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LETTER TO THE EDITOR

The study of laryngopharyngeal reflux needs adequate animal model

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Dear editor,

We read the paper of Ao et al. about the role of Glut-1 and H^+/K^+-ATPase in pepsin-induced mouse laryngeal epithelial proliferation, growth, and development [1]. The authors observed that the exposure of mouse laryngeal epithelium to artificial pepsin-containing gastric juice led to hyperplasia and increased H + /K + -ATPase expression of H^+/K^+-ATPase α, β.

Animal models have to provide a comprehensive functional and anatomic platform for studying pathophysiological mechanisms underlying the development of mucosa modifications. In this case, the animal model needs to be adequate regarding the key laryngopharyngeal reflux (LPR) pathophysiological mechanisms.

In humans, pH-impedance studies reported that most LPR patients (> 70%) have upright and daytime gaseous pharyngeal reflux events [2, 3], which are associated with the deposit of gastroduodenal enzymes into the mucosa [4]. Patients with upright and daytime pharyngeal events reported profile differences (e.g., symptoms, reflux episode duration, and pepsin concentration) than those with both gastroesophageal reflux disease (GERD) and LPR [5]. Indeed, GERD is most frequently associated with upright and supine liquid events [5] and, therefore, a higher concentration of H + and gastroduodenal contents. The pH of refluxate of patients with isolated LPR is more frequently weakly or nonacid [3]. According to these features, the choice of the animal model needs to consider the position of the animal and the characteristics of reflux (gaseous and weakly acid/alkaline). The mouse is a quadruped mammal with a horizontal upper digestive tube [6]. The horizontal position of the mouse involves a higher risk of liquid GERD/LPR than gaseous LPR, which normally occurs upright (vertical position of the upper digestive tube). These differences may influence the findings of the study, limiting the interest of the results for human.

Another point that authors did not consider is the role of other gastroduodenal enzymes, i.e., trypsin, bile salts, or

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lipase, in the development of mucosa hyperplasia. The pharyngeal events in humans may contain bile salts or trypsin [7, 8], which may be active in alkaline pH, playing a key role in some laryngeal mucosa changes (dysplasia and carcinoma) [9]. The consideration of these enzymes and their pH of activity is important in understanding the role of H^+/K^+-ATPase in the development of LPR-related mucosa injury. The last point limiting the drawn conclusion in LPR animal models is the lack of consideration of environmental factors influencing mucosa sensitivity. For example, tobacco or alcohol components could impact the expression of some molecules such as GLUT-1 [10].

In sum, the choice of the animal model is challenging in LPR disease, because it must consider similarities in both laryngopharyngeal mucosa histology, digestive tube position, and related types of refluxes. Nowadays, human laryngopharyngeal biopsies probably remain the best way to study the mucosa abnormalities related to LPR.

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