ABSTRACT

A new comer of Interleukin (IL)-1 family, IL-36γ is known as one of pro-inflammatory cytokines. IL-36γ 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-36γ and infectious lung diseases have been accumulating. In this draft, we focused on infectious lung diseases and involvement of IL-36γ. Then the future direction of IL-36γ/IL-36 receptor axis immune reaction pathway and therapeutic strategy against acute lung injury was also discussed.

Key words: IL-36γ; IL-1 family; Pneumonia

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IL-36γ and infectious pulmonary diseases

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

IL-36γ stimulates proliferation of native CD4 cells and IL-2 production. IL-36γ in bronchial alveolar lavage fluid was report to be elevated with mycoplasma pneumonia patients[14]. In several kinds of viral or bacterial pulmonary infectious experiments, IL-17 stimulates IL-36γ production in bronchial epithelial cell[11,12], and IL-36γ also induces IL-8 and Th17 chemokine, which is promoting neutrophile airway inflammation via activating lung fibroblast[11,13].

IL-36γ deficiency, either by genetic deletion or by antibody neutralization, resulted in significantly increased mortality during Streptococcus pneumoniae-induced pneumonia animal model[14]. And IL-36γ deficiency impaired lung bacterial clearance during Klebsiella pneumoniae-induced pneumonia animal model[14]. 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[15]. These facts that IL-36 subfamily respond to inflammatory stimuli induced by infections suggesting role of IL-36 subfamily in anti-microbial inflammation.

In psoriasis patients, serum IL-36γ level is already reported to be elevated and correlated with disease activity, and IL-36γ is a potential biomarker for the treatment of psoriasis[10]. We suppose that it might be promising with inflammatory lung disease, but there are very little reports describing about IL-36γ as the biomarker for human lung disease. One research reported that IL-36γ mRNA level in biopsies was correlated with severity in recurrent respiratory papillomatosis[17]. The role of IL-36γ in inflammatory pulmonary diseases is under investigation.

Anti-IL-36γ therapy and future direction

Under the consideration of above description, IL-36γ involves in neutrophilic lung injury. And IL-36γ might have a possibility to be the candidate for biomarker of pulmonary diseases and infectious diseases. On the other hand, inhibiting IL-36γ activity might lead to suppress lung inflammation in acute lung injury. For example, IL-36RA and IL-38 releases IL-36γ activity are associated with IL-1RacP[13]. So administration of IL-36RA of inhibiting of IL-1RacP might suppress IL-36γ activity.

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

Taken together, IL-36γ plays an important role for pulmonary infections, and authors suppose that inhibiting IL-36γ 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-36γ related research work.

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

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