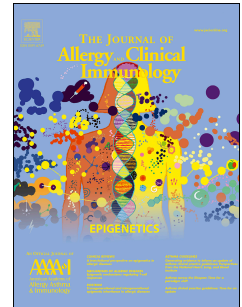


Accepted Manuscript

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PII: S0091-6749(18)31435-0

DOI: [10.1016/j.jaci.2018.09.026](https://doi.org/10.1016/j.jaci.2018.09.026)

Reference: YMAI 13662

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 24 July 2018

Revised Date: 9 September 2018

Accepted Date: 21 September 2018

Please cite this article as: Hill DA, Spergel JM, Epithelial acid imbalance in eosinophilic esophagitis, *Journal of Allergy and Clinical Immunology* (2018), doi: <https://doi.org/10.1016/j.jaci.2018.09.026>.

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Epithelial acid imbalance in eosinophilic esophagitis

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Word count: 842, References: 10, Figures: 1

Funding: DAH is supported by the NIH (K08 DK116668). JMS is supported by the Stuart Starr Endowed Chair of Pediatrics, the Children's Hospital of Philadelphia Eosinophilic Esophagitis Fund, the Food Allergy Research & Education, Inc. Clinical Network, and the Consortium of Eosinophilic Gastrointestinal Disease Researchers (U54 AI117804).

Author Contributions and Disclosures: DAH and JMS contributed equally to this work, and have no conflicts of interest to disclose.

Key words: Eosinophilic esophagitis; acid balance; NHE3

Abbreviations: EoE – eosinophilic esophagitis; DIS – dilated intercellular spaces; GERD – gastroesophageal reflux disease; NHE3 – sodium-hydrogen exchanger member 3; STAT6 – signal transducer and activator of transcription 6; pHe – extracellular pH; pHi – intracellular pH; PPI – proton pump inhibitor; PPI-REE – proton pump inhibitor-responsive eosinophilic esophagitis.

Eosinophilic esophagitis (EoE) is a chronic allergic inflammatory disease of the esophagus that is triggered by specific foods and, if left untreated, can result in considerable morbidity.¹ While the clinical significance of this condition is widely acknowledged, the cellular and molecular mechanisms that underlie its pathophysiology are an active area of research. The *sine qua non* of EoE is the presence of eosinophilic inflammation in the esophagus. However, there are other key histopathologic features of EoE that may provide important insights into the mechanisms of this disease.¹

One key histologic feature of the EoE esophagus beyond eosinophil infiltrates is the development of dilated intercellular spaces (DIS) between epithelial cells.² The development of DIS in EoE has been an area of recent investigational focus because it may contribute to increased mucosal permeability,³ and therefore food allergen exposure. However, DIS are not only present in EoE—they are also characteristic of the esophageal inflammation observed with gastroesophageal reflux disease (GERD). In the case of GERD, DIS are thought to result from exposure of the epithelium to gastric acid, while EoE-associated DIS are ultimately refractory to gastric acid suppression alone and require allergen removal or topical corticosteroid therapy to resolve.² Thus, EoE and GERD share a nonspecific feature of esophageal inflammation that has historically been associated with acid-mediated damage and may impair mucosal integrity.

In this issue of the *Journal*, Zeng and colleagues provided important insights into the etiology of EoE-associated DIS.⁴ The authors found altered expression of gene networks associated with regulation of intracellular pH and acid-protective mechanisms in esophageal biopsy specimens of pediatric patients with EoE. The gene encoding

sodium-hydrogen exchanger member 3 (NHE3), an epithelial sodium-proton exchanger that is expressed in the apical membrane of epithelial cells, was particularly upregulated in EoE epithelia and correlated with disease activity in esophageal biopsies. The authors went on to show that IL-13 upregulates NHE3 expression in a signal transducer and activator of transcription 6 (STAT6)-dependent manner, and that the resulting acidification of the intercellular space contributes to epithelial DIS.

Given these new observations, it is intriguing to speculate as to whether NHE3 upregulation in the context of EoE is pathologic or compensatory. In other disease settings, NHEs seem to play a primarily protective role. For example, these channels are downregulated in experimental models and humans with colitis and infectious diarrhea, and promote the maintenance of normal commensal microbiota under physiologic settings.⁵ In addition, much of what we know of NHE function in the context of disease comes from studies of NHE1 in cancer cells. In this setting, NHE1 helps drive a pathologic reversal of the cellular membrane hydrogen ion gradient resulting in an acidic extracellular pH (pHe) and alkaline intracellular pH (pHi). This “proton reversal” alters the thermodynamic balance and molecular energetics of the cell away from oxidative phosphorylation and towards aerobic glycolysis (a change known as the “Warburg Effect”). This shift in metabolism allows the cell to quickly meet high-energy demands, such as those required for proliferation.⁶

While the proton reversal observed in cancer is clearly pathologic, a similar phenomenon in the setting of EoE could well be adaptive. The resulting shift to glycolytic metabolism may promote protective cell proliferation in response to exposure of the esophageal mucosa to a noxious stimulus. Indeed, NHEs are elevated in the

esophagus of subjects with GERD,⁷ where they are thought to contribute to the epithelial proliferation that precedes the development of Barrett's esophagus. EoE is also associated with a proliferative basal zone hyperplasia,² that may be supported by glycolytic cellular metabolism.

Finally, it is interesting to place this work in context with a subset of EoE patients that initially or partially respond to proton pump inhibitor (PPI) therapy alone—so termed PPI-responsive EoE (PPI-REE).⁸ Researchers have hypothesized that PPI-REE is the result of subclinical GERD exacerbating an antigen-mediated esophageal eosinophilia, or some non-acid related benefit of PPIs such as immune modulation. However, it is also possible that PPIs are acting to influence acid balance in the epithelium. In addition to their well-known role in inhibiting gastric acid secretion, PPIs also inhibit the non-gastric H⁺-K⁺-ATPase (*ATP12A*) and V-type H⁺-ATPases, both of which are expressed in epithelial cells and cause intracellular alkalization in response to type 2 cytokines (**Figure 1**).⁹ Furthermore, V-type H⁺-ATPases are voltage coupled to secondary Na⁺-dependent transporters, providing a potential electrochemical link between these channels and NHEs.⁵ If this mechanism is in play, the initial or partial response to PPI therapy observed in PPI-REE may be a result of direct inhibition of epithelial proton extrusion, with any primary failure or subsequent relapse of PPI therapy in EoE resulting from IL-13-mediated or compensatory upregulation of NHE3.^{1, 10}

In sum, the work by Zeng and colleagues is important because it highlights previously unappreciated cellular acid regulatory pathways are highly active in esophageal epithelial cells of EoE patients. This fundamental observation not only answers a long-standing question in the field regarding the mechanistic origins of DIS,

103 but it also provides new avenues for investigations aimed at understanding the role of
104 epithelial acid balance in EoE pathogenesis.

FIGURE LEGENDS

Figure 1. Major proton extrusion channels of the esophageal epithelium. H⁺-K⁺-ATPases (K⁺ ATPase), V-type H⁺-ATPases (V-ATPase), and sodium-hydrogen exchangers (NHE) are expressed in the esophageal epithelium under various settings. PPIs directly inhibit K⁺ ATPase and V-ATPase function, while cariporide and S3226 inhibit NHEs. V-ATPases are voltage coupled to NHEs.

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Figure 1

