JOSEPH F. FOSTER MEMORIAL
CHEMICAL BIOLOGY AND BIOCHEMISTRY SEMINAR

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3:30 PM, BRWN 4102

"LIMK2-UBE2C Synergy Drives Castration-Resistant Prostate Cancer."

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Abstract:

UBE2C is overexpressed in CRPC and shows strong correlation with lymph nodes metastasis, Gleason score and progression-free survival. Nonetheless, UBE2C inhibitors are currently lacking. We report its first post-translational regulation, which is mediated by LIMK2 kinase. An innovative screen uncovered UBE2C as a direct LIMK2 substrate. LIMK2 exerts multi-faceted control over UBE2C. First, it upregulates UBE2C upon hypoxia. Second, LIMK2 inhibits its ubiquitylation via phosphorylation at S123. Third, LIMK2 increases UBE2C mRNA levels in 22Rv1 cells via upregulating ARv7. In C4-2 and PC3 cells, both of which lack ARv7, it increases UBE2C mRNA levels by enhancing AKT signaling. Thus, LIMK2 ubiquitously increases UBE2C protein stability and mRNA levels in three different cell-types. Furthermore, contrary to its well-known role as an ubiquitylation-promoter, UBE2C stabilizes LIMK2 in a reciprocal loop. This is the first report showing that UBE2C stabilizes its substrate. UBE2C also increases LIMK2 mRNA levels, although the mechanism remains unknown. LIMK2-UBE2C loop is extremely oncogenic creating CRPC pathogenesis in vivo. Targeting LIMK2 provides a potent tool to not only degrade UBE2C, but also degrade LIMK2, thereby significantly inhibiting tumorigenesis, cancer stem cell phenotype and epithelial to mesenchymal transition in vivo.

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