Independent Research Portfolio - Example

Epidermal growth factor receptor (EGFR) is a key regulator of epithelial cell growth and differentiation. Aberrant regulation EGFR pathway is a critical driver ofturmorigenesis in many types of epithelial cancers. Solar ultraviolet (UV) irradiation is the major cause of skin cancer, and my previous studies have revealed that UV irradiation rapidly activates EGFR in human skin cells (keratinocytes). This activation leads to stimulation of multiple signal transduction pathways that promote abnormal cellular function. My research has revealed that the mechanism of EGFR activation by UV irradiation is through oxidative inhibition of receptor type protein tyrosine phosphatase-kappa (RPTP-K). I found that RPTP-K directly dephosphorylates EGFR and thereby maintains EGFR in an inactive state. RPTP-K is the major physiological negative regulator of EGFR in human keratinocytes. Through photochemical reactions, UV irradiation generates reactive oxygen species that inhibit RPTP-K, and this oxidative inhibition is responsible for UV irradiation activation of EGFR. My research has demonstrated that UV irradiation rapidly stimulates EGFR nuclear translocation, thereby allowing EGFR to directly impact gene expression. This translocation is dependent on EGFR phosphorylation, which is under the control of RPTP-K. Therefore, RPTP-K not only controls EGFR activation, but also EGFR nuclear localization and function. I have also demonstrated that RPTP-K mediates functional integration of EGFR and transforming growth factor-beta (TGF-P) signaling pathways in human keratinocytes. Additionally, I have established a skin-specific RPTP-K transgenic mouse model to investigate the regulation of EGFR function by RPTP-K. Based on these research findings, I was awarded an NIH ROl grant as co-principal investigator to study regulation of EGFR pathway by RPTP-K in sun-exposed skin and skin cancer, using tissue culture, animal model, and human skin.

I have extended my research to examine phosphatase regulation of other members of the tyrosine growth factor receptor family. I have discovered that the activity of the hepatocyte growth factor receptor (Met) is directly regulated by receptor protein tyrosine phosphatase-beta (RPTP-p). RPTP-P is the major physiological negative regulator of Met activation. The Met pathway plays pivotal roles in normal epithelial cell functions and is often abnormally-regulated in epithelial cancer. Met often conspires with EGFR in head and neck cancer progression, metastasis, and resistance to chemotherapy. I have found that RPTP-P is a key negative regulator of Met functions in human head and neck cancer cells, and down-regulation ofRPTP-P is a prominent feature in invasive HNSCC cells and tumor samples. These studies were conducted in collaboration with Dr. Thomas Carey and colleagues, Head and Neck Cancer SPORE in the Otolaryngology Department.

In addition to my inter-departmental collaborations within the University, I have initiated and lead an international collaboration with investigators at Wenzhou Medical College and Zhejing Mariculture Research Institute in Wenzhou, China. Together, we have successfully identified compounds in seaweed extracts that protect RPTP-K from oxidative inhibition by UV- irradiation. Ongoing work is focused on translational studies to evaluate the ability these compounds to reduce the damaging effects of solar UV irradiation on human skin.

In summary, I have successfully competed for Foundation and NIH grants, I have a track record of peer-reviewed publications, and I have written invited review articles on topics such as photobiology, receptor protein tyrosine phosphatases, and the Met pathway in head and neck cancer. I have established a unique and independent research program in the field of receptor protein tyrosine phosphatases, which has garnered national/international recognition.