Mechanism of Pepsin-Induced Neutrophil Recruitment and Activation via Epithelial Cells in Mucosal Injury

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Introduction

Pepsin is a core pathogenic factor in laryngopharyngeal reflux (LPR), yet how it initiates and amplifies local inflammatory responses remains incompletely understood. Clinical observations show that neutrophil infiltration is a prominent histological feature of LPR-affected mucosa. This study investigated whether pepsin actively recruits and activates neutrophils via laryngeal epithelial cells, thereby exacerbating tissue injury.

Fig.1 IL-8 ELISA Standard Curve

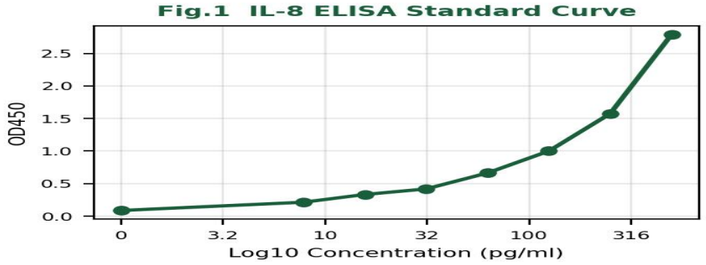
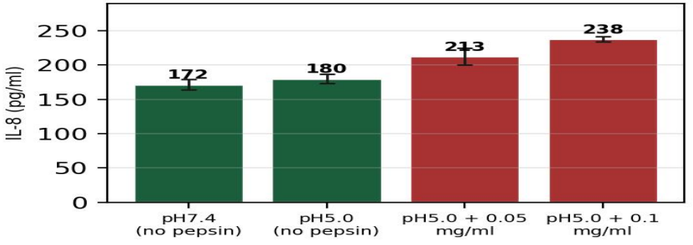
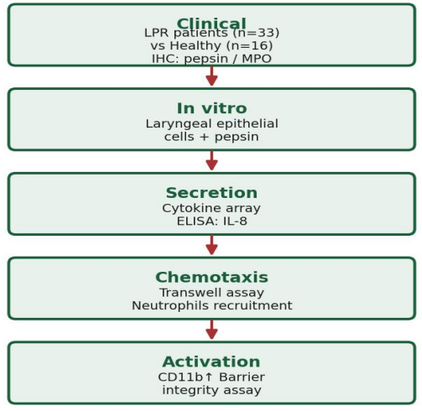


Fig.2 Pepsin Dose-Dependently Induces IL-8



Peak: pH5.0 + Pepsin (0.1 mg/ml) -> IL-8 = 238.0 +/- 3.8 pg/ml (dose-dependent).

Methods



Clinical cohort
LPR (n=33) vs Healthy (n=16); arytenoid mucosa; pepsin & MPO (neutrophil marker) IHC.

In vitro
Human laryngeal epithelial cells stimulated with pepsin; cytokine array + ELISA for IL-8.

Functional assays
Transwell chemotaxis

Table. IL-8 secretion (mean +/- SD, pg/ml) from Fadu cells

Group	IL-8 (pg/ml)
pH7.4 (no pepsin)	171.9 +/- 7.6
pH5.0 (no pepsin)	180.4 +/- 6.8
pH5.0 + 0.05 mg/ml	212.7 +/- 12.4
pH5.0 + 0.1 mg/ml	238.0 +/- 3.8



Results

Clinical evidence
Neutrophil infiltration density was markedly higher in pepsin-positive LPR mucosa than in control tissues and pepsin-negative regions of the same patient, with a positive spatial correlation between pepsin deposition and neutrophil accumulation.

In vitro verification
Pepsin stimulation induced robust IL-8/CXCL8 secretion by laryngeal epithelial cells, and epithelial conditioned media exerted potent chemotactic effects on neutrophils.

Activation & damage
Recruited neutrophils showed an activated phenotype (elevated CD11b), and their culture supernatants significantly compromised epithelial barrier integrity.

Discussion

This study identifies pepsin as an inflammatory orchestrator in LPR. Beyond direct epithelial damage, pepsin triggers epithelial cells to release specific chemotactic signals such as IL-8, which mediate programmed recruitment and activation of neutrophils. The positive spatial correlation between pepsin deposition and neutrophil accumulation in vivo strongly supports this axis. Notably, activated neutrophils release inflammatory mediators that inflict secondary mucosal-barrier damage, suggesting a self-amplifying loop that may sustain LPR pathology. These findings expand the traditional "chemical injury" view of pepsin and identify the IL-8-neutrophil axis as a potential therapeutic target for reflux-related mucosal disease.

Conclusions

Pepsin acts as an inflammatory orchestrator in LPR: it induces epithelial IL-8 release, driving programmed neutrophil recruitment and activation; activated neutrophils then cause secondary barrier damage, forming a self-amplifying inflammatory loop.

Keywords: Laryngopharyngeal reflux (LPR) | Pepsin | IL-8 / CXCL8 | Neutrophil | Mucosal barrier

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