Identification of Environmental Toxicants that Trigger Digestive and Liver Disease

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ABSTRACT

Compounds produced by modern societies are increasingly recognized as potential triggers of human disease, particularly in genetically susceptible individuals. Here, we propose to screen a library of high- risk chemical compounds (NIEHS Tox21 Library) for activity in two human digestive diseases using zebrafish models established by my laboratory. The first condition, Irritable bowel syndrome (IBS), is a motility disorder that is the most common gastrointestinal condition for which adults seek medical attention. The etiology of IBS is unknown but likely involves altered regulation of enteric neuromuscular function. The second, Biliary atresia, is a rare but important disorder that is the leading indication for liver transplantation in the pediatric population. Like IBS, the cause of BA is not known. Exposure to an environmental agent (toxin/toxicant, virus) has long been suspected, but never proven. My lab has developed tools to model both IBS and BA in the zebrafish system that are amenable to in vivo high throughput screening assays. Preliminary mechanistic studies point to a role for altered redox signaling in both the IBS and BA models. Based on these findings, we hypothesize that environmental toxicants capable of inducing oxidative stress could serve as triggers for these disorders. As a first step in identifying such agents, we will screen Tox21 compounds pre-selected for their ability to trigger upregulation of anti-oxidant and heatshock responses in human cells using the zebrafish IBS and BA screening assays. Active compounds identified in these screens will be examined further to understand their mechanism of action and tissue specificity.