

## IL-36 $\gamma$ and Infectious Lung Diseases

Yasuyuki Taooka, Takamasa Hotta, Takeshi Isobe

Yasuyuki Taooka, Department of internal medicine, Akiota hospital, Hiroshima, Japan

Takamasa Hotta, Takeshi Isobe, Department of internal medicine, division of medical oncology and respiratory medicine, Shimane university faculty of medicine, Izumo, Japan

**Conflict-of-interest statement:** The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Yasuyuki Taooka, MD, PhD, FCCP, FACP, Department of Internal Medicine, Akiota Hospital, Shimodomo-gohchi 236, Akiota-cho, Yamagata-gun, Hiroshima, 731-3622, Japan.

Email: [taooka-alg@umin.ac.jp](mailto:taooka-alg@umin.ac.jp)

Telephone: +81-826-22-2299

Fax: +81-826-22-0623

Received: October 16, 2018

Revised: November 1, 2018

Accepted: November 2, 2018

Published online: November 4, 2018

### ABSTRACT

A new member of Interleukin (IL)-1 family, IL-36 $\gamma$  is known as one of pro-inflammatory cytokines. IL-36 $\gamma$  is produced by keratinocytes, intestinal epithelial cells, bronchial epithelial cells, alveolar macrophages, and lymphocytes, and is realized to be involved in maintenance of innate immunity. Recently, knowledge about IL-36 $\gamma$  and infectious lung diseases have been accumulating. In this draft, we focused on infectious lung diseases and involvement of IL-36 $\gamma$ . Then the future direction of IL-36 $\gamma$ /IL-36 receptor axis immune reaction pathway and therapeutic strategy against acute lung injury was also discussed.

**Key words:** IL-36 $\gamma$ ; IL-1 family; Pneumonia

© 2018 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Taooka Y, Hotta T, Isobe T. IL-36 $\gamma$  and Infectious Lung Diseases. *Journal of Respiratory Research* 2018; 4(1): 137-139 Available from: URL: <http://www.ghrnet.org/index.php/jrr/article/view/2451>

### EDITORIAL

#### Member of IL-1 family cytokine

In pneumonia, cytokines are generally involved in maintaining pulmonary innate immunity and lung inflammation<sup>[1,2]</sup>. Although interleukin (IL)-1 family primarily promote inflammation and immune reaction, IL-1 family is also known as both of inflammatory agonist and antagonist. Eleven of IL-1 family member includes IL-1 $\alpha$ , IL-1 $\beta$ , IL-1receptor antagonist (RA), IL-18, IL-33, IL-36 $\alpha$ , IL-36 $\beta$ , IL-36 $\gamma$ , IL-36 RA, IL-37, and IL-38. Among those members, IL-1 $\alpha$ , IL-1 $\beta$ , IL-18, IL-33, IL-36 $\alpha$ , IL-36 $\beta$ , and IL-36 $\gamma$  work as inflammatory agonist, and IL-1RA, IL-36RA, IL-37, and IL-38 work as inflammatory antagonist<sup>[3]</sup>. IL-1 family is divided into 3 groups. They are IL-1 subfamily (IL-1 $\alpha$ , IL-1 $\beta$ , IL-33, IL-1RA), IL-18 subfamily (IL-18 and IL-37), and IL-36 subfamily (IL-36 $\alpha$ , IL-36 $\beta$ , IL-36 $\gamma$ , IL-38 and IL-36RA). As co-receptors of IL-1 family, 10 members are known as following; IL-1receptor(R)1, IL-1R2, IL-1R accessory protein (IL-1RAcP), IL-18Ra, IL-18b, IL-33R, IL-36R, single Immunoglobulin (Ig) IL-1R-related molecule (SIGIRR), three Ig domain-containing IL-1R related-1 (TIGIRR-1), and TIGIRR-2<sup>[3,4]</sup>.

IL-1 family and Toll-like receptor (TLR) family are known to be shared similar functions<sup>[4]</sup>. IL-1 family members affect each other, and most of IL-1 family members is associated with innate immunity. In other words, IL-1 family is controlling innate immunity through development, maintenance, and suppression of inflammation.

In this content, we focus on IL-36 $\gamma$  related lung inflammation. And we also discussed about IL-36 $\gamma$  as the biomarker for inflammatory lung disease, and inhibiting IL-36 $\gamma$  activity as the new therapeutic option of acute lung injury.

