Identifying the oncogenic role of USP10 as the regulator of PTEN function in breast cancer

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Background: The PI3K pathway is the most commonly activated signaling pathway in human cancer. The loss of PTEN further contributes to the tumorigenic impact of the
active PI3K pathway, and have direct effect on prognosis of breast cancer. Although many small molecules are used in clinic to target the PI3K pathway, only minority of breast cancer patients respond to these drugs. This study identified the role of a deubiquitinating enzyme, USP10 in the regulation of PI3K pathway in breast cancer.

**Methods:** A genome wide RNAi screen targeting all known deubiquitinating enzymes was performed and level of phospho-AKT was assessed by western blotting. Significant hits of the screen were validated and mechanism of action in PTEN-mediated regulation of PI3K pathway and resistance to PI3K inhibitors in breast cancer has been investigated.

**Results:** We identified USP10 as a critical regulator of PI3K pathway. MAGI1 has been recently identified as PTEN interacting protein, and along with MEK1 functions to promote PTEN recruitment to the plasma membrane. We found USP10 as a part of complex between MEK1, MAGI1 and PTEN. Functionally, we demonstrated that USP10 stabilizes ITCH which is an E3 ligase for MEK1 resulting in degradation of MEK1 and decreased PTEN plasma membrane localization. We showed that downregulation of USP10 decreases activation of AKT, and results in decreased colony forming ability of breast cancer cells. Furthermore, expression analysis of USP10 revealed significantly higher levels of USP10 in breast cancer patients and its expression was correlated with the tumor progression and poorer overall survival in the breast cancer patients.

Interestingly, we showed the upregulation of USP10 protein level in PI3K inhibitor resistant breast cancer cells as compared to their parental control and further depletion of USP10 resensitized these cells to PI3K inhibitors. In addition, positive correlation between USP10 and PTEN protein levels was observed in the PDX model of breast cancer patients who progressed after receiving PI3K inhibitor.

**Conclusions:** Overall, our results identify overexpression of USP10 as a potential mechanism for loss of PTEN functionality and PI3K pathway in breast cancer patients, and its possible involvement in resistance to PI3K inhibitors.

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