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Modeling Esophageal Cancer: Three-Dimensional Cell Culture Systems

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Esophageal cancer comprises two major types, namely, squamous cell carcinoma and adenocarcinoma. Epidermal growth factor receptor (EGFR) overexpression and p53 mutation are frequent genetic alterations in the premalignant stages and advanced stages of esophageal squamous cell carcinogenesis, respectively. Yet, the molecular basis for the contributions of EGFR and mutated p53 to esophageal carcinogenesis remains unclear. To that end, the biologic roles and functional consequences of EGFR overexpression and p53 mutation are being pursued in vitro and in vivo. These include primary esophageal epithelial cells, esophageal organotypic cell cultures and mouse models with targeted overexpression of EGFR and mutant p53 in the esophagus. Our fundamental hypothesis is that EGFR activation induces a network of cellular responses that facilitate hyperproliferation in the basal cell compartment and induction of migration of such cells into the suprabasal compartment without commitment to differentiation. Although these

processes are necessary, they are not sufficient to cause cancer, and thus, other genetic events, most notably p53 mutation, are required.

Our studies characterize cells overexpressing EGFR and four different p53 mutants grown in three-dimensional cell culture (organotypic culture), which involves a system that explores the biology of epithelial and tumor cells in their microenvironment. We assess the functional effects of EGFR overexpression and p53 inactivation on transformation potential by assessing cell proliferation, migration and invasion capabilities and effects on key signal transduction pathways (focusing on the PI3K/Akt and Ras/MEK/MAPK pathways) in the esophageal squamous epithelium. To understand the in vivo roles of the cooperation of EGFR and mutant p53, mice overexpressing EGFR in esophagus have been generated using the Epstein-Barr virus ED-L2 promoter (L2). These mice are being crossed with keratin 14 (K14)-cre mice to obtain L2-EGFR+/K14-cre mice. A final cross with p53^{LSL.R172H} and p53^{LSL.R270H} mice will lead to expression of mutant p53 specifically in K14 target tissues, including the esophagus. We will use these approaches as a basis in the future to understand the transdifferentiation to Barrett's esophagus and development of esophageal adenocarcinoma.