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Deeper than the epithelium - Role of matrix and fibroblasts in pediatric and adult eosinophilic esophagitis

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Complications of eosinophilic esophagitis (EoE) include esophageal fibrosis, esophageal stricture and progressive esophageal dysfunction that can manifest as symptoms of dysphagia, pain, and recurrent food impaction[1]. As the prevalence of EoE continues to rise and since tissue remodeling persists in some patients after treatment-induced resolution of acute inflammation, a clear need exists to understand underlying pathophysiologic mechanisms responsible for stricture formation in order to identify novel therapeutic targets.

Although a number of Th2 cytokines are considered to play a role in EoE, an increasing body of evidence supports a key role for TGF-β in stimulating remodeling effects in a number of different esophageal cells. For instance, TGF-β has been shown to induce epithelial-mesenchymal transition (EMT), smooth muscle contractility and fibroblast activation[2-6]. In addition, as highlighted by Muir *et al* in this issue of JPGN, tissue distensibility may also be affected and may be a functional target as evidenced by its extracellular matrix composition and effect on cellular substrate rigidity.

The authors seek to further expand our understanding of the mechanical and chemical microenvironmental impact in EoE by studying TGF-β's effects on substrate rigidity as it relates to human esophageal fibroblasts. They hypothesized that the fibroblasts from pediatric patients may respond differently to TGF-β compared to those from adults. Results could explain the clinical finding that fibrostenosis is a progressive problem that is more evident in adults than children.

To begin to address this, the authors use two innovative *ex vivo* model systems including polyacrylamide gel-based platforms with variable stiffness as well as a novel microfabricated-Post-Array- Detectors (m 266 PADs) system. Together these models provide a novel opportunity to measure differences in TGF-β induced remodeling in pediatric and adult fibroblasts.

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Their results show that in a microenvironment rich with TGF-β, human esophageal fibroblasts exhibit increased activation, fibrogenesis and contraction and that fibroblast activation and the *in situ* stiffness of the fibroblast environment may critically influence or perpetuate TGF-β signaling. Muir *et al* highlight how matrix stiffness may influence fibroblast activity in specific disease-associated microenvironments.

They also address the global concept that esophageal fibroblast behavior changes with aging and maturation. For instance, similar TGF- β pro-fibrotic responses were measured in fibroblasts obtained from children and adults subjects without EoE. In contrast, fibroblasts obtained from adults with active EoE responded with greater Type I Collagen synthesis than pediatric EoE fibroblasts. Together these results suggest a developmental paradigm specific to both age and inflammation. Fibroblasts may respond to fibrogenic agonists in a differential manner following inflammatory processes depending on their age and duration of disease activity. Clinically, this finding could explain the perceived propensity for strictures and fibrostenosis to develop more often in adults than in children.

These provocative findings also leave us with some unanswered questions. Is this paradigm true for all patients? Certainly, clinical experiences suggest that some pediatric patients may develop strictures whereas some adults with EoE may not. Is this clinical observation related to a genetic predisposition to develop strictures (i.e. fibrostenotic EoE) or a variable expression of TGF-β and its receptors within the tissue microenvironment? Comparisons of fibroblast stiffness from both pediatric and adult patients with well-defined fibrostenotic disease and non-stricturing disease may help us understand this conundrum. What is the source of TGF-β? Since some non-inflamed tissues may continue to exhibit fibrostenosis, it is suggested that TGF-β may be stored within the matrix and be released depending on tissue stiffness. This may be true, but the biologic activity of the TGF-β in this circumstance is unknown and TGF-β can be synthesized and released by a number of cells including mast cells and eosinophils that may have escaped mucosal biopsy detection. Is fibrosis inevitable in all EoE patients despite successful anti-inflammatory treatments? Can this be a reflection of the persistence of tissue remodeling in some patients after treatment-induced resolution of inflammation. Finally, are there therapeutic interventions that may target TGF-β and not eosinophils? Interestingly, a recent study identified TGF-β as a novel therapeutic target in children with EoE and connective tissue diseases [7]. Their findings support the need for early detection and chronic treatment of this disease.

The authors' findings set the stage for a number of future studies. In addition, they introduce us to important novel technologies that may provide insights for *in vitro* and *ex vivo* EoE models and sheds new light on the potential role of TGF-β in EoE remodeling. *Ex vivo* modeling provides us with some insights into processes that may be occurring in the sub-epithelial layer, an area inconsistently captured by mucosal biopsies, but one in which clinical decisions are often based upon. For instance, lamina propria fibrosis is not infrequently used as an indicator of chronicity or pathological fibrosis. Findings presented here suggest that both control and EoE fibroblasts responded similarly to TGF-β with respect to SMA, fibronectin, collagen 1a, and indicate that fibrosis may be a common finding related to mucosal injury but not to a specific disease state.

Clinical implications of this study relate to age-associated changes in esophageal fibroblast function. Development of fibrosis and increased tissue stiffness may perpetuate further tissue remodeling and thus explain disease progression. These results highlight the importance of early functional assessment of the esophagus with techniques such as manometry or the EndoFLIP (Endolumenal Functional Lumen Imaging Probe), a catheter-based technology that can determine esophageal distensibility as a measure of compliance in both children and adults. The clinical identification of earlier evidence of tissue rigidity may be an important opportunity for therapeutic intervention and the prevention of constitutive fibroblast activation that may be independent of inflammatory stimulus, as is presented in this study. Therapeutic studies targeting TGF-β provide novel approaches to caring for some patients (https://www.clinicaltrials.gov/ct2/show/NCT01808196). As our understanding of tissue remodeling and fibrosis increases, natural history studies (http://www.rarediseasesnetwork.org/cms/cegir/) and those extending beyond the mucosal pinch biopsy that involve the complex interactions among eosinophils, fibroblasts and other cell types involved in tissue remodeling are vital.

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