

# Advancing the Cancer Stem Cell Approach for Early Tumorigenesis: Delineation of p53 Pathways in Differentially Expressed Tumor-Initiating Cells

Liu, Fan

Evidence suggests a small population of tumor-initiating cells, or cancer stem cells, drive tumor heterogeneity which is postulated to account for tumor growth and resistance to chemotherapy. Elucidating the genetic pathways and epigenetic modifications of cancer stem cells before metastasis is crucial. In this project, the role of p53, a tumor suppressor that is mutated in 50% of all tumors, was examined due to its critical role in cancer progression. To model early tumorigenesis, differential gene expression analysis was performed to analyze the effects of stabilizing p53, via the small molecule Nutlin-3, in tumor-initiating cells (BPECs) and differentiated mammary epithelial cells (HMECs). Bioinformatic analysis of microarray data revealed c-Myc's critical role in differentially regulating cellular cycle processes and was validated via western blot. Cell proliferation assays revealed that when tumor-initiating cells (BPECs) were treated with Nutlin-3, there was a higher rate of cell death whereas the differentiated tumor cells (HMECs) continued to proliferate. Thus, in cancers with deregulated p53, targeting the c-Myc/p53 pathway could directly target cancer stem cells. Flow cytometry results also showed differential regulation in apoptotic and necrosis rates. It was postulated that acetylation was responsible for variation in apoptosis and was validated via western blot. Tumor-initiating cells treated with Nutlin-3 and cisplatin, a commonly used chemotherapeutic agent for breast cancer patients, saw a dramatic reduction in stem progenitor cells, implicating a potential way to target tumor-initiating cells specifically. This research provides a relevant approach to target tumor-initiating cells, thereby preventing cancer from metastasizing.