#### IL-36 $\gamma$ and innate immunity

As IL-36 subfamily members, IL-36 $\alpha$ , IL-36 $\beta$ , IL-36 $\gamma$ , IL-38 and

IL-36RA are known. IL-36 $\alpha$ , IL-36 $\beta$ , and IL-36 $\gamma$  were previously named as IL-1F6, IL-1F8, and IL-1F9<sup>[5]</sup>. These all members bind to IL-36R and form signal complex with IL-1R accessory protein (AcP) as a co-receptor<sup>[6]</sup>. After that, nuclear factor- $\kappa$ B and mitogen-activated protein kinases (MAPKs) are activated, then leading to activate IL-8 promoter reporter lesion and secretion of IL-6<sup>[5,6]</sup>. IL-1 family including IL-36 subfamily generally mediates innate immunity, and IL-36 subfamily is known to be involved in antiviral innate immunity<sup>[7]</sup>. And IL-36RA acts as receptor antagonist<sup>[7]</sup>. For innate immunity, human macrophages constitutively product IL-36 $\beta$  and IL-36RA<sup>[5,7,8]</sup>, but IL-36 $\gamma$  expression is increased by TLR stimulation<sup>[5,7]</sup>. For example, stimulation with ligands for TLR2 and TLR4 induced IL-36 $\gamma$  production in human monocyte line<sup>[8]</sup>. IL-36 $\gamma$  is produced by keratinocytes, intestinal epithelial cells, bronchial epithelial cells, alveolar macrophage, and mononuclear cells<sup>[7]</sup>. And another previous paper using IL-36 $\gamma$  knock out mouse showed that deletion of IL-36 $\gamma$  or IL-36R resulted in *Pseudomonas aeruginosa*-induced attenuated lung injury<sup>[9]</sup>. In that report, IL-36 $\alpha$  and IL-36 $\gamma$  were released from alveolar macrophages and pulmonary epithelial cells<sup>[9]</sup>.

### IL-36 $\gamma$ and infectious pulmonary diseases

Already, many scientific reports about IL-36 $\gamma$  related inflammation has been published, but number of reports about IL-36 $\gamma$  and infectious pulmonary diseases is not sufficient, yet. Therefore mechanism of IL-36 $\gamma$  mediating lung inflammation is not well elucidated, and further study would be necessary. In those situation, several research papers were already discussed about IL-36 $\gamma$  mediating lung inflammation.

IL-36 $\gamma$  stimulates proliferation of native CD4 cells and IL-2 production. IL-36 $\gamma$  in bronchial alveolar lavage fluid was report to be elevated with mycoplasma pneumonia patients<sup>[10]</sup>. In several kinds of viral or bacterial pulmonary infectious experiments, IL-17 stimulates IL-36 $\gamma$  production in bronchial epithelial cell<sup>[11,12]</sup>, and IL-36 $\gamma$  also induces IL-8 and Th17 chemokine, which is promoting neutrophilic airway inflammation via activating lung fibroblast<sup>[11,13]</sup>.

IL-36 $\gamma$  deficiency, either by genetic deletion or by antibody neutralization, resulted in significantly increased mortality during *Streptococcus pneumoniae*-induced pneumonia animal model<sup>[14]</sup>. And IL-36 $\gamma$  deficiency impaired lung bacterial clearance during *Klebsiellae pneumoniae*-induced pneumonia animal model<sup>[14]</sup>. On the other hand, IL-38 has recently also been described to act as an antagonist for IL-36R in an *Aspergillus* infection model mouse<sup>[15]</sup>. These facts that IL-36 subfamily respond to inflammatory stimuli induced by infections suggesting role of IL-36 subfamily in antimicrobial inflammation.

In psoriasis patients, serum IL-36 $\gamma$  level is already reported to be elevated and correlated with disease activity, and IL-36 $\gamma$  is a potential biomarker for the treatment of psoriasis<sup>[16]</sup>. We suppose that it might be promising with inflammatory lung disease, but there are very little reports describing about IL-36 $\gamma$  as the biomarker for human lung disease. One research reported that IL-36 $\gamma$  mRNA level in biopsies was correlated with severity in recurrent respiratory papillomatosis<sup>[17]</sup>. The role of IL-36 $\gamma$  in inflammatory pulmonary diseases is under investigation.

### Anti-IL-36 $\gamma$ therapy and future direction

Under the consideration of above description, IL-36 $\gamma$  involves in neutrophilic lung injury. And IL-36 $\gamma$  might have a possibility to be the candidate for biomarker of pulmonary diseases and infectious diseases. On the other hand, inhibiting IL-36 $\gamma$  activity might lead to suppress lung inflammation in acute lung injury. For example, IL-36RA and IL-38 inhibits IL-36R activity are associated with IL-

1RacP<sup>[18]</sup>. So administration of IL-36RA of inhibiting of IL-1RcP might suppress IL-36 $\gamma$  activity.

