary, ethmoidal or sphenoidal mucosa from patients with CRSsNP and to nasal polyp tissue from patients with CRSwNP. Both groups confirmed increased levels of IL-32 protein in nasal polyps compared with healthy controls by ELISA or western blot [27■,41■]. These results suggest that IL-32 is reproducibly elevated in nasal polyps compared with control sinus mucosa. Whether there is upregulation of IL-32 in ethmoid tissue of CRS patients requires further study.

Immunohistochemistry by Keswani *et al.* demonstrated IL-32 staining in the mucosal epithelium, glandular epithelium, and in submucosal inflammatory cells. Although they found clear evidence that IL-32 mRNA was elevated in epithelial cells of CRSsNP, there was no difference in staining intensity in epithelial cells from CRSwNP, CRSsNP, and healthy controls [27■]. Because immunohistochemistry is not a quantitative method, it will require the generation of a highly sensitive assay system for the detection of IL-32 protein to confirm the elevation of IL-32 in the epithelium of CRSsNP. In contrast to epithelial cells, Keswani *et al.* found an elevation of tissue IL-32 protein in nasal polyps and found greater numbers of IL-32-positive inflammatory cells in nasal polyps. Immunofluorescence studies demonstrated colocalization of IL-32 with CD3<sup>+</sup> T cells and CD68<sup>+</sup> macrophages and indicated that the expression of IL-32 mRNA in nasal polyp tissue positively correlated with expression of CD3 and macrophage mannose receptor. These results suggest that T cells and macrophages are the major IL-32-producing cells in CRS and that the elevation of IL-32 in nasal polyps may be due to the infiltration of these IL-32<sup>+</sup> inflammatory cells [27■]. Soyka *et al.* [41■] demonstrated immunofluorescent staining for IL-32 in some glandular elements in nasal polyps. However, it was not clear whether IL-32 staining was observed in glandular epithelial cells or infiltrated inflammatory cells.

IL-32 has been shown to be induced by Th1-associated cytokines, which would suggest that IL-32 plays a role in Th1-mediated inflammation. However, both Soyka *et al.* [41■] and Keswani *et al.* [27■] demonstrated that IL-32 expression was elevated in sinonasal tissue samples of CRSwNP, which has a more characteristically Th2 polarized cytokine milieu. In addition, IL-32 has also been linked to many characteristically Th2-related disorders such as atopic dermatitis, allergic rhinitis, and asthma [10,26■,31]. Recent publications indicate that severe forms of these diseases are characterized by both Th1 and Th2 inflammation [42,43]. Soyka *et al.* [41■] reported that IL-32 mRNA positively correlated with IFN- $\gamma$  in sinonasal tissue, although nasal polyps showed more Th2 inflammation. IL-32 was also strongly induced by dsRNA, a mimic of viral infections [27■]. Clinically, CRS exacerbations are

known to occur more frequently during respiratory virus season. These results suggest that IFN- $\gamma$  and viral infections may play a role in the upregulation of IL-32 in nasal polyps and possibly in the worsening of CRS. More research will be needed to better characterize the complex interplay of cytokines, including IL-32, in CRS.

IL-32 has been shown to be a regulator of cytokine production and apoptosis, particularly as seen with keratinocyte apoptosis in atopic dermatitis [10]. The role of IL-32 in CRS centers on its ability to serve as a dual function protein, acting as both a proinflammatory cytokine and a regulator of cytokine production. One potential mechanism for the involvement of IL-32 in the pathogenesis of CRS is via an amplification of the inflammatory response to infection. IL-32 is known to synergistically enhance NOD-dependent and TLR2-dependent production of proinflammatory cytokines, which are known to be elevated in nasal polyps, including IL-6 and IL-8 [7,44–46]. Importantly, *Staphylococcus aureus* frequently colonizes the nasal cavity in CRSwNP and it contains both TLR2 and NOD ligands capable of synergizing with IL-32 [44,47,48]. There is evidence that *S. aureus* is able to survive within host cells as a facultative intracellular pathogen [49]. As IL-32 has been shown to inhibit intracellular *M. avium*, it may play a role against intracellular *S. aureus* in CRS. Elevated IL-32 in response to *S. aureus* may lead to amplification of the inflammatory cascade. Another potential mechanism for IL-32 is to act directly as a proinflammatory cytokine. IL-32 is known to directly induce IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$ , which are all suggested to be involved in CRS [3,7–9]. The weight of the available evidence, thus, suggests that IL-32 may play a role in the exaggerated inflammatory response seen in CRS.

## CONCLUSION

CRS is a complex, heterogeneous disease in which an interplay of cytokines is implicated in creating an exaggerated inflammatory state. IL-32, a multifunction protein involved in inflammation, apoptosis, and host defense, has been shown to be elevated in CRS and may play a role in the pathogenesis of this common chronic disease. Future studies to clarify the function of IL-32 in CRS may lead to exciting new therapeutic strategies in CRS.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 119–120).

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