FOXO: A TARGET FOR PROSTATE CANCER PREVENTION

Focus Area: Prostate Cancer
Research Type: Translational
Funding Source: National Cancer Institute

Description:
Epidemiological studies and clinical observations suggest that persistent chronic inflammation is important in prostate carcinogenesis. The chronic inflammatory lesions frequently observed in prostate tissue biopsies and radical prostatectomy specimens are consequence to the aging process and precursor to prostate cancer development. These findings are supported by the reports that long-term use of anti-oxidant decreases the risk of prostate cancer. Members of the FOX family group 'O' control important network of genes that influence cell proliferation, inflammation, repair DNA damage, and oxidants/antioxidants balance. In the absence of growth signal, the FOXO family members remain transcriptionally active in the nucleus. Upon stimulus via PI3K-Akt pathway, FOXO proteins are phosphorylated and translocates to the cytoplasm, abrogating its transcriptional activity. We have recently demonstrated (Submitted in the Late-Breaking Session at the Annual Meeting of American Association for Cancer Research, 2008 and as preliminary data in the proposal) deregulation and redistribution of FOXO proteins in the cellular compartments in human prostate cancer cell lines and tissues.

Furthermore, levels of FOXO3A were significantly higher in the cytosolic fraction than the nucleus as a function of age and disease progression. Hyperactivation of Akt causes increased Foxo3a binding with 14-3-3 and its accumulation in the cytoplasm of TRAMP mice prostates, compared to non-transgenic littermates at 20-28 weeks of age. This decreased Foxo3a levels correlated with downregulation of the basal levels of p21/WAF1, MnSOD and Cu/ZnSOD in the prostates of TRAMP mice thereby shifting the oxidants/antioxidants balance towards increased oxidative stress and cancer progression. Based on these interesting findings we suggest FOXO signaling pathway as a key molecular target for the development of preventive strategies against prostate cancer. The present proposal capitalizes on these novel findings and is designed to investigate the cancer preventive potential of apigenin, a plant flavonoid present in common fruits and vegetables, by targeting FOXO signaling pathway. This proposal will employ TRAMP model which is an appropriate animal model to test our working hypothesis as it mimics progressive forms of human prostatic disease. Validation of this hypothesis may have implications for prostate cancer in humans.