One candidate for therapeutic option is neutralization of IL-36 $\gamma$  or IL-36R. And another candidate is neutrophil-derived protease antagonist<sup>[19]</sup>. Since, neutrophil-derived cathepsin G and elastase are potent IL-36-activating enzymes, and IL-36 $\gamma$  must be cleaved at the N-terminus to become active form<sup>[19]</sup>. Recently, Suliva GP et al showed that neutrophil-derived proteases antagonist suppressed activation of IL-36 subfamily cytokines and related inflammation<sup>[20]</sup>. They might be less having adverse effect compared with anti-IL-36 $\gamma$  antibody and/or anti-36R antibody, when trying clinical trial for pneumonia patients.

Taken together, IL-36 $\gamma$  plays an important role for pulmonary infections, and authors suppose that inhibiting IL-36 $\gamma$  activity has a possibility to act as therapeutic option for lung injury. However, accumulation of scientific evidence at laboratory would be necessary before putting into practice at bedside. And we can pay attention for the future of IL-36 $\gamma$  related research work.

## ACKNOWLEDGMENT

Yasuyuki Taooka thanks Megumi, Shintaro, and Kohei Taooka for their help. Author's contributions: All authors contributed in critiquing the manuscript. All authors have read and approved the final manuscript.

**List of abbreviations:** Interleukin (IL), receptor antagonist (RA), IL-1R accessory protein (IL-1RAcP), Immunoglobulin (Ig), Toll-like receptor (TLR), Immunoglobulin (Ig), three Ig domain-containing IL-1R related-1 (TIGIRR-1).

## REFERENCES

1. Taooka Y, Maeda A, Hiyama K, Ishioka S, Yamakido M: Effects of neutrophil elastase inhibitor on bleomycin-induced pulmonary fibrosis in mice. *Am J Respir Crit Care Med* 1997; **156**: 260-265. [PMID: 9230758]; [DOI: 10.1164/ajrcm.156.1.9612077]
2. Taooka Y, Ohe M, Chen L, Sutani A, Higashi Y, Isobe T. Increased expression levels of integrin  $\alpha$ 9 $\beta$ 1 and CD11b on circulating neutrophils and elevated serum IL-17A in elderly aspiration pneumonia. *Respiration* 2013; **86**: 367-375. [PMID: 23257917]; [DOI: 10.1159/000345390]
3. Garlanda C, Dinarello CA, Mantovani A: The interleukin-1 family: back to the future. *Immunity review* 2013; **39**: 1003-1018. [PMID: 24332029]; [DOI: 10.1016/j.immuni.2013.11.010]
4. Van de Veerdonk FL, Netea MG: New insights in the immunobiology of IL-1 family members. *Front Immunol* 2013; **4**: 167. [PMID 23847614]; [DOI: 10.3389/fimmu.2013.00167]
5. Dinarello CA: Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunol Rev* 2018; **1**: 8-27. [PMID: 29247995]; [DOI: 10.1111/imr.12621]
6. Afonina IS, Müller C, Martin SJ, Beyaert R. Proteolytic processing of interleukin-1 family cytokines: Variations on a common theme. *Immunity* 2015; **42**: 991-1004. [PMID: 26084020]; [DOI: 10.1016/j.immuni.2015.06.003]
7. Bassoy EY, Towne JE, Gabay C. Regulation and function of interleukin-36 cytokines. *Immunol Rev*. 2018; **281**: 169-178. [PMID: 29247994]; [DOI: 10.1111/imr.12610]
8. Parker LC, Whyte MK, Vogel SN, Dower SK, Sabroe I. Toll-like receptor (TLR)2 and TLR4 agonists regulate CCR expression in human monocytic Cells. *J Immunol* 2004; **172**: 4977-4986. [PMID: 15067079]; [DOI: 10.4049/jimmunol.172.8.4977]
9. Aoyagi T, Newstead MW, Zeng X, Najo Y, Petets-Golden M, Kaku M, Standiford TJ. Interleukin-36 $\gamma$  and IL-36 receptor signaling mediate impaired host immunity and lung injury in

