Unveiling the Impact of Cancer Mutations in Phosphosites in Signaling Networks

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Signal transduction is predominantly mediated by phosphorylation events; however, phosphosites are inhibited or over-activated in cancer tissues.

In this study, we focused on patient-specific mutations in TCGA that overlaps with residues that can be phosphorylated, such as Serine (S), Tyrosine (Y), Threonine (T) and leverage these mutations to understand the pathway-level signaling alterations in cancer. This change may be from S, Y, or T to any amino acid, which we call "lost-phosphosite mutation" or from any amino acid to S, Y or T, which we call "gained-phosphosite mutation". Our fundamental purpose is to reveal the perturbed pathways and upstream kinases inhibited by such mutations. For this purpose, we integrated patient-specific mutation profiles of more than 10,000 tumor samples with three different databases -PhosphoSitePlus, Omnipath, and Netphorest- that known phosphorylation sites are annotated. Thus, we obtained 5624 unique interactions of kinase-substrate. PAK1, PKA, PKB were found as the most affected kinases. Those interactions may be altered due to the lost-phosphosite mutations so that we investigated how many mutated residues were mapped to annotated PPI interfaces. This type of mutations may lead to loss-of-function and eventually dramatic alterations in pathways. We obtained 3889 unique kinase-substrate interactions composed of 305 unique substrates. Among the kinases, EGFR has the highest number lost interactions because of mutated phosphosites on its substrates. Besides, EGFR is the most affected substrate with seven mutated phosphosites. The most commonly mutated phosphosite across patients is S37 in CTNNB1. Next, we analyzed the most commonly mutated substrates in the patient cohort and found adherens junction, ERBB signaling pathway and carbon metabolism in cancer were significantly enriched.

In our ongoing work, we construct the patient-specific perturbed signaling networks and through a detailed comparison of these networks we will reveal the tumor subtype-specific affected pathways.