Peptide Inhibitors Targeting Protein Kinases

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Abstract: Phosphorylation by protein kinases is a central theme in biological systems. Aberrant protein kinase activity has been implicated in a variety of human diseases, therefore, modulation of kinase activity represents an attractive therapeutic approach for the treatment of human illnesses. Development and design of specific inhibitors for protein kinases thus became a major strategy in many drug discovery programs. Inhibition of protein kinase activity may be achieved by blocking the phosphorylation activity or by disrupting protein-protein interactions. Peptides that can mimic most truly these regulatory modes are favorite choice for protein kinase-targeting.

In this paper we focus on important motifs regulating the protein kinase signaling network and described how they may be exploited for peptide drug design.

Protein kinases are important regulators of most, if not all, biological processes. Their abnormal activity has been implicated as causal factors in many human diseases, including cancer, diabetes and neurodegenerative disorders [1-3]. Protein kinases are thus attractive targets for drug design and compounds that manipulate their cellular activity are of enormous therapeutic potential. With a target in hand, medicinal chemists can generate low molecular weight compounds that bind the target with high affinity and alter its biological behavior. In many cases, however, drugs fail as they lack appropriate pharmaceutical properties and are of limited specificity resulting in unfavorable side effects. Under these circumstances, the use of peptides, which copy 'natural' motifs that specifically influence kinase activity and/or its intracellular interactions with cognate partners, may be a promising approach for selective inhibition of protein kinases. In this review we focus on the strategies to design such peptide inhibitors, focusing mainly on the serine/threonine protein kinase family.

PROTEIN KINASE DOMAINS

The protein kinase super family accounts for nearly 2% of the genes in the human genome and codes for about 545 kinases [4, 5]. The eukaryotic protein kinases are subdivided into two major classes, the serine/threonine and the tyrosine kinases. The two classes share extensive sequence and structure homologies. The catalytic domain was initially classified into 11 conserved subdomains [6] that are architecturally folded into a small N-terminal lobe and a larger C-terminal lobe [6]. The N-terminal lobe contains a glycine-rich loop (P-loop) for ATP binding and the C-terminal domain contains a conserved activation loop (also called 'T-loop' or activation segment) which is itself regulated by phosphorylation [6-9]. Phosphorylation occurs within a cleft formed between the two lobes, and the phosphate donating ATP molecule is bound in a deep cavity next to the P-loop. The substrate binding interface is often large and includes also grooves located on the surface of the N- and C-terminal lobes, which confer kinase specificity [7].

Although all 'classical' protein kinases share a common catalytic fold, these proteins show remarkable diversity in their substrate specificity and signal transmission. This is mainly attributed to additional elements, such as distinct regions located outside the catalytic core, regulatory domains, or adaptor molecules that can directly affect the interaction with substrates or other components within the signaling network. Protein kinases are frequently controlled by protein interactions, generally involving interaction between large globular domains, evidence suggests that interactions can also occur between protein kinases and short 'linear' peptides (or linear epitopes) that bind to specific docking grooves within the protein kinase and apart from the substrate binding site (reviewed in [10-12]). As docking-mediated interactions are particularly prevalent in serine/threonine kinases (which are the main focus of this review), and are a key in their signal specificity, search for new docking peptide sequences is an active area of research, and the use of peptide-based interacting motifs has become a favorite tool for targeted disruption of kinase activity.

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In order for peptides to act as high affinity, specific inhibitors, there are several considerations to be taken into account: the motif mimicked by the peptide must be surface exposed, its amino acid composition should not be highly conserved, finally, it is desired that the peptide will be able to adopt the 'active' conformation of the copied motif. This last requirement is a major determinant in peptides failure to produce biological response (due to loss of constrain when they are out of the context of the parent protein), and unfortunately, unlike the other two limitations, it is difficult to predict.