- cytotoxic *Pseudomonas aeruginosa* pulmonary infection: Role of prostaglandin E2. *PLoS Pathog* 2017; **13**: e1006737. [PMID: 29166668]; [DOI: 10.1371/journal.ppat.1006737]
10. Chen Z, Zhao X, Zhang X, Zhang G, Sun H, Jiang W, Wang Y, Zhu C, Ji W4 Yan Y. Increased concentrations of soluble B7-H3 and interleukin 36 in bronchoalveolar lavage fluid of Children with *Mycoplasma pneumoniae* pneumonia. *BMC Infect Dis* 2016; **16**: 2012. [PMID: 27188891]; [DOI: 10.1186/s12879-016-1555-6]
  11. Chustz, RT, Nagarkar DR, Poposki JA, Favoreto S, Avila PC, Schleimer RP, Kato A. Regulation and function of the IL-1 family cytokine IL-1F9 in human bronchial epithelial cells. *Am J Respir Cell Mol Biol* 2011; **45**: 145-153. [PMID: 20870894]; [DOI: 10.1165/rcmb.2010-0075OC]
  12. Aoyagi T, Newstead MW, Zeng X, Kunkel SL, Kaku M, Standiford TJ. IL-36 receptor deletion attenuates lung injury and decreases mortality in murine influenza pneumonia. *Mucosal Immunol* 2017; **10**: 1043-1055. [PMID: 27966554]; [DOI: 10.1038/mi.2016.107]
  13. Fujie H, Niu K, Ohba M, Tomioka Y, Kitazawa H, Nagashima K, Ohru T, Numasaki M. A distinct regulatory role of Th17 cytokines IL-17A and IL-17F in chemokine secretion from lung microvascular endothelial cells. *Inflammation*. 2012; **35**: 1191-1131. [PMID: 22219048]; [DOI: 10.1007/s10753-011-9419-0]
  14. Kovach MA, Singer B, Martinez-Colon G, Newstead MW, Zeng X, Mancuso P, Moore TA, Kunkel SL, Peters-Golden M, Moore BB, Standiford TJ. IL-36 $\gamma$  is a crucial proximal component of protective type-1-mediated lung mucosal immunity in Gram-positive and -negative bacterial pneumonia. *Mucosal Immunol* 2017; **10**: 1320-1334. [PMID: 28176791]; [DOI: 10.1038/mi.2016.130]
  15. van de Veerdonk FL, Stoeckman AK, Wu G, Boeckermann AN, Azam T, Netea MG, Joosten LA, van der Meer JW, Hao R, Kalabokis V, Dinarello CA. IL-38 binds to the IL-36 receptor and has biological effects on immune cells similar to IL-36 receptor antagonist. *Proc Natl Acad Sci* 2012; **109**: 3001-3005. [PMID: 22315422]; [DOI: 10.1073/pnas.1121534109]
  16. D'Erme AM, Wilsman-Theis D, Wagenpfeil J, Hölzel M, Ferring-Schmitt S, Sternberg S, Wittmann M, Peters B, Bosio A, Bieber T, Wenzel J. IL-36 $\gamma$  (IL-1F9) is a biomarker for psoriasis skin lesions. *J Invest Dermatol*. 2015 2014; **135**: 1025-1032. [PMID: 25525775]; [DOI: 10.1038/jid.2014.532]
  17. DeVoti J, Hatam L, Lucus A, Afzal A, Abramson A, Steinberg B, Bonagura V. Decreased Langerhans cell responses to IL-36 $\gamma$ : Altered innate immunity in patients with recurrent respiratory papillomatosis. *Mol Med* 2014; **20**: 372-380. [DOI: 10.2119/molmed.2014.00098]
  18. Ding L, Wang X, Hong X, Lu L, Liu D. IL-36 cytokines in autoimmunity and inflammatory disease. *Oncotarget* 2018; **9**: 2895-2901. [PMID: 29416822]; [DOI: 10.18632/oncotarget.22814]
  19. Macleod T, Doble R, McGonagle D, Wasson CW, Alase A, Stacey M, Wittmann M. Neutrophil Elastase-mediated proteolysis activates the anti-inflammatory cytokine IL-36 Receptor antagonist. *Sci Rep* 2016; **6**: 24880. [PMID: 27101808]; [DOI: 10.1038/srep24880]
  20. Sullivan GP, Henry CM, Clancy DM, Mamentnabiev T, Belotcerkovskaya E, Davidovich P, Sura-Trueba S, Garabadzhu AV, Martin SJ. Suppressing IL-36-driven inflammation using peptide pseudosubstrates for neutrophil proteases. *Cell Death Dis* 2018; **9**: 378. [PMID: 29515113]; [DOI: 10.1038/s41419-018-0358-4]