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Invited Review

A historical overview of protein kinases and their targeted small molecule inhibitors

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ABSTRACT

Protein kinases play a predominant regulatory role in nearly every aspect of cell biology and they can modify the function of a protein in almost every conceivable way. Protein phosphorylation can increase or decrease enzyme activity and it can alter other biological activities such as transcription and translation. Moreover, some phosphorylation sites on a given protein are stimulatory while others are inhibitory. The human protein kinase gene family consists of 518 members along with 106 pseudogenes. Furthermore, about 50 of the 518 gene products lack important catalytic residues and are called protein pseudokinases. The non-catalytic allosteric interaction of protein kinases and pseudokinases with other proteins has added an important regulatory feature to the biochemistry and cell biology of the protein kinase superfamily. With rare exceptions, a divalent cation such as Mg^{2+} is required for the reaction. All protein kinases exist in a basal state and are activated only as necessary by divergent regulatory stimuli. The mechanisms for switching between dormant and active protein kinases can be intricate. Phosphorylase kinase was the first protein kinase to be characterized biochemically and the mechanism of its regulation led to the discovery of cAMP-dependent protein kinase (protein kinase A, or PKA), which catalyzes the phosphorylation and activation of phosphorylase kinase. This was the first protein kinase cascade or signaling module to be elucidated. The epidermal growth factor receptor-Ras-Raf-MEK-ERK signaling module contains protein-tyrosine, protein-serine/threonine, and dual specificity protein kinases. PKA has served as a prototype of this enzyme family and more is known about this enzyme than any other protein kinase. The inactive PKA holoenzyme consists of two regulatory and two catalytic subunits. After binding four molecules of cAMP, the holoenzyme dissociates into a regulatory subunit dimer (each monomer binds two cAMP) and two free and active catalytic subunits. PKA and all other protein kinase domains have a small amino-terminal lobe and large carboxyterminal lobe as determined by X-ray crystallography. The N-lobe and C-lobe form a cleft that serves as a docking site for MgATP. Nearly all active protein kinases contain a K/E/D/D signature sequence that plays important structural and catalytic roles. Protein kinases contain hydrophobic catalytic and regulatory spines and collateral shell residues that are required to assemble the active enzyme. There are two general kinds of conformational changes associated with most protein kinases. The first conformational change involves the formation of an intact regulatory spine to form an active enzyme. The second conformational change occurs in active kinases as they toggle between open and closed conformations during their catalytic cycles. Because mutations and dysregulation of protein kinases play causal roles in human disease, this family of enzymes has become one of the most important drug targets over the past two decades. Imatinib was approved by the United States FDA for the treatment of chronic myelogenous leukemia in 2001; this small molecule inhibits the BCR-Abl protein kinase oncoprotein that results from the formation of the Philadelphia chromosome. More than two dozen other orally effective mechanism-based small molecule protein kinase inhibitors have been subsequently approved by the FDA. These drugs bind to the ATP-binding site of their target enzymes and extend into nearby hydrophobic pockets. Most of these protein kinase inhibitors prolong survival in cancer patients only weeks or months longer than standard cytotoxic therapies. In contrast, the clinical effectiveness of imatinib against chronic myelogenous leukemia is vastly superior to that of

Abbreviations: AKAP, A-Kinase Anchoring Protein; ALL, acute lymphoblastic leukemia; A.S., activation segment; CDK, cyclin-dependent kinase; CML, chronic myelogenous leukemia; C-spine, catalytic spine; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GIST, gastrointestinal stromal tumor; HΦ or Φ, hydrophobic; IGF-1R, insulin-like growth factor-1 receptor; NSCLC, non-small cell lung cancer; PDGFR, platelet-derived growth factor receptor; Ph^+, Philadelphia chromosome positive; PKA, protein kinase A; pY, phosphotyrosine; R-spine, regulatory spine; Sh, shell; VEGFR, vascular endothelial growth factor receptor.

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any other targeted protein kinase inhibitor with overall survival lasting a decade or more. However, the near universal and expected development of drug resistance in the treatment of neoplastic disorders requires new approaches to solve this therapeutic challenge. Cancer is the predominant indication for these drugs, but disease targets are increasing. For example, we can expect the approval of new drugs inhibiting other protein kinases in the treatment of illnesses such as hypertension, Parkinson's disease, and autoimmune diseases.

Contents

1. The protein kinase enzyme family

Protein kinases play pivotal roles in nearly every aspect of cellular function [1]. They control metabolism, transcription, cell division and movement, programmed cell death, and they participate in the immune response and nervous system function. Protein phosphorylation involves the balanced action of protein kinases and phosphoprotein phosphatases making phosphorylation–dephosphorylation an overall reversible process [1,2]. Owing to the overall importance of protein phosphorylation, considerable effort has been expended to determine the assorted functions of protein kinase signal transduction pathways [1]. Moreover, dysregulation of protein kinases occurs in many diseases including cancer and inflammatory disorders.

Protein kinases can modify the function of a protein in almost every conceivable way. Protein phosphorylation can increase or decrease enzyme activity and it can alter other biological activities such as transcription and translation. Moreover, some phosphorylation sites on a given protein are stimulatory while others are inhibitory. Phosphorylation may stabilize or destabilize a