Brief Summary:

The work showed for the first time that HER2 dimerization domain mutants namely G309A, S310Y and P523S can change the interaction pattern of HER2 from HER2:HER2 homo-dimer to HER2:HER3 hetero-dimer. We also showed that the receptor switching due to interaction domain mutations changes the downstream signalling from MAPK in HER2-WT and S305C expressing mutants to PI3K-AKT in G309A, S310Y and P523S expressing mutants in breast cancer cells. The observation of this switch was also observed in the patient transcriptome data, ERK signalling pre-dominant in HER2-WT and S305C harbouring patient to AKT signalling pre-dominant in G309A and P523S harbouring patient. HER2-WT and S305C expressing breast cancer cells formed HER2:HER2 homodimer and expectedly, were highly sensitive to both Trastuzumab and Neratinib. Interestingly, we also found that breast cancer cells harbouring the G309A, S310Y and P523S mutations were more aggressive and were resistant to Trastuzumab (first line of treatment) and Neratinib (last line of treatment). Treating these breast cancer cells did not cause any change in the short-term, long-term as well as anchorage-independent growth of these mutation harbouring breast cancer cells.

The work highlights the change in the interaction dynamics of HER2 due to dimerization domain mutations, also dictating the response of the mutation harbouring breast cancer cells against HER2 targeted therapy prescribed in clinics.

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