Investigating CDK4/6 Palbociclib resistance mechanisms in MCF7 breast cancer cell line

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Deregulation of the cyclin D-CDK4/6-INK4-RB pathway leading to uncontrolled increased cell proliferation, is observed in various cancer types including breast cancer. Palbociclib is one of the selective CDK4/6 inhibitors approved for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. Despite initial response to Palbociclib, intrinsic or acquired resistance emerges eventually. Understanding resistance mechanisms to CDK4/6 inhibitors enables us to design drug combination regimen to overcome or delay resistance onset, to identify biomarkers to predict therapy outcome that can be utilized to stratify patients who benefit from the treatment and to identify novel druggable targets in the CDK4/6 drug resistance milieu.

To investigate proteome alterations leading to Palbociclib resistance, we established resistant sublines of MCF7 breast cancer cell line by culturing the cells in a) under constant pressure of 1uM Palbociclib and b) in drug holiday after 1uM Palbociclib for several cycles. We then performed RPPA (Reverse Phase Protein Array) technology to analyse 384 protein targets in the two groups compared to parental Palbociclib sensitive MCF7 cells as well as comparing the two resistant sublines. Pathways analyses between the sensitive vs. resistance cells showed significant changes in cell cycle dependent and independent pathways. To validate the proteome alterations, we are performing RNAseq analysis on the cell line pairs.

The pathways that change most dramatically in resistant cells include the EGFR pathway, p53 pathway, and the JAK-STAT pathway. These pathways are closely related to the occurrence, development and metastasis of cancer. Drugs that target these pathways may provide new therapeutic strategies for Palbociclib-resistant patients. It is also a potential combination drug therapy strategy.