Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers with CDK4/6 Inhibitors
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Presenter: Pei-Chuan Ho  Date/Time: 2016/11/17, 16:10 - 17:00
Commentator: PhD. Nan-Shan Chang  Location: Room 601, Med College Building

Background:
Overexpression of the human epidermal growth factor receptor 2 (HER2) receptor tyrosine kinase is typically triggered by amplification of the wild-type ERBB2 gene, which encodes for HER2 and serves as a real oncogene. Despite successful HER2-directed therapies, many patients with HER2-positive breast cancer will succumb to their disease once tumor cells develop resistance. A number of mechanisms have been proposed to mediate the resistance of HER2-positive breast cancers to targeted therapy. Notably, correlative science from clinical trials has yet to validate any of these mechanisms.

Objective/Hypothesis:
To uncover mechanisms of resistance to HER2-pathway blockade.

Results:
This study shows that the Cyclin D1/cyclin-dependent kinase 4 (CDK4) pathway can mediate this resistance to targeted therapy for HER2-positive breast cancer. Inhibition of CDK4/6 not only reduces retinoblastoma protein (Rb) phosphorylation, but also suppresses tuberous sclerosis complex 2 (TSC2) phosphorylation and thus partially decreases mTORC1 activity. This relieves feedback inhibition of upstream EGFR family kinases, resensitizing tumors to EGFR/HER2 blockade. Therefore, dual inhibition of EGFR/HER2 and CDK4/6 invokes a more potent suppression of TSC2 phosphorylation and hence mTORC1/S6K/S6RP activity. The suppression of both Rb and S6RP enhances G1 arrest and a phenotype resembling cellular senescence. Combined HER2-CDK4/6 inhibition synergistically blocks cell proliferation, controls tumor growth in vivo, and delays tumor recurrence in a transgenic mouse model.

Conclusion:
The authors observe that a small number of cyclin D1-expressing tumor cells survive HER2 withdrawal, and that targeting these cells with a CDK4/6 inhibitor can prolong the time to tumor recurrence. These results invite speculation regarding the role of CDK4/6 inhibitors as an adjuvant therapy for breast cancer.

References: