Journal Highlight: Development of Human Esophageal Explants for Eosinophilic Esophagitis

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Eosinophilic esophagitis (EoE) is a chronic and inflammatory disease of the esophagus. It is clinically characterized by esophageal dysfunction which includes dysphagia and food impaction, excessive fibrosis of esophageal tissue, and greater than fifteen eosinophils per high power field in a tissue biopsy. Although EoE is increasingly prevalent in children and adults, there is no curative treatment. Therapeutic strategies which include dietary elimination of food groups and medications such as proton pump inhibitors or topical steroids are solely for inflammation and symptom relief. In this article, Kurten *et al.* developed an *ex vivo* human esophageal mucosa explant system to further explore the genetic and proteomic profile of EoE. Kurten *et al.* confirmed that their explant system retains the contractile and elastic functions of the human esophagus following an extended period of time in culture. Furthermore, the authors demonstrated that they were successful in inducing a disease phenotype *ex vivo*. By treating the esophageal explants with a Th2 cytokine cocktail that mirrored the EoE inflammatory environment, they were able to induce transcriptional activation of genes associated with EoE *in vivo*, observe changes in cell-cell barrier organization and an increase in mucosal rigidity – all hallmark characteristics of patients with EoE. In summary, this article introduces a novel system to explore EoE biology *ex vivo*, confirming retention of functional properties of the human esophagus in a healthy and disease state, and demonstrating the applicability of the system to various hypotheses in EoE research.

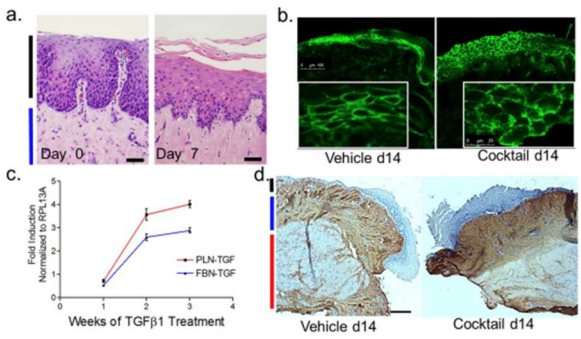

Figure 4. Properties of esophagus *ex vivo*. (**a**) Regeneration of superficial squamous cells of the stratum spinosum on day 7 after gentle scraping on day 0 (both untreated). (**b**) E-cadherin staining demonstrates squamous epithelial differentiation in full thickness esophageal mucosal explants cultured *ex vivo* for 14 days in vehicle or Th2 cytokine cocktail. 14 days of Th2 cytokine cocktail causes disruption of the epithelial barrier as occurs in the *in vivo* EoE active disease state. (**c**) Gene expression of phospholamban (PLN) and fibronectin (FBN) in LSM over 4 weeks of TGFβ1 treatment (***$p < 0.0001$). (**d**) Collagen1 staining in human esophageal mucosa following 14 days of vehicle or Th2 cocktail treatment (black line: epithelium, blue line lamina propia). Scale bars represent 50 (**a**) and 100 (**d**) microns if not otherwise labeled.

Kurten RC, Rawson R, Shoda T, Duong LD, Adejumobi D, Levy R, Newbury RO, Rothenberg ME, Akuthota P, Wright BL, Dohil R, Jones SM, Aceves SS. Development and Application of a Functional Human Esophageal Mucosa Explant Platform to Eosinophilic Esophagitis. *Sci Rep*. 2019 Apr 17;9(1):6206. doi: 10.1038/s41598-019-41147-8.

Question and Answer with Senior Author Dr. Seema S. Aceves

Q: What was your watershed moment that led you to decide you wanted to dedicate your career to eosinophil research?

A: It was really a clinical need that made me pursue eosinophilic diseases in the GI tract. I had a group of children with EoE/EGID who were not being taken care of in a systematic manner. That was

understandable since we did not know much about the pathogenesis. I was a fellow in Dr. David Broide's lab working on asthma remodeling. When we saw the trajectory to stricture formation it seemed likely that the process was akin to airway remodeling. I wanted to help the kids with the complications and to prevent the strictures by understanding the disease mechanisms as based on clinical phenotype. In addition, EoE is a unique opportunity to study eosinophilic inflammation and its consequences longitudinally since tissue is repeatedly obtained as part of disease management.
My mentors have been key to my decisions, especially Dr. David Broide, Dr. Marc Rothenberg who gave a talk at the San Diego Allergy Society when I was fellow, allowed me to participate in his EoE clinical trial, and solidified my interest in the disease, and Dr. Glenn Furuta who invited me to take part in the first consensus recommendations

Q: How do you plan to take this research forward?
A: My goal is to understand the intersections between inflammation and fibrosis and molecular mechanisms by which physical changes in the tissue environment like rigidity can affect a Th2, eosinophilic disease like EoE. The ultimate goal is to generate novel therapies to treat severe disease and alter disease progression. To do this, we use human model systems and have developed a new mucosal explant system (that we presented at the IES meeting in July 2019). I am particularly interested in how a structurally rigid and altered extracellular matrix alters the function of structural cells such as muscle cells and fibroblasts. We think at a certain point in the chronic disease stage, the physical environment sends cues that change the structural cells so that they begin to regulate pathogenesis in an inflammatory cell independent manner.

Q: Can you elaborate on the clinical applicability of your current findings?
A: We are working on new molecules that could be targets for therapeutic intervention.

Q: What advice do you have for trainees aspiring to enter the field of biomedical research?
A: Work hard, don't give up, and trust your instincts. If you follow the scientific path that calls you and make it your own then you're likely to succeed. After that, let the science tell you the story.

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