Drug screening Arrays at Protein/protein Interfaces in Cancer

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Protein/protein interactions regulate the function of living cells. However, some protein/protein interactions support the survival of pathogenic cells by blocking the favorable biological activity of one of the proteins involved in the interaction. Cancer is the second leading cause of death among Americans. An estimated 1 out of 4 deaths in the United States is caused by cancer.[1] Despite major research efforts,[2] the discovery and development of anticancer drug is quite expensive ($ 1-2 million) and time consuming (~ 10 years).[3] One emerging method of drug development is based on dismantling the protein/protein interface associated with cancer by weakening the key sites of interaction using small molecules or peptide mimics.[4]

Computational methods can predict a large number of potential therapeutic compounds against a protein-protein 'interface' (the permanent contact surface via key sites of interaction between 2 proteins) target. However, the experimental screening at present is highly time consuming, lacks high-throughput, and needs multiple techniques to identify a single drug candidate. Hence, the design of simple high-throughput imaging methods is crucial to screen several drugs against a protein-protein interface target of a disease, and thus reduce the drug development time and cost.

We present here a rapid, simple and specific optical imaging arrays made of undesirable protein-protein interfaces of cancer cells as drug targets for drug screening. As proof-of-concept systems, we constructed model protein-protein interfaces of cancer on monolayer functionalized Au-array chips. Then model drugs were screened for their inhibition/dissociation effects on the interfaces by imaging the refractive index changes with respect to internal controls. We additionally optimized the experimental conditions with respect to pH, protein concentration, surface chemistry, and electrolyte composition to obtain reproducible screening results. The described optical imaging arrays have great potential in the rapid and cost-effective drug screening against the undesirable permanently existing protein-protein interfaces in cancer and other diseases.

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