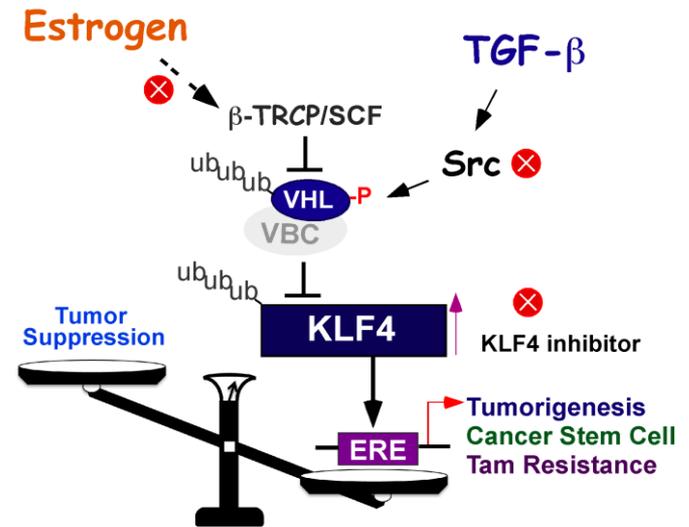


Crosstalk between estrogen receptor and TGF- β signaling in breast tumor initiation, progression and invasion

Defective regulation of estrogen receptor (ER) and transforming growth factor beta (TGF- β) signaling pathways can predispose breast cells towards carcinogenesis. Our recent findings have revealed a previously unknown mechanism that centers on the interplay between KLF4, an oncogenic transcriptional factor, and VHL/VBC (E3 ligase) as well as between VHL and b-TRCP/SCF (E3 ligase) in cell cycle control and proliferation. Their functional interaction is critical in orchestrating the crosstalk between ER and TGF- β signaling pathways, which in turn determines whether breast cells retain their homeostasis or are transformed to initiate oncogenic growth. Our observations have provided insight into the pathological mystery previously observed by us and others that over 70% of human mammary cancers exhibited cellular accumulation of KLF4 and decreased levels of VHL protein and that disruption in b-TRCP function in mice could result in tumor initiation and progression. We are currently studying the molecular basis of the interplay between KLF4 and VHL/VBC as well as VHL and b-TRCP/SCF in their regulation of ER and TGF- β signal transduction and determining how impaired KLF4 proteolytic regulation due to dysregulated VHL/VBC or b-TRCP/SCF



would impact breast tumorigenesis using a breast cancer animal model. Outcomes from this project could provide a more effective strategy to modulate the ER signaling pathway by exploiting components of the b-TRCP/SCF - VHL/VBC - KLF4 cascade. Controlling the ER signaling pathway has long been a key focus in the field to develop new methods for chemoprevention and endocrine therapy for breast cancer treatment. This project is recently funded by NIH/NCI R01 grant (CA202948).

Killing breast tumor-initiating cell by synergizing molecular axes of PARP-KLF4 and EGFR-KLF4

PARP1, ionizing irradiation and EGF receptor signaling profoundly promote renewal of tumor-initiating cells. Synergistic blockade of PARP1-KLF4 and EGFR-KLF4 cascade could efficiently kill breast cancer cells. One of the most recent striking findings in stem cell and tumor-initiating cell field is that PARP1 could elevate iPS induction-rate by 100 folds, while ionizing irradiation significantly enhances subpopulation of breast tumor-initiating cell resulting in increases in cancer heterogeneity. We and others have observed that KLF4 is an important factor that facilitates the effect of PARP1 and ionizing irradiation. In addition, we also observed EGF2 is critical to alter subpopulation of breast tumor-initiating cell. Accordingly, we are now addressing the mechanism of how PARP1, ionizing irradiation and EGFR synergistically orchestrate KLF4 resulting in increased breast tumor-initiating cell population, and we are therefore proposing a synthetic lethality based strategy to treat breast tumor-initiating cell using combination of PARP1 and EGF2 inhibitors in human breast cancer xenograft mouse model.

