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Augmenting Epithelial Restorative Capacity to Attenuate Opportunistic Infection

Dr. Eisenhoffer is an Assistant Professor and CPRIT Scholar in Cancer Research in the Department of Genetics at The University of Texas MD Anderson Cancer Center. Dr. Eisenhoffer received his undergraduate degree from the University of Texas at Austin and his PhD from the University of Utah. Dr. Eisenhoffer's research focuses on understand how cell proliferation and death are coordinated to control overall cell numbers. Dr. Eisenhoffer's lab studies the birth and death of epithelial cells using the developing zebrafish as a model system to elucidate the mechanisms that regulate epithelial cell function under physiological conditions, after tissue damage, and after genetic perturbation to gain a better understanding of how specific changes drive pathogenesis.

Abstract:
Epithelial tissues provide the first line of defense against foreign pathogens, and sustain a functional barrier by removing aberrant or unfit cells by a process called cell extrusion. Disruption of epithelial homeostasis by widespread damage caused by trauma or cytotoxic chemotherapy frequently allows for opportunistic fungal infections to arise. The interaction of fungal pathogens with the epithelial cells that comprise mucosal surfaces is a key early event associated with invasion, and therefore, enhancing epithelial defense mechanisms may mitigate potential infections. The technical challenges to perturb living epithelia in the presence of fungi and image subsequent changes in real time has thus far prevented a detailed characterization of how tissue damage can contribute to invasive fungal disease. To overcome these limitations, we expose zebrafish larvae to different medically important human fungal pathogens after inducing epithelial cell extrusion and define fungal interactions with damaged mucosa and the local and systemic immune responses. Using in vivo time-lapse imaging and assessment of fungi defective in adherence or filamentation, we demonstrate epithelial cell loss by extrusion exposes laminin that is associated with increased fungal attachment, invasion and larval lethality. Transcriptional profiling identified significant upregulation of the epidermal growth factor receptor ligand epigen

(EPGN) upon cell extrusion and mucosal damage. Treatment with recombinant human EPGN suppressed epithelial cell extrusion through a MEK–ERK signaling mechanism to prevent decreased integrity and provide protective effects against opportunistic infection, leading to reduced fungal invasion and significantly enhanced survival. Together, these data support the concept of augmenting epithelial restorative capacity to attenuate pathogenic invasion of fungi associated with human disease.