kinases and phosphatases

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Editorial

Editorial: Human Protein Kinases: Development of Small-Molecule Therapies

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1. Introduction

Human protein kinases are ubiquitously expressed throughout the human body and embedded in signaling pathways that mediate diverse biology. When their function becomes aberrant due to mutation(s) and/or changes in expression, resultant kinase dysfunction can propagate disease. Fortunately, kinases represent highly tractable proteins that can be pharmacologically inhibited to impact disease progression. Capitalizing on this feature, industrial and academic labs have pushed more than 80 small molecule kinase inhibitors through FDA approval, resulting in the distinction of kinase inhibitors as one of the most important drug classes [1]. While most of these kinase-targeting drugs have been approved for oncological indications, kinase function can be similarly modulated to impact other progressive diseases, such as those impacting the heart or brain. Another aspect of these approved drugs to consider is their binding mode. There are a few examples, such as trametinib, asciminib, and deucravacitinib, of FDA-approved kinase drugs that bind to an allosteric site outside of the ATP-binding pocket to elicit kinase inhibition [2]. These allosteric sites can be proximal to (type III kinase inhibitor) or distal from (type IV kinase inhibitor) the ATP-binding pocket [2]. A deeper look into the kinase targets of FDA-approved drugs reveals that they inhibit only a small fraction of the human kinome [3]. In light of the historic success of drugging human kinases, one may consider whether inhibiting those kinases in the lesser studied portion of the human kinome could result in new drugs and/or expand the diseases that can be assuaged through kinase inhibition.

Building on our foundational understanding of kinase function and kinase inhibitor drugs, this research topic is aimed at capturing novel perspectives and approaches related to kinase inhibitor development. The goal is to explore broader applications of kinase inhibitors inside and outside of the oncological space. Pathway analyses, structural studies, and characterization of disease pathology are essential parts of a data package that supports the in vivo translation of a small molecule kinase inhibitor. This Special Issue includes seven reviews that highlight one or more of these areas for specific kinases. The papers are written from diverse lenses related to kinase inhibition and its therapeutic ramifications, as discussed further in the sections that follow.

2. Balancing Challenges and Benefits When Using Kinase Inhibitors for Cancer Therapy

This section contains two reviews aimed at targeting either specific kinases (IKKs) or kinase signaling cascades to combat cancer [4,5]. Although studies related to IκB kinases (IKKs) have historically centered around their role in the NF-κB pathway and the modulation of immune and inflammatory responses, Abdrabou points to the function of IKKs in regulating tumorigenesis. Crosstalk of IKKs with other kinase signaling cascades,

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such as MAPK and PI3K pathways, further contributes to the complex biology that these kinases mediate. A deep dive into IKKs in this review provides the reader with the foundation upon which more effective therapeutics targeting IKKs may be designed. The review by Valero-Diaz et al. also explores the interplay between different kinase signaling pathways but in the context of a specific type of cancer: cutaneous T-cell lymphomas (CTCLs). Highlighted signaling pathways are altered in CTCLs and suggested as causative of these malignancies. While selectively targeting kinases in the JAK/STAT, MAPK/ERK, PI3K/AKT, and NF-κB pathways is viewed as a promising therapeutic strategy for CTCLs, challenges still exist with respect to combating adverse side effects.

3. Kinase Inhibition as a Strategy for Progressive, Non-Oncological Diseases

This section summarizes three reviews with slightly different foci, but a uniting theme centered around the development of kinase inhibitors for progressive diseases other than cancer [6–8]. In the first of these reviews, Nakashima et al. provide an in-depth analysis of the role of ubiquitously expressed adenosine monophosphate-activated protein kinase (AMPK) in autophagy and/or mitophagy and how targeting it could be a beneficial strategy for cardiac disorders. Downstream effectors of AMPK are detailed, supporting it as a master regulator of many essential pathways that regulate autophagy and/or mitophagy. Finally, preclinical observations related to AMPK modulation by nutraceuticals are provided as evidence of the potential clinical benefit of targeting AMPK with small molecule inhibitors for the treatment of heart diseases.

The remaining two reviews highlight the role of specific kinases, LYN and ROCK, in disorders affecting the brain. Weerawarna et al. offer a comprehensive discussion of the structure and how specific domains and residues of LYNA and LYNB participate in its endogenous activation and inhibition mechanisms. The functional consequences of downstream phosphorylation of immunoreceptor tyrosine-based inhibitory motifs (ITIMs) and immunoreceptor tyrosine-based activator motifs (ITAMs) by these kinases are detailed. To connect substrate phosphorylation to disease, the LYNs are finally examined from a therapeutic lens and their roles in cancer, autoimmune disease, and especially neurodegenerative diseases are highlighted. The importance of targeting kinases for diseases affecting the brain is also a theme in the review by Montagnoli et al. RhoA/Rho-associated protein kinase (ROCK) inhibition is discussed in the context of cerebral cavernous malformations (CCM), a disease impacting vascular biology, based on the finding that the ROCK pathway is activated in subsets of patients harboring this disease. How ROCK family members could be contributing to the formation of vascular lesions and other aspects of CCM and the development of CNS-acting ROCK inhibitors are topics covered in this review.

4. Cyclic Peptides as Kinase Inhibitors

A unique contribution to this Special Issue is a review centered around cyclic peptides that inhibit protein kinases [9]. Following a broader summary of protein kinases and small molecule inhibitors, Martínez-Alcantar et al. detail the differences between cyclic peptides and small molecules as well as between cyclic peptides and linear peptides. Advantages and disadvantages of these different small molecule modalities are presented for consideration. Next, the diverse therapeutic applications of cyclic peptides, with a focus on those targeting kinases, are discussed. The review concludes with an in-depth exploration of cyclodipeptides, their association with protein kinases, and disease relevant applications for these distinctive small molecules.

5. Kinase Allostery and Its Impact on Function

The final review in this Special Issue focuses on protein kinase A (PKA) and what we have learned by studying this important enzyme [10]. Studying the interplay between the domains of PKA has taught us much about kinase structure and function. It is understood that allosteric activation of PKA by cAMP is elicited through its binding to the PKA regulatory domain. A complete mechanistic understanding of PKA allostery, however, has not yet been realized and studies are ongoing with this endpoint in mind.

6. Perspectives

To summarize, this research topic generated a collection of seven reviews that share a theme of kinase inhibition as a therapeutic strategy. Thoughtful consideration of these submissions can be informative and inspiring in the campaign for novel therapies where they are needed. While the clinical use of kinase inhibitors is well established for cancer, the benefit of using them to treat cardiac, neurological, and other disorders is still being explored. Similarly, allosteric kinase modulation could hold therapeutic promise, but it is an area of research that still requires attention to be fully understood.

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