

Editorial



Impact of the Long-Lived Plasma Cells in Patients With Chronic Rhinosinusitis With Nasal Polyps

Roza Khalmuratova ,¹ Hyun-Woo Shin ^{1,2,3,4,5*}

¹Obstructive Upper airway Research (OUaR) Laboratory, Department of Pharmacology, Seoul National University College of Medicine, Seoul, Korea

²Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

³Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

⁴Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul, Korea

⁵Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, Seoul, Korea

► See the article “Evidence for the Presence of Long-Lived Plasma Cells in Nasal Polyps” in volume 12 on page 274.

OPEN ACCESS

Received: Dec 12, 2019

Accepted: Dec 14, 2019

Correspondence to

Hyun-Woo Shin, MD, PhD

Obstructive Upper airway Research (OUaR) Laboratory, Department of Pharmacology, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Korea.

Tel: +82-2-740-8285

Fax: +82-2-745-7996

E-mail: charlie@snu.ac.kr

Copyright © 2020 The Korean Academy of Asthma, Allergy and Clinical Immunology · The Korean Academy of Pediatric Allergy and Respiratory Disease

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Roza Khalmuratova

<https://orcid.org/0000-0002-8518-4034>

Hyun-Woo Shin

<https://orcid.org/0000-0002-4038-9992>

Disclosure

There are no financial or other issues that might lead to conflict of interest.

Chronic rhinosinusitis (CRS) is a multifactorial and highly heterogeneous disease that persists for at least 12 weeks and affects approximately 12% of the general population. CRS is often divided into 2 subtypes: CRS without nasal polyps (NP) and CRS with NP (CRSwNP).^{1,2} CRS is a complex disease that is likely driven by multiple mechanisms, and many recent studies indicate that plasma cells may play an essential role in the pathogenesis of this disease.^{3,4} Long-term plasma cell survival and sustained immunoglobulin (Ig) secretion require a special environment that provides the appropriate prosurvival features.⁵ Several studies suggest that inflamed tissue might provide a supportive microenvironment for plasma-cell maintenance and antibody production in CRS patients.^{4,6-8} Although these findings suggest involvement of plasma cells in the pathophysiology of CRS, to date the exact role of plasma cells remains unclear.

In the current issue of the *Allergy, Asthma and Immunology Research*, Zhang *et al.*⁹ aimed to investigate the presence of long-lived plasma cells (LLPCs) and specific survival niche for LLPCs in patients with CRSwNP. They hypothesize that B-cell lymphoma 2 (BCL2)⁺ CD138⁺ plasma cells may possibly contribute to long-time Ig production in NP and elevated expression of neurotrophins (NTs) and their receptors may provide a microenvironment for plasma cell survival. To identify these hypothesis, sinonasal tissues were collected from 28 patients with eosinophilic CRSwNP, 30 patients with noneosinophilic CRSwNP and 24 control subjects. The authors performed double immunofluorescence staining to detect BCL2⁺ CD138⁺ plasma cells in NP tissue samples. Nasal mucosal samples were cultured with an air-liquid interface system and the Ig levels in culture supernatants were analyzed by enzyme-linked immunosorbent assay. Quantitative real-time polymerase chain reaction analysis was utilized to evaluate the messenger RNA (mRNA) expression level of nerve growth factor (NGF), brain derived neurotrophic factor, NT 3, tropomyosin receptor kinase (Trk) A, TrkB, TrkC, and p75 NT receptor. NGF and TrkA protein expression levels detected by immunohistochemistry and Western blot analysis.

According to the results obtained in the study, a significantly increased number of BCL2⁺ CD138⁺ plasma cell numbers was detected in patients with eosinophilic and non-eosinophilic

NPs. No significant difference in the number of BCL2⁺ CD138⁺ plasma cells was observed between eosinophilic and non-eosinophilic NPs. The authors found that BCL2⁺ CD138⁺ plasma cells survived 32 days after *ex vivo* culture. In addition, sustained Ig production from NP tissues were documented. Thus, these results implied a potential role for LLPCs in chronic inflammation in patients with CRSwNP.

The authors found that NGF expression was greater in the epithelial cells of NPs compared with control subjects. Moreover, double immunofluorescence staining showed that tryptase-positive cells and eosinophils were the main sources of NGF among immune cells. NGF protein levels were significantly increased in NP tissue samples from patients with eosinophilic and non-eosinophilic CRSwNP. Collectively, human NPs had increased NGF expression in epithelial cells and infiltrating immune cells.

TrkA (a high-affinity receptor for NGF) protein levels were increased in NP tissue. The TrkA⁺ inflammatory cell counts were significantly higher in both patients with eosinophilic and non-eosinophilic CRSwNP than in control subjects. The mRNA expressions of NGF and TrkA were up-regulated in eosinophilic and non-eosinophilic NP tissue samples. Furthermore, BCL2⁺ CD138⁺ plasma cells had significant positive correlations with NGF and TrkA mRNA levels. Accordingly, the increased expressions of NGF and TrkA in NPs suggest that they may play an essential role in plasma cell survival in NPs. It also shows that NGF and TrkA could be new targets for therapy in CRS.

However, it is necessary to examine other factors that promote cell survival in inflamed tissue. For instance, the hypoxic environment could be one of the factors that contribute to the long-term survival of plasma cells in CRSwNP patients.³

In summary, the present study helps better understand the survival niche for LLPCs. Such studies deserve to be expanded to further elucidate the unique contributions of each component to the long-term survival of plasma cells.

REFERENCES

1. Hamilos DL. Chronic rhinosinusitis: epidemiology and medical management. *J Allergy Clin Immunol* 2011;128:693-707.
[PUBMED](#) | [CROSSREF](#)
2. Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. *Annu Rev Pathol* 2017;12:331-57.
[PUBMED](#) | [CROSSREF](#)
3. Khalmuratova R, Park JW, Shin HW. Immune cell responses and mucosal barrier disruptions in chronic rhinosinusitis. *Immune Netw* 2017;17:60-7.
[PUBMED](#) | [CROSSREF](#)
4. Tan BK, Peters AT, Schleimer RP, Hulse KE. Pathogenic and protective roles of B cells and antibodies in patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2018;141:1553-60.
[PUBMED](#) | [CROSSREF](#)
5. Lightman SM, Utley A, Lee KP. Survival of long-lived plasma cells (LLPC): piecing together the puzzle. *Front Immunol* 2019;10:965.
[PUBMED](#) | [CROSSREF](#)
6. Hulse KE, Norton JE, Suh L, Zhong Q, Mahdavinia M, Simon P, et al. Chronic rhinosinusitis with nasal polyps is characterized by B-cell inflammation and EBV-induced protein 2 expression. *J Allergy Clin Immunol* 2013;131:1075-83, 1083.e1-1083.e7.
[PUBMED](#) | [CROSSREF](#)

7. Van Zele T, Claeys S, Gevaert P, Van Maele G, Holtappels G, Van Cauwenberge P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy* 2006;61:1280-9.
[PUBMED](#) | [CROSSREF](#)
8. Song J, Wang H, Zhang YN, Cao PP, Liao B, Wang ZZ, et al. Ectopic lymphoid tissues support local immunoglobulin production in patients with chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol* 2018;141:927-37.
[PUBMED](#) | [CROSSREF](#)
9. Zhang YN, Song J, Zhai GT, Wang H, Luo RZ, Li JX, et al. Evidence for the presence of long-lived plasma cells in nasal polyps. *Allergy Asthma Immunol Res* 2020;12:274-91.
[CROSSREF](#)