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Targeting Protein Kinase Substrate Docking in Cancers

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Cancers are characterized by uncontrolled cell growth, increased cell survival, remodeling of tumor microenvironment, neovascularization, invasion and metastasis. Each of these processes involves perturbation of key regulatory pathways. Disruption of these pathways is often caused by mutations and modifications in proteins that occupy hub positions, resulting in either disruption of their function or aberrant activation. Protein kinases are an excellent example of a class of enzymes whose activity if often found to be deregulated in diseases including cancers [1,2]. Protein kinases mediate the covalent addition of phosphate group to amino acid side chains in proteins thereby modifying them post-translationally. The hydroxyl groups of serine, threonine, tyrosine or histidine amino acid side chains are the most common phosphoacceptor sites on proteins. Reversible protein phosphorylation plays an important role in essentially every aspect of life including cellular processes that mediate metabolism, cell cycle progression, proliferation, apoptosis, differentiation, cytoskeletal dynamics, cell migration, immune response, and intracellular transport.

Recent technological advances have enabled rapid identification of downstream targets of protein kinases deregulated in cancer [3,4]. Aberrant protein phosphorylation has been observed in many human cancers and has been shown to affect the stability and function of key oncogenes and tumor suppressors [5-8]. Although protein kinases have emerged as attractive druggable anti-cancer targets, successful selective targeting of protein kinases has proven difficult. A major impediment has been off-target effects of the many extant small molecule protein kinase inhibitors. This stems from the fact that the catalytic fold of different protein kinases, which is often the target for rational drug design share significant structural similarity with each other. Interestingly, many protein kinases use additional protein-protein interaction domains to establish specific kinase-substrate interaction in addition to the target site preferences on substrates defined by stereochemical complementarity with active site. For instance, the SH2 and SH3 domains in tyrosine kinases have been shown to be important in substrate binding [9]. Several Ser/Thr protein kinases including Cyclin-dependent kinases (CDKs), Mitogen activated protein kinases (MAPK), Polo-like Kinase 1 (PLK1), 3-phosphoinositide-dependent kinase -1 (PDK1) and Glycogen Synthase Kinase 3ß (GSK3ß) possess additional docking domains, which are important in substrate recruitment [10-12].

Short linear recognition elements of length three to ten amino acids have been shown to be important in mediating most docking interactions [11]. Docking domains on MAPKs are among the best characterized [10]. MAPKs have been shown to have two dockings motifs. D-motifs binds to the sequence $(R/K)_{1-2}$-$(X)_{2-6}$-$\Phi_{-x-}\Phi$; where Φ denotes a hydrophobic residue) found in activators and substrate proteins [11]. D-motifs are present in all mammalian MAPK families (ERK, p38 and JNK) and are conserved from yeast to humans. The second docking domain in MAPKs is the ERK-specific domain, which binds to a so-called DEF motif with an FxFP consensus sequence [11]. The docking grooves in these kinases bind short peptide motifs of the substrate protein that are separate from peptide sequence that is phosphorylated at the active site of the kinase [11]. Crystal structures now exist for most of these MAPK docking complexes [13].

Docking domains plays an essential role in linking protein kinases such as MAPKs with their signaling partners. Thus, blocking the docking domain mediated protein kinases-downstream effector interaction provides an alternative strategy for selective kinase inhibition in diseases. Cell permeable peptides that mimic the recognition sequences on substrates that interact with the docking domains on protein kinases can thus serve as potential competitive kinase inhibitors. High-throughput structure-based screens can also be used to identify small chemical compounds that can specifically bind to the docking domain of protein kinases. This strategy has been successfully adopted to identify small molecule docking site inhibitors of MAPKs, which is known to be hyper activated in many cancers. In addition to enabling selective targeting of protein kinases, this strategy can also be adopted and developed to target specific kinase-substrate pair thereby offsetting potential off-target effects arising from global inhibition of a particular kinase.

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