PEPTIDES AS COMPETITIVE INHIBITORS

The specificity of protein kinases for substrate phosphorylation typically depends on the primary amino acid sequences immediately flanking the site of phosphorylation, called the 'consensus sequence'. The numbers and types of interactions with residues surrounding the phosphorylation site vary considerably among kinases, reflecting differences in sequence specificity. This consensus sequence can serve as a template for a peptide that will act as a competitive inhibitor.

The serine/threonine protein kinase family is classified into basophilic, acedophilic and proline-directed kinases [8, 13]. The first group, which includes kinases such as cAMP dependent protein kinase (PKA), protein kinase B/Akt (PKB), and protein kinase C (PKC), prefers positively charged residues within the recognition motif. The consensus sequences of acidophilic group kinases, like casein kinase1/2, have acidic residues near the phosphorylation site. The largest family is the proline-directed kinases (Mitogen activated protein kinase (MAPK's), cyclin dependent protein kinases (CDK's), glycogen synthase kinase-3 (GSK-3)) and the recognition motifs of these kinases all include proline.

Peptides that mimic these recognition sequences can serve as substrate competitive inhibitors. For example, the natural PKA inhibitor protein, PKI, contains an RRNL motif that resembles the RRXS consensus sequence of PKA, except that the phosphoacceptor serine is replaced by alanine. Synthetic short peptides derived from the PKI sequence (5-22 residues) are effective inhibitors [14, 15]. Another example are the peptide inhibitors derived from the unique recognition motif of GSK-3, S³XXS(p), in which the second serine (S³) is pre-phosphorylated by a different kinase [16, 17]. Peptide inhibitors with sequence motifs of CREB (cAMP response element binding protein, KRRREILARPS(p)YR)
PKA, Ca<sup>2+</sup>/CaM-dependent protein kinase II (CaMK-II), myosin
Auto-inhibitory domains are found also in the regulatory subunit of
phosphorylation and inhibited its ability to phosphorylate respective
whereas peptides derived from the D-site of MEK4 reduced JNK
MEK1 were used to inhibit ERK1/2 phosphorylation [34, 36],
allows specificity [33-35]. Peptides derived from the D-site of
was identified in MEK, the kinase upstream of MAPK and is found
transmission. A high-affinity docking region, termed the D-motif,
isoforms that assemble the MAPK cascade [30-32]. Apparently, the
32] and contains multiple MAPK's and MAPK kinase (MEK's)
kinase (MAPK) family coordinates diverse signaling pathways [30-
mitogen activated protein kinase-substrate interactions or may increase the local concentration
proteins. Scaffold proteins act as organizing platforms that recruit
context of pYEE, whereas SH3 domains are found in oncoproteins and mediate sig-
In contrast to the serine/threonine kinases, the tyrosine kinase
SH2/SH3 Domains in Tyrosine Kinases
In contrast to the serine/threonine kinases, the tyrosine kinase
(TK) docking motifs tend to be found in modular domains that are
separate from the kinase domains. Non-receptor TKs have well-
derived interaction domains, the Src homology domain termed SH2
and SH3, that are small modular protein motifs (about 100 and 60
amino acids, respectively). The SH2 domains interact with phos-
pho-tyrosine residues in the context of pYEE, whereas SH3 do-
domains are found also in oncogenes and may participate in
binding to upstream kinases. SH3 domains are present in many kinases and
are involved in substrate binding [60-63]. Based on these ob-
servation the KinAce technology provides a 'general recipe' for
inhibition. In MAPK, the activation loop is phosphorylated at the 'TEY'
motif by the upstream kinase MEK. Apparently, this phosphoryla-
tion triggers a conformational rearrangement of the activation loop.
This rearrangement is also triggered by the corresponding phos-
phorylated peptide. Interestingly, this peptide did not inhibit MEK,
whereas the non-phosphorylated peptide did inhibit MEK activation
of MAPK presumably due to competition with MEK [59]. It is clear from these studies that the structure changes induced by phosphoryla-
tion are important elements for recognition. In this particular case, the
non-phosphorylated peptide mimicked the interaction of MEK with its substrate MAPK [59].

