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## **Combined EGFR Overexpression and p53 Inactivation in Esophageal Epithelial Cells Leads to Increased Tumorigenic Potential**

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**Background:** Esophageal squamous cell carcinoma (ESCC) is a highly malignant gastrointestinal cancer that is associated with a high mortality rate. Epidermal growth factor receptor (EGFR) overexpression and p53 mutation are frequent genetic alterations in esophageal squamous cell carcinogenesis; however, the molecular basis for the contributions of EGFR and mutant p53 to ESCC remain unclear. These studies tested the hypothesis that in ESCC, EGFR overexpression results in increased proliferation 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.

**Methods:** To test our hypothesis, human esophageal epithelial cells overexpressing EGFR alone or in combination with mutant p53 were studied to determine the role of these genetic alterations in ESCC. We also tested four different p53 mutants (V143A, R175H, R248W and R273H). Cells were grown in monolayer and three-dimensional

organotypic culture. Effects on proliferation, migration and invasion capabilities were assessed.

**Results:** Cells overexpressing EGFR and mutant p53 showed increased proliferation compared with cells overexpressing EGFR alone. Combined overexpression of EGFR and mutant p53 also resulted in increased migration and invasion capabilities. When grown in an organotypic culture, cells overexpressing EGFR and all four p53 mutants tested resulted in increased invasion into the underlying matrix compared with control cells. However, the different p53 mutants resulted in pleiotropic effects on the extent and type of invasion.

**Conclusion:** These studies suggest that combined overexpression of EGFR and mutant p53 gives rise to a stronger malignant phenotype compared with EGFR overexpression alone. Additionally, the magnitude of this phenotype may be influenced by the type of p53 mutation present.