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Progress with covalent small-molecule kinase inhibitors

Zheng Zhao and Philip E. Bourne

Department of Biomedical Engineering, University of Virginia, Charlottesville, VA 22908, USA

With reduced risk of toxicity and high selectivity, covalent small-molecule kinase inhibitors (CSKIs) have emerged rapidly. Through the lens of structural system pharmacology, here we review this rapid progress by considering design strategies and the challenges and opportunities offered by current CSKIs.

Introduction

Kinase signaling pathway dysregulation is associated with a variety of conditions, such as cancer, inflammatory disease, cardiovascular disease, neurodegenerative disease, and metabolic disease [1,2]. Consequently, protein kinases represent important therapeutic targets [3]. However, designing small-molecule therapeutics is challenging. This is particularly true when targeting the ATP-binding pocket, because of the similarity of the binding site across the human kinome [2,4,5]. With an increase in structure-based knowledge [6,7] of protein kinases, additional grooves and fine differences have been discovered in the vicinity of the binding site where the adenine base of ATP binds [8,9]. Consequently, since the first kinase-targeted inhibitor, imatinib, was approved by the US Food and Drug Administration (FDA) in 2001, the ability to selectively target kinases has improved [10–13] and a variety of kinase inhibitors have been developed [8,14]. Inhibitors are classified as type I when targeting the active state of the kinase, type II when targeting the inactive state, type III when targeting an allosteric site, and type IV when targeting a pocket distant from the ATP-binding site, a hydrophobic pocket, or a pocket on the surface of the kinase [6–8].

Type I–IV inhibitors can be covalently or noncovalently bound [15–17]. Typically, covalent kinase inhibitors have a scaffold capable of accommodating a reaction moiety, otherwise known as the warhead, which improves the binding affinity and selectivity by forming a covalent interaction with a kinase reactive residue [16,18]. It is reported that the covalent reaction-related residues in kinases can be cysteines [8], lysines [19,20], aspartic acids [21], and others [22]. Most frequently, the covalent reactive residues are poorly conserved noncatalytic cysteines located near the ATP-binding site [18,23]. With a deliberately designed warhead, a balance between toxicity and efficacy can be found, such that covalent kinase inhibitors provide an effective therapeutic strategy. In the case of cancer therapy, covalent inhibitors have proven even better than reversible kinase inhibitors, in part because of the occurrence of drug resistance [24,25]. Over the past few years, four covalent kinase inhibitors, afatinib (2013, an inhibitor of EGFR and HER2), ibrutinib (2013, an inhibitor of BTK), osimertinib (2015, an inhibitor of EGFR) and neratinib (2017, an inhibitor of EGFR and HER2) [26–29], have been approved by the FDA. This recent success of covalent inhibitors has resulted in a renewed research effort [16]. Hence, a new generation of covalent kinase-targeted inhibitors is anticipated for an increased number of tumor types with reduced drug resistance [5]. Not every kinase is appropriate for covalent targeting [8,30]. Gray *et al.* described the distribution of accessible cysteines and binned the cysteines into five groups across the whole kinome [8,18]. Subsequently, Zhao *et al.* [31] prioritized the top five positions of 'easily available' cysteines for facilitating the design of covalent inhibitors. From a drug perspective, a large amount of data on kinase active compounds has been made available. NIH LINCS had 193 sets of kinase inhibitor profiling data (www.lincsproject.org/) and CHEMBL had collected 54 189 kinase-active compounds (www.ebi.ac.uk/chembl/sarfari/kinasesarfari) as of March 2017. Acknowledging the progress in covalent kinase inhibitors [23,32] and using the resources described, it should be possible to launch an efficient and novel drug-design path [14,33].

Corresponding author: Bourne, P.E. (peb6a@virginia.edu)

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To this end, we first hand-curate all released CSKIs and then provide a comprehensive analysis using techniques from structural system pharmacology. Finally, we provide a perspective on a design strategy for CSKIs.