A recently developed technology termed KinAce identified conserved motifs common to all protein kinases as potential tem-
plates for design of peptide inhibitors. Crystal structures of kinases
complexed with peptide substrates identified two regions termed αD and HJ-αG located at the subdomains V and X, respectively,
that are involved in substrate binding [60-63]. Based on these ob-
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Self Docking Motifs
Some peptide inhibitors mimic motifs within the kinase itself. These peptides do not bind directly to the kinase; rather, they com-
pete with the kinase for binding to its targets. The three-
dimensional structures of several protein kinases have revealed distinct regions that bind downstream or upstream partners. Fukami
et al. characterized the activation loop encompassing the DFG-APE
motif, found in all protein kinases, as a potential template for inhibi-
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Members of the AGC kinase family are regulated via phos-
phorylation of a hydrophobic motif ('HM') (FXXFS/TF/Y), located C-terminal to the protein kinase catalytic core [53, 54]. Phosphory-
lration at this site can stabilize the active conformation of the activation
loop [53, 54]. Apparently the HM motif of protein kinase C-
related protein kinase (PKR-K2), p90 ribosomal S6 kinase (RSK), 70 S6 kinase (S6K) were shown to bind with their upstream regulator,
PKD1, via interaction with hydrophobic binding pocket (PIF) located
within the small lobe of PKD-1 [55-57]. Interaction with PIF enhanced PKD1 catalytic activity to enable phosphorylation of the
docked substrates [55-57]. Indeed, a 24 amino acid peptide derived from the hydrophobic motif in PKR-2 interacted with the PIF
pocket of PKD1 and enhanced the kinase activity presumably via conformational changes in the catalytic core [57]. Hence peptides
or small compounds that mimic the interaction of HM with the PIF pocket may function as allosteric modulators of PKD1 [58].

PEPTIDES TARGETING BINDING SITES
Mimics of Docking Sites in Binding Partners
Protein complexes represent a major mechanism for kinase-
mediated signaling pathways. These can represent direct interac-
tions with substrate proteins, or effects may be mediated by scaffold
proteins. Scaffold proteins act as organizing platforms that recruit
both the kinase and the substrate binding partners to the same
complex. These different modes of recognition provide a simple
way to meet the requirement for increased specificity of the protein
kinase-substrate interactions or may increase the local concentration
of the substrate near the kinase. The mitogen activated protein
kinase (MAPK) family coordinates diverse signaling pathways [30-
and contains multiple MAPK's and MAPK kinase (MEK's)
isoforms that assemble the MAPK cascade [30-32]. Apparently,
pecific docking interactions enable their specificity in signal
transphosphorylation. A high-affinity docking region, termed the D-motif,
was identified in MEK, the kinase upstream of MAPK and is found
in MAPK's substrates and phosphatases [33-35]. The D-site motif is
typed by a cluster of basic residues followed by a hydrophobic
sub-motif with some variability in the amino acid composition that
allows specificity [33-35]. Peptides derived from the D-site of MEK1 were used to inhibit ERK1/2 phosphorylation [34, 36],
whereas peptides derived from the D-site of MEK4 reduced JNK
phosphorylation and inhibited its ability to phosphorylate respective
substrates [34, 36]. D-site-like motives were found also in other
binding partners of MAPK, including its direct substrate S6 riboso-
mal protein kinase, p90 RSK, and MAPK kinase dual specific
phosphatases (MKPs) [37, 38]. An interacting protein of JNK
(JIP1) is a scaffold protein that facilitates the assembly of JNK-
cascade components [39-42]. Synthetic peptides corresponding to
the D-site of JIP1 proteins were described in several studies and
showed high and selective inhibition potency toward JNKS, in vitro and in vivo [43-45]. Structures of the unbound and peptide-bound-
MAPK's showed that the D-motif peptides induced different con-
formational changes in the different MAPK isomers (ERK2, p38,
JNK) [46, 47]. These could be well attributed to the specificity the MAPK's recognition of its substrates or upstream regulators [46,
A second class of MAPK docking sites are the 'FXFP' sites found in several transcription factors substrates of ERK such as
Ekl-1, SAP-1, LIN-1, and Fos [48-50]. This site was shown to mediate high-affinity interactions between ERK and its substrate pro-
teins [48-50]. Synthetic peptides patterned after the FXFP motif
were shown to antagonize MAPK's ability to phosphorylate its sub-
strates and reduce MAPK-mediated signaling [48, 51, 52].
naling pathways in cancer cells, SH2 and SH3 domains interaction inhibitors are potential antitumor agents. Unlike most of the docking sites found in Ser/Thr kinases, the SH2/SH3 domains have defined structures and three-dimensional structures of peptides complexed with these domains have allowed structure-based peptide drug design. However, peptides designed to bind to these interaction sites do not show high efficacy. The SH3-directed peptides have low affinity, whereas the phosphorylated SH2-directed peptides have limited cell permeability. Numerous studies have focused on development of peptidomimetics that target SH2/SH3 domains. These peptidomimetics are chemically modified with non-natural amino acid substituents and with hydrophobic residues to improve specific binding and in vivo efficacy [68-70]. These inhibitors have been developed for Src, Lck, PI-3K and Zap70 [69, 71].

