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Estrogen Receptor Signaling in Oral Squamous Cell Carcinoma

Oral cavity squamous cell carcinoma (OSCC) accounts for 2.0% of new cancer cases and 1.8% of cancer deaths worldwide. OSCC-associated mortality is high with a 30-50% 5-year overall survival in advanced-stage disease. While OSCC most commonly affects males with a history of tobacco and alcohol use, there is an increasing incidence of OSCC in female nonsmokers and nondrinkers which is not attributed to human papilloma virus infection. ER alpha (ERα) and ER-beta (ERβ) modulate cell proliferation and survival in many cancer types, and emerging data has identified ERα an indicator of improved prognosis in head and neck cancers. The prognostic significance of ERα and ERβ expression has not been validated in OSCC. Our preliminary analysis of the OSCC dataset within The Cancer Genome Atlas (TCGA) have identified a trend towards improved overall survival for OSCC with high ERα and high ERβ expression as compared to all other ERα and ERβ expression patterns. The overall hypothesis of this proposal is that ERα and ERβ co-expression is a predictor of improved overall survival in OSCC and is associated with decreased OSCC cell proliferation and cell survival. We propose two specific aims. Aim 1 will validate ERα and ERβ expression as a predictor of overall survival in OSCC and develop a risk stratification score in combination with clinicopathologic features. Aim 2 will characterize the effects of ERα and ERβ signaling on cell proliferation and survival in OSCC through cell cycle modulation and p53 signaling using in vitro studies. Overall, these studies are anticipated to enhance our understanding of the role of ERα and ERβ pathways in OSCC tumorigenesis. Successful outcome of this study will create a paradigm shift in how surgeons and oncologists manage and risk-stratify OSCC and will provide scientific support for future in vivo studies further characterizing ER signaling in OSCC tumorigenesis, with the ultimate goal of developing a new mechanism-based therapy for patients with OSCC.