Chronic Rhinosinusitis and Structural Remodeling

Philip M Muthoka*

Ministry of Health, Disease Surveillance and Response Unit, University of Nairobi, Kenya

Abstract

Rhinosinusitis is a significant health problem that affects both adults and children, and when it becomes chronic results in a unique disease burden. About 50% of the worldwide population suffer from rhinosinusitis at one time or another and 20% seek some form of medical assistance. Many of these people go on to develop chronic rhinosinusitis (CRS), such that the worldwide prevalence is 10% but can vary from 7% to 27% (1). CRS is currently defined as nasal and/or sinus symptoms that persist more than 12 weeks, and is confirmed by either endoscopy or computed tomography imaging.

Accepted on 25 November, 2021

Introduction

CRS places a significant burden on the health care system and significantly alters a CRS patient's quality of life. Discharge, nasal blockage, loss of smell, migraine, facial pain, and other symptoms of upper-airway inflammation are well recognized; however, the fact that 40% of patients with CRS are clinically depressed. Moreover, the impact of CRS on quality of life and social functioning is greater than that of back pain, chronic heart disease, or even chronic obstructive pulmonary disease (COPD). It is estimated that 31 million Americans suffer from CRS, and the financial costs—both direct (due to medical care) and indirect (for example, due to lost work) are estimated at 22 billion. This does not take into account money spent on over-the-counter therapies or other alternative and complementary remedies that are used in all-too-often failed attempts to gain control over symptoms. The fact that patients rely on such complementary or alternative approaches suggests that our current therapies are not particularly effective. For instance, Newton and colleagues found that 63% of patients had used some form of complementary or alternative therapy (6), and this is likely an underestimate. One such therapy, nasal irrigation, has been around for over a hundred years, and the rationale for this is supported by a recent Cochrane Collaboration review suggesting a possible benefit. Lastly, there are many well-recognized diseases that are associated with CRS, including aspirin-exacerbated respiratory disease (also known as aspirin idiosyncrasy or Samter's Triad), cystic fibrosis, asthma, and even COPD. CRS is also a known risk factor for asthma, and there is currently a debate as to whether it is a cause or a coexistent phenomenon (according to the united airways disease hypothesis) (8). Smoking is also a well-known risk factor for CRS, which may explain the connection of CRS to COPD. CRS is frequently divided into two distinct phenotypes: CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). The latter tends to be associated with asthma and more severe disease expression, whereas CRSsNP is associated with collagen deposition. The immunological mechanisms underlying CRS with and without NPs differ. CRSsNP is thought to be regulated via a TH-1 pathway disorder, with increased expression of that is associated with collagen deposition and has been linked to bacterial infection. Conversely, CRSwNP is considered a TH-2 pathway response with increased levels, and an eosinophil predominance. Careful studies on the molecular pathways of CRS in the literature, however, are relatively sparse.

In this issue of the Journal, Homma and colleagues report increased expression of the tissue remodeling and repair factors epiregulin (EREG) and matrix metalloproteinase in CRS, and discuss how these factors may regulate remodeling in the nose. These two signals were initially identified from a microarray analysis, and hence the initial goal was to investigate whether they have a functional role in remodeling during CRS. To that end, the authors examined expression of EREG and MMP-1 in upper-airway tissue and NPs obtained from patients with CRS. As determined from tissue specimens, EREG and MMP-1 mRNA and protein were upregulated only in the patients with CRSwNP. Immunohistochemical analysis of tissue specimens showed that expression of EREG increased in both the polyp tissue and sinonasal tissue obtained from these subjects, with the strongest staining in the epithelial layer of the tissue. MMP-1 was constitutively present in all tissues examined, including controls. Finding these signals in the epithelial layer led the investigators to obtain nasal cell scrapings, which revealed correlations between expressions of EREG and MMP-1. To establish a functional relationship between the two, they stimulated bronchial epithelial cells with heat-killed Staphylococcus aureus (HKSA), a species strongly linked to CRS, and found upregulation of both EREG and MMP-1. They next established a mechanistic link between the expressions of EREG and MMP-1 by blocking the epidermal growth factor receptor. Finally, these observations were confirmed in primary cells from patients.

This study is novel in that it describes a previously unappreciated and robust signaling pathway that regulates tissue remodeling in CRS, and as such may present new opportunities to unravel the enigmatic causes of CRS and polyp formation. As this pathway may be important in both CRSwNP and CRSsNP, targeting the EREG pathway could be broadly effective in CRS. The intriguing finding that this pathway is functional in both upper- and lower-airway cells may indicate a broader role of the EREG pathway beyond CRS. The mechanisms illustrated by Homma and colleagues may

therefore lead to insight into other lung disorders linked to CRS, such as COPD and asthma. Finally, as there are currently no Food and Drug Administration–approved therapeutics for CRS in the United States, this study could provide new therapeutic targets that might relieve the suffering of the many people with CRS.

References

1. Bousquet J, Schünemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, Bonini S, Boulet LP, Bousquet PJ, Brozek JL, et al., World Health Organization Collaborating Center for Asthma and Rhinitis. Allergic rhinitis and its impact on asthma (ARIA): achievements in 10 years and future needs. J Allergy Clin Immunol 2012;130:1049–1062.
2. Borish L. Rethinking chronic rhinosinusitis phenotypes. J Allergy Clin Immunol 2016;138:1354–1355.
3. Newton JR, Santangeli L, Shakeel M, Ram B. Use of complementary and alternative medicine by patients attending a rhinology outpatient clinic. Am J Rhinol Allergy 2009;23:59–63.
4. Stevens WW, Lee RJ, Schleimer RP, Cohen NA. Chronic rhinosinusitis pathogenesis. J Allergy Clin Immunol 2015;36:1442–1453.
5. Fokkens, WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen N, Cervin A, Douglas R, Gevaert P, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinology 2012;50(Suppl 23):1–298.