PEPTIDES COMPETING WITH ANCHORING AND TARGETING PROTEINS

Modular binding partners target some Ser/Thr kinases to their specific substrates via changes in cellular localization. Binding of a peptide to this targeting domain may prevent the interaction of the kinase with its substrates. The PKC isozymes are known to translocate from cytosol to particulate fractions in response to various stimuli. A family of adaptor molecules, termed RACKs (from Receptors for Activated C-Kinase), interact with the various PKC isoforms and facilitate their cellular translocation [72, 73]. The RACK binding domain is a short sequence located in the PKC’s N-terminal-subdomain and is different in each isoform. Thus, the translocation of PKC isoforms could be disrupted selectively using peptides derived from the specific RACK docking region [64, 67]. The use of such peptides has enabled analysis of the functions of individual PKC isozymes. For example, peptides derived from the C-2 region of PKC-βII prevented hormone-induced membrane translocation of PKCβIII and inhibited insulin-induced Xenopus oocyte maturation [74]. Peptides derived from V1 region of PKCε and PKCS selectively blocked cellular translocation in heart membranes and different cardio-protection effects were observed in ischemic hearts depending on the isozyme targeted [75, 76].

Another example is the cellular regulation of PKA, which is controlled through interactions with a family of distinct but functionally homologous proteins called AKAPs (A-Kinase Anchor Proteins) [77, 78]. Each AKAP contains an amphipathic helix binding motif that anchors the PKA-regulatory subunit (R) into cellular structures binding site, activation loop and specific docking sites) is illustrated in Fig. (1).

NEW TECHNOLOGIES FOR DESIGN AND SELECTION OF PEPTIDE INHIBITORS

Historically, the consensus motif of a given protein kinase was extracted from individual substrates that were experimentally tested. The use of chemical libraries and computational analyses enhanced our ability to identify phosphorylation and interaction motifs. Originally peptide libraries were designed to identify optimal consensus sequences favored by certain protein kinases [4, 85]. In these experiments, a degenerate library of peptides with a fixed serine, threonine or tyrosine residue was subjected to phosphorylation in vitro and the subset of the phosphorylated peptides was retrieved from the peptide mixture and sequenced. The sequences obtained were then scored for preferred amino acids at each position. In many instances, the optimal peptide sequence motifs determined by this method closely matched the known phosphorylation sites, additionally, new motifs were identified [85, 86]. For example, an optimal peptide substrate sequence for Akt (PKB), ARKERTYSGHHA, determined using a screen of a peptide library, had high affinity for the kinase [87]. The peptide has been recently used in the development of small peptide inhibitors of Akt [88].

