Title

Spatio-temporal dynamics of signaling pathways altered by “undruggable proteins” in cancer using peptide discovery and protein engineering

Abstract

Cancer has become a leading cause of death worldwide, almost 14 million new cases were diagnosed in 2012 and the number is expected to rise by 70% in next two decades [1]. Tumor stratification based on morphological assessment and surface receptor levels [2] often yield a varying clinical outcome to the cancer therapy. Recently, a compelling evidence suggests the genome-based stratification based on the mutation profile would be a promising way for tumor stratification. The mutated proteins in cancer gain a diverse set of functions include higher phosphorylation / kinase activity [3], and increased cellular signaling [4]. An important pathway of cell signaling, PI3K-AKT-mTOR is affected in more than 45% of breast cancer and a kinase PI3K is mutated in >40% the breast cancer [5]. Design of molecules to study this aberrantly altered pathway caused by the “undruggable” mutant protein variants is undeniably needed. There are no molecule exists that specifically binds to mutant PI3K to study the signaling dynamics.

Peptides offers an opportunity to expand and study the repertoire of “druggable proteins” due to their intermediate size and high specificity towards a target. We have planned to design and engineer mutant specific cyclic peptide inhibitors of PI3K using bacterial surface display, flow cytometry, and molecular dynamics simulations. The designed peptide will be used to study the role of mutant protein in altering downstream signaling processes. The PI3K-AKT-mTOR pathway will be studied in real time by developing a genetically encoded fluorescent biosensor that specifically detect AKT kinase activity in live cell. We will use confocal imaging of live cancer cell (stratified based on the mutations) to study the spatio-temporal dynamics of the AKT kinase and the effect of a novel peptide inhibitor on AKT translocation. I will briefly summarize my PhD work on engineering a phytase enzyme (commercialized by BASF, Germany) and development of novel methods for protein engineering [6, 7]. A summary of my postdoctoral work on a *de novo* cyclic peptide discovery for tumor associated proteases [8] and on designing novel fluorescent biosensor for nicotine to study a pathway of nicotine addiction will be discussed.

References

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