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Structure-based Methods for Predicting Target Mutation-induced Drug Resistance and Rational Drug Design to Overcome the Problem

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Abstract

Drug resistance has become one of the biggest challenges in drug discovery/development and attracted great research interests worldwide. During the last decade, computational strategies have been developed to predict target mutation-induced drug resistance. Meanwhile, various molecular design strategies, including targeting protein backbone, targeting highly conserved residues, and dual/multiple targeting, have been used to design novel inhibitors for combating the drug resistance. This is a brief review of recent advances in development of computational methods for target mutation-induced drug resistance prediction and strategies for rational design of novel inhibitors that could be effective also against the possible drug-resistant mutants of the target.

Introduction

With the development of computer science and structure biology, structure-based drug design has become one of routine approaches of drug discovery today. Aided by structure-based design, many pharmacologists usually focus on improving the potency of drug candidates from micromolar to nanomolar even picomolar level. However, the stronger the selection pressure, the more rapidly resistance develops because drug target has been proved to be very plastic [1]. Take HIV-1 virus as an example, it has been estimated that there are 10^4 to 10^5 mutations every day for each single residue in an untreated HIV-1 infected individual [2]. Hence, it is an interesting task and urgent demand to develop new strategies to combat drug resistance.

Generally speaking, drug resistance can be divided into several categories (Figure 1) [3], including target mutation, epigenetic modifications represented by gene expression variations of the target protein [4], and drug bypass signaling [5–6]. It is desirable to account for the possible drug resistance in the course of drug discovery in order to overcome the

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drug resistance as much as possible. Thus, it is interesting to computationally predict the possible target mutation-induced drug resistance and design possible inhibitors that are also effective against the resistant variants (RV inhibitors). This review is focused on recent advances of structure-based approaches to drug resistance prediction and molecular design strategies to combat target mutation-induced resistance.

Structure-based prediction of mutation-induced drug resistance

The fast and precise prediction of drug resistance mutations could help to avoid therapy failure and/or facilitate therapy redesign after failure. Hence, various computational methods have been used to carry out mutation-induced drug resistance prediction based on the known resistant variants (RV) of the target. Commonly, the side chains of amino acids in the target protein structure are replaced by the corresponding ones in a mutant during the computational modeling which aims to model the mutant structure. Molecular docking [7–8], molecular dynamics (MD) simulation [9–13], and computational mutation scanning [14–15] methods have been used to determine the binding structures of a drug in various mutants.

Because of the high efficiency of the computation, molecular docking is a good choice for the resistance prediction of a large number of mutants or compounds. For a potential problem, the simple docking cannot deal with the highly flexible protein-inhibitor complex structures very well. As well known, MD simulation has an advantage in conformational flexibility sampling and researchers can peer into the motion at atom level from the obtained MD trajectories. On the down side, the MD method is relatively more time-consuming and might not be suitable for simulating a large number of mutants.

In order to predict mutation-induced shift of the binding free energy for a given mutant, Hao *et al.* [15] developed a novel drug resistance prediction method – computational mutation scanning (CMS), which is a reasonable combination of the MD simulation on wild-type (WT) protein target and subsequent mutational scanning (one-step perturbation) for a larger number of mutants. For the possible limitation of the methodology, the CMS method can be accurate only under a presumption that the mutation does not considerably change the binding mode of the drug. In other words, the CMS calculation could significantly overestimate the drug resistance associated with the mutant when the mutation actually causes a considerable change in the binding mode. Based on the CMS calculations, the mutation-induced drug resistance mechanisms include the following categories: (1) decrease in the enthalpy contribution to the binding affinity; (2) decrease in the entropic contribution to the binding affinity; (3) decrease in both the enthalpy and entropic contributions; (4) no significant change in the enthalpy and entropic contribution; (5) decrease in the enthalpy contribution compensated with increase in the entropic contribution; and (6) decrease in the entropic contribution compensated with increase in the enthalpy contribution.

Statistical learning methods [16] have also been used for sequence-based drug resistance predictions. By using these purely empirical approaches, one only needs to know the primary structure (sequence) of the target protein, but a large number of known resistance and non-resistance mutants are required for the model training. Well trained models could have satisfactory predictive ability which is measured by the prediction accuracy of the resistance level (Table 1).

Further, there have been efforts to develop other effective computational approaches to the drug resistance prediction based on a combined use of structure- and sequence-based methods [17]. In particular, Zhang *et al.* [18] proposed a unique procedure that combines Bayesian statistical modeling with MD simulations to investigate complex interactions of drug resistance mutations of the HIV-1 protease and reverse transcriptase. They presented a

statistical procedure that first detects mutation combinations associated with drug resistance and then the molecular basis of their statistical predictions was further studied by carrying out MD simulations and free energy calculations to infer detailed interaction structures of these mutations. Their proof-of-concept study has demonstrated that the insights obtained from the MD simulations guided by the Bayesian inference can shed light on how to improve the potency of drugs to combat the resistance.

