

LIFE SCIENCES CAFÉ

Seminar Series • Fall 2017



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Date: Monday, Sept. 18
Senita C, Student Pavilion

Seminar:
11:45 a.m.-12:45 p.m.

Eat and Greet:
12:45-1:15 p.m.

Human Intestinal Enteroids: Translating Stem Cell Biology to Understand Gastrointestinal Virus Infection

Introduction. A limitation in translational research in the gastrointestinal tract has been the absence of models that recapitulate the diverse nature of the epithelium. Human intestinal enteroids (HIEs) contain the normal complement of intestinal epithelial cell types (stem, enterocyte, goblet, enteroendocrine, and Paneth cells).

Methods. We have utilized HIE cultures as pre-clinical models to study the response of the epithelium to common viral pathogens such as human rotavirus (HRV) and human noroviruses (HuNoV), which each kills almost 200,000 children annually by causing dehydrating gastroenteritis. Studies on HRVs have been limited because they are difficult to culture in transformed cell lines and do not infect small animals and HuNoVs were non cultivatable until 2016.

Results. We established HIEs derived from patient small intestinal tissue, showed they support HRV infection, and demonstrate previously unappreciated pathophysiologic and molecular responses to infection. Undifferentiated HIEs, consisting primarily of immature enterocytes, Paneth and stem cells, are less susceptible to infection compared to fully differentiated HIEs that consist predominately of mature enterocytes, confirming in vivo findings that the villus enterocyte is the primary target of HRV infection and replication. Enteroendocrine cells also are infected suggesting signaling that may be related to pathogenesis. Infection increases proliferation and cell death and alters cellular metabolism pathways and innate immune responses. HIEs also are susceptible to infection with the previously noncultivable human noroviruses (HuNoVs) providing the native intestinal milieu is mimicked. Host-specific phenotypes and strain-specific requirements needed for successful HuNoV cultivation have been identified.

Conclusions. These findings establish HIEs as new models to understand the intestinal epithelial response to human gastrointestinal infections such as HRV and HuNoVs. HIEs allow us to address new questions about human host-pathogen interactions such as innate immune responses, stem cell activity, cell-cell communication within the epithelium and to identify and test new drug therapies to prevent/treat diarrheal disease.