論文 / 著書情報
Article / Book Information

題目(和文)	Ig-Hepta/Gpr116欠損マウスにおける肺胞マクロファージ の活性化と肺気腫の発症機序
Title(English)	Emphysema-like phenotype in Ig-Hepta/Gpr116-deficient mice linked to alveolar macrophage activation
著者(和文)	アリエスタンティドンナマレッタ
Author(English)	Donna Maretta Ariestanti
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論 文 要 旨

THESIS SUMMARY

専攻： Department of	生体システム　専攻	申請学位（専攻分野）： Academic Degree Requested	博士　(Science) Doctor of
学生氏名： Student's Name	Donna Maretta Ariestanti	指導教員（主）： Academic Advisor(main)	中村信大
		指導教員（副）： Academic Advisor(sub)	

要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

Ig-Hepta/GPR116 is a member of the adhesion family of G protein-coupled receptors (GPCRs) with a pair of long immunoglobulin (Ig)-like repeats in the extracellular region and is highly expressed in alveolar type II cells. Previously, it has been shown that mice lacking Ig-Hepta exhibit abnormal lung structure and progressive accumulation of pulmonary surfactant, indicating its essential role in surfactant homeostasis. Pulmonary surfactant is phospholipid-protein-rich material secreted by alveolar type II cells that line the air-liquid interface of the alveoli. The most prominent surfactant function is to reduce surface tension in the air-liquid interface of alveoli, preventing the lungs from collapsing at the end of expiration.

Ig-Hepta knockout mice also exhibit emphysema-like symptoms with enlarged alveoli, accumulation of foamy alveolar macrophages (AMs), and increased expression of matrix metalloproteinase (MMP)-12. These abnormalities are similar to those seen in patients and animal models with emphysema, suggesting its role in emphysema pathogenesis. Emphysema is a type of lung diseases that marks a key feature of chronic obstructive pulmonary disease (COPD), one of leading causes of mortality and morbidity worldwide. It's the third most common causes of death in the world according to WHO report in 2012. Emphysema is defined as enlargement of airspaces of the lung, accompanied by destruction of the walls of the alveoli. These structural changes are associated with decreased lung elastic recoil, increased lung compliance, and lung hyperinflation which in turn causing trouble of breathing. Emphysema develops through an imbalance between proteases released from inflammatory cells in the lower respiratory tract and the antiproteolytic defenses of the lung, a process that results in destruction of lung matrix and development of the enlarged airspaces that characterize emphysema. Smoking is known to be the main risk factor for emphysema.

AMs are phagocytic for pathogens and are important in both innate and acquired immunity in the respiratory tract. Evidence shows a marked increase of AM population in the alveoli of patients with emphysema, indicating the correlation of AMs in the pathophysiology of emphysema. AMs are not only known to secrete various inflammatory mediators, but also known to produce proteinases that are capable of degrading elastin, including cathepsins and MMPs. AMs also generate ROS which led to oxidative stress, another important feature in emphysema. ROS have been shown to induce the expression of MMPs through activation of the transcription factor nuclear factor-kappa B (NF-κB). MMPs are a family of zinc-dependent proteinases that degrade various extracellular matrix (ECM), including collagens, elastins and gelatins. MMPs are regarded as the cause of excessive airway remodeling which has been implicated in emphysema.

In this study, an intriguing finding showed that bronchoalveolar lavage fluid (BALF) obtained from *Ig-Hepta*$^{-/-}$ mice contains high levels of inflammatory mediators, lipid hydroperoxides (LPOs), and MMPs, which are produced by AMs. I examined the level of ROS in AMs of *Ig-Hepta*$^{-/-}$ and wild type (WT) mice by using H_2DCFDA staining, a fluorogenic probe for intracellular ROS. Accumulation of ROS was observed in *Ig-Hepta*$^{-/-}$ but not in WT mice. This excessive ROS causes oxidative stress, showed by a marked increase of LPO level, an oxidative stress marker, both in BALF and lung tissue of *Ig-Hepta*$^{-/-}$ mice. Oxidative stress has been associated with activation of transcriptional pathways such as NF-kB to mediate inflammatory response. Western blot analysis of subcellular fractionation showed the nuclear localization of p65 in the AMs of *Ig-Hepta*$^{-/-}$ mice. Consistently, immunofluorescent confocal microscopy also showed nuclear localization of p65 in AMs of *Ig-Hepta*$^{-/-}$ mice. Taken together, these results indicate activation of NF-kB in AMs of *Ig-Hepta*$^{-/-}$ mice. Next, I examined the level of MMP-2 and MMP-9 that previously known to be implicated in emphysema. Western blot analysis demonstrated that expression of MMP-2 and MMP-9 was significantly increased in BALF of *Ig-Hepta*$^{-/-}$ mice compared to WT mice. To confirm whether the increased MMPs expression is mediated by oxidative stress-induced NF-κB activation, the AMs of *Ig-Hepta*$^{-/-}$ mice were treated with inhibitors of oxidants and NF-κB. The results demonstrated that the release of MMP-2 and MMP-9 from the AMs was strongly inhibited by treatment with these inhibitors. Through ELISA analysis, I also found that the level of monocyte chemotactic protein-1 (MCP-1) is increased in the embryonic lungs of *Ig-Hepta*$^{-/-}$ mice at 18.5 days postcoitum (dpc), when AMs are not accumulated and activated.

As a conclusion, Ig-Hepta-/- mice exhibit emphysema-like symptoms, in which AMs are activated and

release MMPs through ROS-mediated NF-κB activation. The macrophage activation is likely to be mediated by MCP-1 induced by Ig-Hepta deletion, but the underlying mechanism, including Ig-Hepta-mediated signaling, should be elucidated in future studies. My findings suggest that Ig-Hepta responsible for ensuring homeostasis of the internal environment of the alveoli, such as surfactant homeostasis, to prevent macrophage activation and emphysema. Therefore, I propose that *Ig-Hepta*$^{-/-}$ mice are a useful model to gain insights into the pathogenesis and treatment of emphysema.

備考 ： 論文要旨は、和文 2000 字と英文 300 語を 1 部ずつ提出するか、もしくは英文 800 語を 1 部提出してください。

Note : Thesis Summary should be submitted in either a copy of 2000 Japanese Characters and 300 Words (English) or 1copy of 800 Words (English).

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