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Inhibitors of Protein Kinases and Protein Phosphates

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Springer
Nearly all aspects of cell life (and death) are controlled by the phosphorylation of proteins, which is catalysed by protein kinases (PKs) and reversed by protein phosphatases (PPs). The role of PKs can be likened to that of interpreters, who translate stimuli and signals into biochemical events. For this reason, PKs and PPs are themselves interlinked and highly regulated, forming complex communicative networks. Not surprisingly, therefore, the deregulation of PKs results in cell malfunction, eventually resulting in neoplastic growth and other diseases. This makes PKs attractive targets for drugs not only to combat cancer, but also for other global diseases, notably diabetes, inflammatory and infectious diseases, stroke, hypertension and Alzheimer's. Actually about half of all proto-oncogenes so far identified encode PKs, and oncogenesis frequently results from the activation and/or overexpression of PKs. For example, overexpression of the epidermal growth factor receptor tyrosine kinase is the cause of many cancers of epithelial cell origin. In other instances, however, the link of PKs with neoplasia is not so straightforward, and depends on defective interactions with cellular partners of PKs, susceptibility to particular metabolic conditions, abnormal levels of other regulatory components or the combination of several of these factors.

The attractiveness of PKs as targets is enhanced by the fact that they are enzymes, which are targetable molecules par excellence. Thus their biological activity can be turned off very easily and precisely by drugs that block the catalytic site. Virtually all PKs belong to the largest single family of enzymes, numbering over 500 and accounting for almost 2% of the proteins encoded by the human genome. They share similar catalytic domains that catalyse the transfer of phosphate from ATP to serine, threonine or tyrosine residues in key regulatory proteins. Nevertheless, the structures of the catalytic domains of PKs are sufficiently distinctive that it is possible to develop compounds that are highly selective for a particular PK. Even the highly conserved binding site for the substrate ATP is surrounded by structural elements with variable features that can be exploited for the design of specific inhibitors, and most of the PK inhibitors currently undergoing human clinical trials are of this type. Two PK inhibitors are already in clinical use for the treatment of cancers (Gleevec and Iressa), while another is the immunosuppressant of choice to prevent tissue rejection after organ transplantation (rapamycin). At least 30 other PK inhibitors are undergoing human clinical trials to treat cancers and other diseases. These have the potential to provide a significant impact.
on the management of epithelial cancers, such as breast and lung cancer. The approval of Gleevec for the treatment of a form of leukaemia by the FDA in May 2001 and more recently for the treatment of stomach cancers was a landmark because it is the first drug to be developed by targeting specific PKs. Moreover, its spectacular clinical effects, with minimal side effects, have had an enormous impact on the pharmaceutical and biotechnology industry. As a result, PKs have become the second most important family of drug targets, 20%–30% of all drug development programmes now being concentrated in this area. Although most PK inhibitors currently under investigation as potential drugs are ATP site-directed ligands, the field is still in its infancy, and there is tremendous potential to develop different types of drugs that target the binding sites for the protein substrates or which prevent the activation of PKs, since many of these enzymes are arranged in ‘cascades’ in which one PK activates or inhibits another one. Longer-term strategies would involve approaches based on gene therapy in which the mutant PK would be replaced by the wild-type enzyme.

PPs have received less attention to date as potential drug targets than PKs. The empirical discovery of an immunosuppressant drug that revolutionised organ transplantation (ciclosporin) and the subsequent recognition that it is a specific inhibitor of one PP indicates that PPs can be effective drug targets. An anticancer agent also discovered empirically (fostrieclin) is now recognised to be a PP inhibitor. Other PPs, such as PTP1B, are currently under active investigations as drug targets for the treatment of diabetes and other diseases. As with PKs, known PP inhibitors at present target the active site but since many PPs are complexes with regulatory subunits, there is a potential for developing drugs that target the binding site of these regulatory subunits or their interaction with regulators. Thus the expansion of PPs as suitable drug targets may eventually follow that of PKs.

This volume of HEP highlights the tremendous pharmacological potential of PK and PP inhibitors, by providing a thorough overview of the most remarkable achievements in the field and illustrating how beneficial these studies can be for the advancement of both basic knowledge on biological regulation and deregulation and for the clinical treatment of a wide spectrum of diseases.
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