Large-scale screening made possible through the development of phosphoproteomics analysis based on mass spectroscopy (MS) is being used to catalog thousands of in vivo phosphorylation sites that can be screened for important and new phosphorylation motifs [89, 90]. In a recent bioinformatics analysis of a large database of phospho-peptides obtained from HeLa cells protein extracts hundreds of phosphorylation motifs were found; some were novel and some matched known consensus sequences of protein kinases [91]. This large-scale analysis increases our data base of phosphorylated sequences that can be further implicated in rational drug design.

A different approach was recently described to screen motifs for protein-protein interactions. In this technique, a combinatorial library of conformationally constrained peptides is attached to a platform protein such as thioredoxin A (termed ‘peptide aptamer’) and utilized in a yeast two hybrid screen [92, 93]. This approach can be used to identify peptides that interact with a specific motif within a kinase. In the studies of Colas et al. [94], a set of aptamers that recognized different epitopes at the CDK-2 (cyclin dependent protein kinase) surface were identified using a peptide library and the yeast two-hybrid strategy. One of the selected peptide aptamer, termed pep8, was shown to bind to the active site of Cdk2 and to inhibit its catalytic activity. Treatment with pep8 resulted in inhibition of cell cycle progression in human cells [95] and defective embryogenesis of Drosophila [94, 96]. Moreover peptide aptamers containing signals that alter cellular localization may be created that change the target’s compartmentalization and manipulate its activity [94]. Altogether, peptide aptamer strategy can identify important motifs within the proteins and may also serve as a tool for development of high affinity peptide-based drugs. This new knowledge is helpful in the design of biological tools to modulate protein–protein interactions in vivo.

COMPUTATIONAL STRUCTURE-BASED DRUG DESIGN

The growing number of sequences and three-dimensional structures of protein kinases provides an important starting point for bioinformatic analyses, such as the identification of targeting motifs and specific docking sites (reviewed in [12, 97-100]), followed by design and screening of putative peptide inhibitors. Prediction of the interaction geometry between proteins and peptides is a difficult task due to the high flexibility of the peptide ligand. Nevertheless, successful interface design studies have been presented, which modified and improved the specificity of protein-peptide interfaces [101-103]. The interactions of peptides with protein kinases are further complicated by the conformation changes that many kinases undergo upon ligand binding, such as domain movements and local changes in the glycine rich P-loop, the C helix and the activation loop [104]. The computational study by Helms and McCammon indicated that binding of the inhibitory PKI peptide 5-24 to the C-AMP dependent protein kinase stabilizes a closed (active) conformation of the kinase, whereas in the absence of the peptide the open state or an intermediate ATP bound state are favored [105]. Brinkworth et al. used the active conformations of two protein kinases and showed that the calculated enthalpy of kinase/peptide binding
can distinguish good peptide substrates from non-substrates, although the catalytic efficiencies for the tested cases were not predicted well [106]. Both studies relied on experimentally resolved structures of kinase/peptide complexes and their results emphasize the difficulty in predicting the structure of such complexes.

Protein kinase/peptide interaction geometry was predicted for the complex GSK-3β/pCREB [107]. The unphosphorylated GSK-3β adopts the active form and upon phosphorylation of Y216 undergoes only a local side chain conformation change. Computational docking of pCREB to GSK-3β identified several docking sites on the surface of the kinase, which are separate though spatially close to the active site. Residues Phe 67, Gln 89, Asn 95 of GSK-3β were shown to be involved in pCREB and other substrates binding by numerous experimental assays (Fig. 2) [107]. Identification of such specific interactions is of high importance in drug design because they provide a docking template for peptides or small molecules designed to confer specific GSK-3 inhibition. Recently, a general computational procedure has been described for predicting protein kinase peptide specificity, namely prediction of putative docking sites in kinases and preferred peptide substrates [108]. These recent modeling studies will hopefully lead to development of specific peptide inhibitors.

