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NOTCH SIGNALING IS INVOLVED IN THE DEVELOPMENT OF OESOPHAGEAL MUCOSAL INJURY CAUSED BY GASTRO-oesophageal reflux: THE FIRST REPORT FROM HUMAN MODEL
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Objectives: Gastro-oesophageal reflux is a common complication for patients after oesophagectomy and gastric interposition, which could serve as an ideal human reflux model to study the molecular pathogenesis of oesophageal mucosal damage by gastro-oesophageal reflux. This study was conducted to investigate the role of Notch signaling in reflux injury of oesophageal mucosa.

Methods: Forty-eight patients who underwent Ivor-Lewis oesophagectomy with gastric interposition between 2011 and 2012 were prospectively included. Follow-ups were scheduled at 6 months, 18 months and 36 months postoperatively, including reflux symptoms assessment and endoscopic evaluation of oesophageal mucosal damage (MUSE classification). Biopsies were taken for detection of histological mucosal damage, Notch1 and its downstream target gene Hes1 expressions (Q-PCR for mRNA and IHC for protein).

Results: Forty-five of 48 patients completed three follow-ups. Both endoscopically visualized and histologically evidenced damage were more often in samples with a longer postoperative period ($P < 0.05$). The mRNA expression of Notch1 and Hes1 were decreased in a time-dependent manner after operation ($P = 0.026$). Notch1 mRNA expressions were significantly lower in MUSE positive patients than in MUSE negative patients ($P = 0.018$). Similarly, Notch1 mRNA expressions were lower in patients with pathological evidence of mucosal damage than in patients with normal biopsies ($P = 0.043$). The rates of positive IHC stainings for Notch1 and Hes1 were decreased in a time-dependent manner as well. Samples with metaplasia exhibited much more weaker IHC staining of Notch1 compared with biopsies without any evidence of reflux damage ($P = 0.022$). There was also a trend toward seeing weaker Hes1 IHC staining in oesophageal mucosa subject to long-term postoperative reflux ($P = 0.061$).

Conclusion: This is the first report studying Notch signaling in human model of gastro-oesophageal reflux disease over a long period of time. Our findings suggest that suppression of Notch signaling is involved in the development of mucosal damage after gastro-oesophageal reflux.

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