Table 1 summarizes the results associated with different methods reported in recent years. Predictive ability of these studies is mainly evaluated by qualitative or quantitative indicators. Qualitatively, drug resistance can be divided into different levels, in which prediction accuracy is in the range of 82%–96% for structure-based methods, 80%–95% for sequence-based methods, and 65%–80% for consensus methods. Quantitatively, the predictive ability can also be evaluated by the prediction accuracy or standard deviation of the computational values from the corresponding experimental values. In the quantitative analysis, correlation coefficient (R^2) and the standard deviation between the computational and experimental binding affinities are widely used. Usually, the R^2 value ranges from 0.61 to 0.92 in structure-based methods, 0.55 to 0.94 in sequence-based methods, and 0.47 and 0.90 in consensus methods. The standard deviation of the binding energy calculation is usually under 1.5 kcal/mol.

Structure-based design of resistance variant (RV) inhibitors

It is interesting to design and develop more effective drugs that can be active for both the WT protein target and its possible variants. Detailed analysis on a wide range of X-ray crystal structures of protein-drug complexes, along with biological data on drug-resistant mutations, has identified structural factors important for rational design of new inhibitors whose binding affinity with the target is not (or less) affected by the target mutations.

Targeting protein backbone

Amino-acid mutations change the side chains of mutated residues, but do not change the backbone. Inhibitors designed to have strong hydrogen-bond interactions with the backbone atoms of the target protein can likely reserve important interactions with the mutants and, thus, effectively combat drug resistance (Figure 2A and Scheme 1A) [19–22]. For example, a series of 1-[(2-hydroxyethoxy) methyl]-6-(phenylthio)thymine (HEPT) analogues were computationally designed and synthesized [23] to form two hydrogen bonds with the backbone carbonyl group of Lys101 of HIV-1 reverse transcriptase. Most of these compounds are highly potent inhibitors of WT HIV-1 reverse transcriptase and its resistant mutants.

It is well known that darunavir displayed ultrahigh HIV protease inhibitory potency ($K_i = 16$ pM) and retained the potency against many highly drug-resistant HIV mutants by forming hydrogen bonds between bis-tetrahydrofuran (bis-THF) moiety and the backbone NH groups of Asp29 and Asp30 [24]. Ghosh *et al.* [25] further predicted that the incorporation of another tetrahydrofuran ring on the bis-THF ligand could provide additional favorable binding with the backbone atoms. The prediction guided them to design and synthesize a series of novel oxatricyclic ligands that “displayed potent activity against a variety of multidrug-resistant clinical HIV-1 strains, with EC_{50} values ranging from 0.6 to 4.3 nM, a nearly 10-fold improvement over darunavir” [25].

Targeting highly conserved residues

The analysis of the reported resistant mutants demonstrated that few drug-resistant mutations happened on highly conserved residues [26]. Hence, another widely accepted strategy is to design inhibitors that have significant interactions with only the highly

conserved residues so as to minimize the dependence of the activity on the non-conserved residues (Figure 2B and Scheme 1B) [27–30].

β -Lactam antibiotics have long been used for treatment of bacterial infections since they bind irreversibly to Penicillin-Binding Proteins (PBPs) that are vital for the cell wall biosynthesis. Many pathogens express drug-insensitive PBPs to render β -lactams ineffective, which reveals a need for new types of PBP inhibitors that are active against the resistant mutants. Contreras-Martel *et al.* [31] identified boronic acid inhibitors that are active against clinically relevant pathogens and may overcome β -lactam resistance by mimicking the tetrahedral catalytic intermediate.

In addition, Schiffer *et al.* developed a “substrate envelope” hypothesis that inhibitors located within the overlapping consensus volume of the substrates were less likely to be susceptible to drug-resistant mutations than inhibitors that protrude beyond this envelope [32]. As mutations impacting such inhibitors would simultaneously impact the process of substrate perception [33–37]. For an ideal inhibitor located within the substrate envelope, there will be no chance for drug-resistance mutation except for the rare co-evolution of the protein and substrate [38]. In order to evaluate this hypothesis, over 130 new inhibitors of HIV-1 protease were designed and synthesized with and without the substrate-envelope constraints [37]. In general, inhibitors that t within the substrate envelope have alter pro les with respect to drug-resistant protease variants than inhibitors that protrude beyond the substrate envelope. Thus, the acquired results from testing this hypothesis are encouraging as they have demonstrated that combining the substrate-envelope hypothesis with structure-based drug design may result in new inhibitors that are less susceptible to drug-resistant mutations.