Status of CSKIs

Distribution of CSKIs

We hand-curated all CSKIs from recently published reviews [18,23,34] and the databases [see IUPHAR/BPS Guide to Pharmacology database, version 2017.01 (www.guidetopharmacology.org) and Cyteinome, version 2016 (www.cysteinome.org)]. Excluding probes and repeated CSKIs, a total of 202 CSKIs formed our CSKI data set (see Table S1 in the Supplemental information online). Furthermore, their corresponding targets are distributed across 55 kinases, which cover the lipid kinase family and all major protein kinase groups except CK1 [35] (Fig. 1a). Among the 55 kinases, EGFR had the highest number of released CSKIs with 61, which is not surprising given that three of the four FDA-approved covalent kinase drugs target EGFRs. For every kinase, the amino acid residues involved in the covalent interaction are

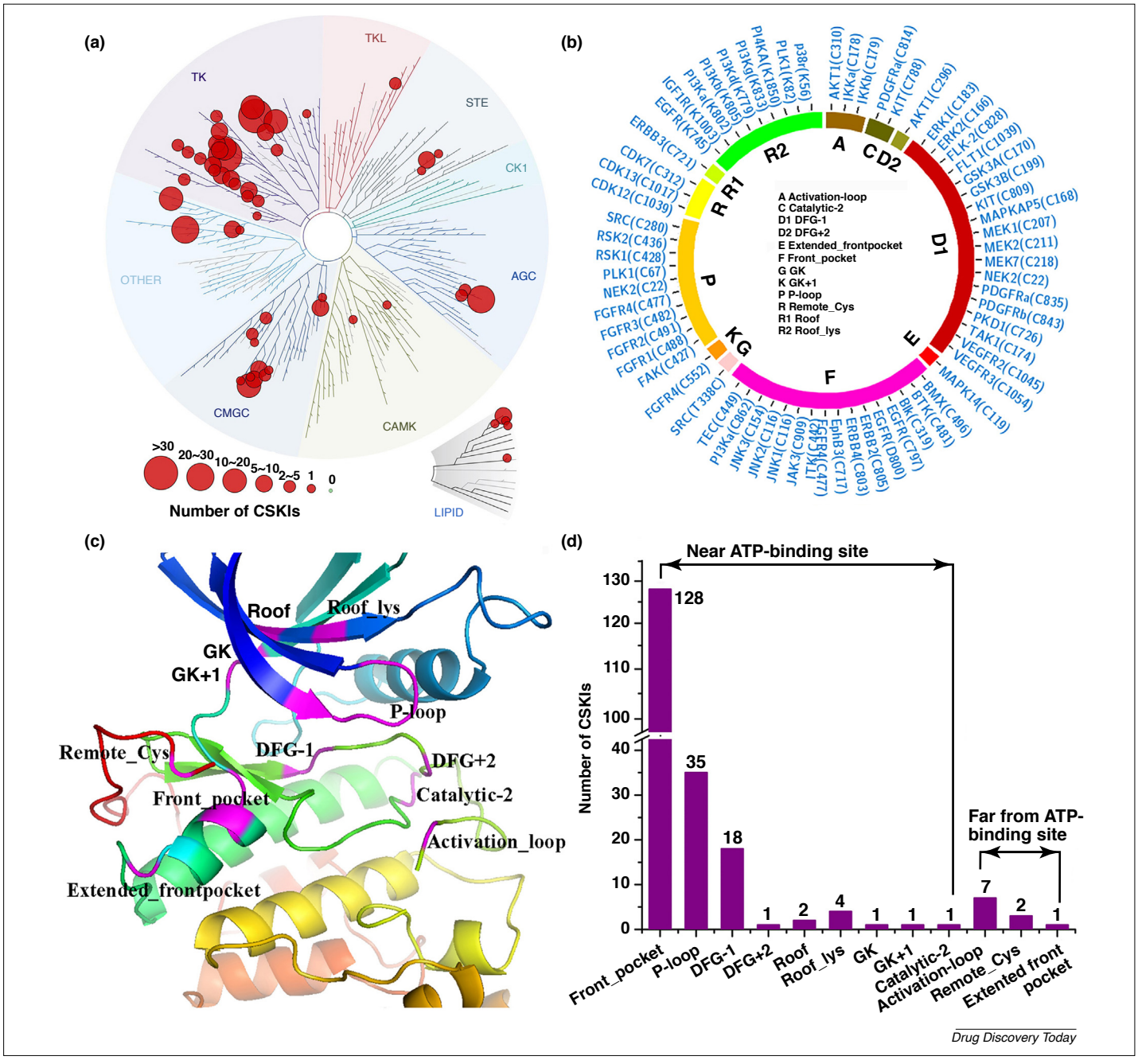

FIGURE 1

Distribution of CSKIs. (a) Distribution of kinases and the number of covalent small-molecule kinase inhibitors (CSKIs) for every targeted kinase across the human kinome. (b) Distribution of specific kinases, amino acids, and locations for recognized CSKIs. (c) Distribution of reactive cysteines in the tertiary kinase domain (magenta) (template, Protein Data Bank ID 5efq). (d) The number of CSKIs in each kinase region. Produced using TREEspot (www.discoverx.com) (a) and Circos software (http://circos.ca/) (c).