論文の内容の要旨

獣医学専攻

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論文題目　Investigation of the role of prostanoids in acute lung injury

（急性肺障害におけるプロスタノイドの役割解明）

Background and aim

ALI is a lethal respiratory disorder caused by various stimuli such as aspiration of gastric contents, fat embolism, and bacterial mass infection. Although the mortality rate is high, there is no effective pharmacological therapy.

Prostanoids are inflammatory lipid mediators produced by COX. Since these prostanoids are detected in lung tissue of ALI patients, researchers have investigated the therapeutic effect of inhibition on ALI. Although COX inhibition suppress inflammation in the experimental ALI model, COX inhibition did not show the anti-inflammatory effect on ALI in the clinical study. Thus, we need to clarify the role of each prostanoids on ALI progression.

In the present study, I investigated the role of TXA_2 and PGD_2 signaling in ALI progression by using mice ALI models.

Results

I. The role of TXA_2-TP signaling in ALI

TXA_2 is one of prostanoids produced by COX and TXS. It is known that TXA_2 causes platelet aggregation and vasocontraction via its specific receptor, TP receptor. Recently, some studies showed the pro-inflammatory role of TXA_2-TP signaling on ALI progression, the detailed mechanism is still unknown.

I investigated the role of TXA_2-TP signaling in ALI progression by using three different ALI mice models using HCl, LPS+OA, or LPS. The administration of HCl induced hemorrhage accompanied with edema formation and neutrophil accumulation. LPS+OA administration caused severe edema formation and neutrophil accumulation. The administration of LPS only induced neutrophil accumulation, but not edema formation. In these models, the treatment with TP receptor antagonist suppressed edema formation without affecting neutrophil accumulation. Furthermore, the level of TXA2 production has positive correlation with the level of edema formation.

Immunobiological assay showed that inflamed epithelial cells express TXS. Miles assay showed that the administration of TP receptor agonist caused vascular hyper-permeability by disrupting the endothelial barrier. In vitro assay also showed that TP signaling disrupts endothelial barrier via intracellular Ca^{2+} influx and the activation of Rho kinase.

II. The role of L-PGDS-derived PGD_2 in ALI

PGD_2 is another one of prostanoids produced by COX and its specific synthases; H-PGDS and L-PGDS. H-PGDS is known to be expressed in blood cells and suppress inflammation by producing PGD_2. Our group showed that H-PGDS-derived PGD_2 suppresses ALI progression in LPS-induced ALI mice model. On the other hand, L-PGDS is known to be expressed in central nervous system and the role of L-PGDS-derived PGD_2

in peripheral tissue is unknown.

I investigated the role of L-PGDS-derived PGD_2 in ALI progression by comparing with the role of H-PGDS-derived PGD_2 using HCl-induced ALI mice model. The administration of HCl caused inflammation and respiratory dysfunction accompanied by edema formation and neutrophil accumulation in WT mice. Both L-PGDS- and H-PGDS-deficiency aggravated respiratory dysfunction. In addition, L-PGDS-derived PGD_2 suppressed edema formation, while H-PGDS-derived PGD_2 suppressed neutrophil accumulation. I confirmed the suppression effect of L-PGDS-derived PGD_2 on ALI progression by using mice which have L-PGDS point-mutation of the active site of PGD_2 production.

Immunobiological assay showed that stimulated epithelial cells and endothelial cells express L-PGDS, while neutrophils strongly express H-PGDS. In addition, the transplantation of WT-derived bone marrow to L-$PGDS^{-/-}$ mice did not rescue aggravated ALI symptoms. Miles assay showed that L-PGDS-derived PGD_2 suppressed HCl-induced vascular hyper-permeability via one of PGD_2 specific receptor, DP receptor. *In vitro* assay showed that DP signaling enhance endothelial barrier, but not epithelial barrier.

Conclusion

In the ALI progression, inflamed epithelial cells might produce TXA_2 via the activity of TXS. Produced TXA_2 binds to TP receptor, resulting in endothelial barrier disruption via the intracellular Ca^{2+} influx and the activation of Rho kinase. The disrupted endothelial barrier cause lung dysfunction by edema formation.

On the other hand, inflamed epithelial cells and endothelial cells produce PGD_2

by the L-PGDS activity. The L-PGDS-derived PGD_2 suppress edema formation by binding to DP receptor in endothelial cells.

This study provides a new insight on ALI progression and leads a novel therapeutic strategy.