p53-mediated molecular recycling and environmental carcinogens exposure
Anil Rustgi, MD

Abstract
Environmental carcinogens present in tobacco smoke and alcohol metabolites contribute to the pathogenesis of esophageal squamous cell carcinoma (ESCC) where gain-of-function (GOF) mutations of p53 tumor suppressor gene promote malignant transformation of esophageal epithelial cells. The overall objective in this proposal is to define *a novel p53 function that limits endocytic recycling and subsequent protein degradation of molecules such as EGFR essential in cell survival and oncogenic signaling*. Deregulation of the endocytic recycling pathway has emerged as a hallmark of malignant attributes in a variety of human cancers. While long-term exposure to environmental carcinogens induces p53 mutations, these carcinogens impair endocytic recycling. Our *central hypothesis* is that p53 suppresses environmental carcinogen-mediated malignant transformation via endocytic recycling. This hypothesis has been formulated based on our strong preliminary data using esophageal cell lines carrying GOF-p53 mutations and novel mouse models of ESCC induced by 4-nitroquinoline 1-oxide (4NQO), a tobacco smoke-mimetic esophageal carcinogen. This hypothesis will be pursued in interrelated *Specific Aims*: (i) Define the role of p53 mutations to facilitate 4NQO-mediated neoplastic transformation; and (ii) Determine dysfunctional endocytic recycling in EGFR signaling in p53-mutant ESCC cells. We will use novel genetically engineered mouse models of ESCC, coupled with e*x vivo* analyses of esophageal 3D organoids and genetic modifications of cells to interrogate endocytic recycling *in vitro*. These studies will provide novel insights into the functional interplay between environmental carcinogens and p53 tumor suppressor in ESCC pathogenesis. These results may be applicable to other squamous cell carcinomas. Furthermore, these studies will advance our understanding of a potential mechanism of p53 action as well as the endocytic recycling pathway, which can provide novel targets for ESCC prevention and therapy. Finally, this project will help the applicant to prepare for a future NIH/NIEHS grant submission for further study in this field.