Sub-Group of PIK3CA WT breast cancer patients have hyperactive S1P and LPA signaling tumors responsive to PI3K inhibitors: functional signaling test identifies new patient group who may benefit from PI3K inhibitors

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Background

Less than 20% of PI3KCA mutated late stage breast cancer patients achieved an objective response in a Phase III clinical trial with alpelisib, a recently approved PI3K inhibitor. The suggested factors other than PI3KCA signature status likely to be in remission when identifying patients eligible for PI3K inhibitors. The most recent work has shown that even patients with PIK3CA WT tumors can benefit from PI3K inhibitors if they have hyperactive S1P or LPA signaling. S1P, LPA and other lipid mediators can stimulate cellular processes through their specific GPCRs, either in an autocrine or paracrine fashion. This specific GPCR signaling may result in increased phospholipid agonists due to lipid metabolism abnormalities in breast cancer cells. The accumulation of phospholipid agonists of specific GPCRs may be a new causal factor in tumor progression.

The accumulation of phospholipid agonists of specific GPCRs, due to lipid metabolism abnormalities in cancer cells, may be a causal factor in tumor progression.4

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A new assay using an impedance biosensor designed to quantify cellular adhesion changes was developed to measure phospholipid-GPCR-initiated signaling activity in live tumor cell response in real-time to specific S1P and LPA agonists and PI3K antagonists to diagnose breast tumors with PI3K-involved hyperactive signaling.

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Results

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Functional signaling test identifies new patient group who may benefit from PI3K inhibitors

PI3K Involvement in S1P/LPA/HER1/HER3 Signaling

Summary of Results

Conclusions

Results

Figure 2: Analysis of PI3K Involvement in S1P/LPA/HER1/HER3 Signaling in p110α Mutant HCC1954

- The accumulation of phospholipid agonists of specific GPCRs, due to lipid metabolism abnormalities in cancer cells, may be a causal factor in tumor progression.4
- PI3K inhibitors may provide a novel therapeutic strategy to target hyperactive S1P and LPA signaling.

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