The SH2 domain of tyrosine kinases is relatively rigid, as it does not undergo significant conformation changes upon ligand binding. This led to several modeling studies in which the interaction energies of SH2 with phosphorylated and non-phosphorylated peptides were calculated [109-113]. The computed binding energies in most of these studies show good agreement with experimental data suggesting that computations can be used for predicting protein-protein interactions mediated via SH2 domains and that such data can be used to improve and extend experimentally derived cellular signaling and protein interaction maps. Similar computations were used to evaluate the interaction energy between peptides and the Abl-SH3 domain, whereby putative binding partners were predicted in good agreement with experiment. Notably, predictions of interaction geometries are rare. Reasonably accurate binding geometries to SH2 domains were predicted for several short peptides by Zhou et al., with minimal restraints, such as the location of the phosphate group [109].

The studies discussed above aimed at elucidating the interaction energies and/or interaction geometries of peptides to the catalytic domains or to regulatory domains of protein kinases. These data can be used for identifying specific protein/peptide interactions that can subsequently be used for designing specific peptide or peptide-

Fig. (1). Protein kinase domains and targeted motifs. A Schematic presentation of domain structure of protein kinase with conserved bilobal catalytic domains, N-lobe (green) and C-lobe (red), composed of 11 conserved subdomains. Conserved domains including P-loop involved in ATP binding, and activation loop with the DFG….APE motif are marked. B. Motifs targeted by peptide inhibitors are mapped onto the ribbon diagram of PKA (PDB entry 1atp). Shown are the positions of the activation loop (orange), the αD region (purple), the HJ-αG region (dark green) and the C-terminal hydrophobic pocket (brown). The substrate binding position is represented by the inhibitory peptide PKI (the black ribbon). ATP is shown as a stick diagram colored by the atoms (green for C, red for O, blue for N and magenta for P).
mimicking inhibitors. An alternative computational method to elucidate inhibitors is to design peptides that bind to the kinase substrates or to other modulators of their activity [64, 114].

Hence, it is a worthwhile cause to re-examine the opportunities that peptides provide as potential drug compounds with appropriate technology and design.

PROSPECTIVES
Selecting inhibition of protein kinases is an extremely challenging goal of many drug discovery programs. Here we highlighted the main strategies for the design of peptide inhibitors of protein kinases and suggest that peptides offer a number of advantages relative to other types of drugs such as ease of discovery, specificity, and safety. Traditionally, peptides have been considered less attractive than ‘small molecule’ drugs, due to several limitations of peptides. These include metabolic instability, inability to readily cross cell membranes, potential immunogenicity, and the inability to be administered orally. However, several new strategies were shown to improve the bioavailability and stability of peptides. Chemical modifications can make the peptide more stable towards an enzymatic attack and various formulation techniques can be used to protect the peptide from proteosomal degradation. Formulations evaluated include liposomes, nanoparticles, microparticles and matrix tablets comprising various auxiliary agents such as enzyme inhibitors and multifunctional polymers [115-118]. In addition, Pumps, buccal sprays, intra-nasal delivery, and transdermal patches offer attractive alternatives to injections [117, 119-121].

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ABBREVIATIONS
PKA = cAMP Dependent protein kinase
GSK-3 = Glycogen synthase kinase-3
FRAT = Frequently rearranged in advanced T-cell lymphoma
GBP = GSK-3-Binding protein
GID = GSK-3-Interacting domain
CDK = Cyclin dependent kinase
JNK = c-Jun N-terminal kinase
AKAP = A-Kinase anchoring proteins
PKC = Protein kinase C
P90 RSK = p90 Ribosomal S6 kinase
MLCK = Myosin light chain kinase
MAPK = Mitogen-activated protein kinase
MEK = MAPK kinase
JIP = JNK-Interacting protein
ERK = Extracellular signal-regulated kinase
(PMAPK)
PRK = Protein kinase C-related protein kinase
PDK-1 = Phosphoinositide-dependent kinase
PKB = Protein kinase B
PIF = PDK-1 Interacting fragment
CAMK = Calcium/calmodulin-dependent protein kinase
HIV-TAT = TAT protein from human immunodeficiency virus
CaM = Calmodulin
RACK = Receptor for activated C-kinase
CREB CAMP = Response element binding protein

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