Role of the Coagulation System in Mucin Production of Sinonasal Inflammation

Shino Shimizu

Department of Otorhinolaryngology, Shiga University of Medical Science

INTRODUCTION

Thrombin, an effector enzyme of coagulation system, has important biological functions not only in thrombosis and hemostasis but also in inflammation. While thrombin's precise role in sinonasal inflammation remains unknown, indirect evidence suggests that it is basic. We found that thrombin contributed to tissue remodeling by stimulating platelet-derived growth factor (PDGF) secretion and fibroblast or smooth muscle cell proliferation. Natural anticoagulant–activated protein C decreased PDGF expression and suppressed fibrosis in lung fibrosis mouse model. We explored thrombin presence in the upper airways and whether it affects mucin secretion.

METHODS

A clinical study enrolling 15 subjects with allergic rhinitis, used primary nasal epithelial cells, normal bronchial epithelial cells, and airway epithelial cell lines for in vitro evaluation and rats as in vivo animal models.

RESULTS

Total thrombin concentration was measured in nasal secretion from those with allergic rhinitis exposed to house dust mite before and after provocation, finding that thrombin concentration after provocation with a house dust mite disc increased significantly compared to before allergic provocation (Fig. 1).

Airway epithelial cells expressed thrombin receptors (PAR-1, PAR-3, and PAR-4) (Fig. 2). Thrombin and its agonistic receptor peptide induced significant MUC5AC secretion in primary nasal cells, normal bronchial epithelial cells, and airway epithelial cell lines (Fig. 3, 4). EGFR tyrosine kinase inhibitor suppressed thrombin-induced MUC5AC secretion. Thrombin also induced epidermal growth factor receptor (EGFR) expression in nasal epithelial cells.

Intranasal thrombin instillation induced hypertrophic and metaplastic changes of goblet cells in rat nasal epithelium (Fig. 5). Intranasal instillation of activated protein C (APC), a natural anticoagulant, significantly inhibited thrombin–induced mucus production in the rat nasal epithelium (Fig. 5).

DISCUSSION

Results of increased thrombin generation in nasal secretion induced by allergen stimulation in those with allergic rhinitis, and increased mucin secretion after thrombin instillation in rat septum epithelial cells suggest that the coagulation system is activated at allergic reaction sites and that its product, thrombin, actively

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Fig. 1 Thrombin concentration of nasal secretion in those with nasal allergy. Allergen challenge significantly increased nasal secretion thrombin concentration 5 minutes after intranasal challenge.
Thrombin and PAR\(_1\) agonist peptide significantly increased MUC5AC secretion from nasal and bronchial epithelial cells, indicating that the thrombin effect on mucin production is mediated through the PAR\(_1\) receptor. EGFR tyrosine kinase inhibitor suppressed thrombin\(_1\) induced MUC5AC secretion, suggesting that the EGFR pathway may be important to thrombin\(_1\)-induced MUC5AC secretion. We also found that thrombin stimulates EGF receptor expression from nasal epithelial cells. Taken as a whole, these observations show that thrombin induces mucin secretion directly and indirectly by increasing inflammatory cytokine and EGF receptor expression from airway epithelial cells. To confirm the coagulation system’s role in upper airway, we treated rats with intranasal APC instillation together with thrombin. Intranasal anticoagulant APC instillation significantly decreased mucin secretion in vivo. Thrombin and PAR\(_1\) agonist peptide significantly increased MUC5AC secretion from nasal and bronchial epithelial cells, indicating that the thrombin effect on mucin production is mediated through the PAR\(_1\) receptor.
septum epithelium induced by thrombin in rats, suggesting that the activation of the coagulation system plays a fundamental role in the upper airways.

In summary, our results showed that coagulation system factors including thrombin and APC regulate upper airway inflammatory and allergic response (3–5).

REFERENCES