Dual/multiple targeting

It has been well-known that drug combination (combination therapy) has been known as an effective strategy to overcome drug resistance. To improve patient compliance, two or more drugs can also be co-formulated into a single tablet. On the down side, complex pharmacokinetic (PK)/pharmacodynamic (PD) profiles and unpredictable drug-drug interaction could have a significant impact on the risks and costs of developing multi-component drugs [39]. Dual/multiple targeting strategy, which uses a single molecular entity to inhibit multiple protein targets, could significantly reduce the likelihood of drug resistance without the extra patient compliance problem (Figure 2C and Scheme 1C). For a particular example, *ABCB1* (ATP-binding cassette, sub-family B, *MDR1*) overexpression protects leukaemia cells from drug-induced apoptosis and decreases sensitivity of leukaemia cells to cytotoxic chemotherapeutic agents. Mutations in *ABCB1* are one of the mechanisms for chemoresistance common to a wide spectrum of cancers. Recent studies showed that myeloid cell leukaemia sequence 1 (BCL2-related) gene (*MCL1*) was upregulated in numerous haematological and solid tumour malignancies. Ji *et al.* demonstrated that *MCL1* mediated drug resistance through a different mechanism and the depletion of both *MCL1* and *ABCB1* showed an additive effect in reversing drug resistance and promoting drug-induced apoptosis [40]. So, simultaneous targeting of *MCL1* and *ABCB1* could be an effective approach to overcome drug resistance in leukaemia. However, a key challenge of dual/multiple targeting is attaining a balanced activity at each target of interest while simultaneously achieving a wider selectivity and a suitable pharmacokinetic profile.

Conclusions and perspectives

Recent studies have revealed that the efficacy of many small-molecule drugs can be hampered by the rapid emergence of drug-resistance mutations on the target proteins and that the battle against mutation-induced drug resistance has become increasingly intense

[41–42]. Rational strategies to combat mutation-induced drug resistance should be accounted for in the course of drug discovery/development to prevent the emergence of resistance as much as possible.

The structure-based methods are particularly useful for computational prediction of resistant mutants and RV inhibitor design. The primary challenge of structure-based drug resistance prediction is how to appropriately balance the prediction accuracy and computational efficiency. It would be an ideal approach to efficiently predict the drug resistance level and understand the resistance mechanism associated with each resistant mutant through an appropriately combined use of structure-based methods and statistical learning methods. Besides, targeting protein backbone, targeting highly conserved residues, and dual/multiple targeting have been recognized as effective strategies for rational design of novel inhibitors with reduced resistance risk. Structure-based drug design could eventually lead to the discovery and development of novel, more potent and safer drugs with potentially different resistance profiles compared to the existed drugs. It would be interesting to further develop and validate novel strategies and/or make an appropriately combined use of available strategies. One can reasonably expect that the use of structure-based methods will become more and more popular in the battle against drug resistance.

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Research Highlights

- Recently developed structure-based computational methods are capable of predicting target mutation-induced drug resistance.
- It is possible to account for possible mutation-induced drug resistance during the drug discovery.
- Various molecular design strategies have been used to rationally design novel drugs with reduced resistance risk.
- The use of structure-based methods will become more and more popular in the battle against drug resistance.

Figure 1.

Illustration of drug resistance mechanisms. Drug resistance can be divided into two main categories: target mutation and non-target mutation. Target mutation affects the binding of the inhibitor (1). Non-target mutations include epigenetic modifications (2) and drug bypass signaling (3). Epigenetic modifications can be grouped into DNA methylation, histone modifications, and nucleosome positioning. A representative is gene expression variations of the target protein (2). Resistance can also occur on drug bypass signaling pathway, which results in less drug accumulation by increasing drug elimination or metabolizing (3).

Figure 2.

Schematic illustration of various strategies used to design novel inhibitors for combating the drug resistance. **(A)** Inhibitors designed to have strong hydrogen-bond interactions with the backbone atoms of the target protein can likely reserve important interactions with the mutants and, thus, effectively combat drug resistance. **(B)** Designing inhibitors that have significant interactions with only the highly conserved residues can minimize the dependence of the activity on the non-conserved residues. **(C)** Dual/multiple targeting strategy, which uses a single molecular entity to inhibit multiple protein targets, could significantly reduce the likelihood of drug resistance.

A. Targeting Protein Backbone GRL-0519A
HIV-1 Protease Inhibitor HEPT analogue
HIV-1 reverse transcriptase Antiandrogen
Androgen Receptor Antagonist 4-(phenylamino)quinazoline
EGFR inhibitor**B. Targeting Highly Conserved Residues** C6-extended PBO
HIV-1 Reverse Transcriptase Inhibitor Zanamivir
H5N1 Neuraminidase Inhibitor CARB-AD37
HIV-1 Protease Inhibitor Boronate Ligand
Penicillin-Binding Proteins**C. Dual/Multiple Targeting** HA 14-1
Bcl-2, Bcl-X_L, and Bcl-w Inhibitor BIBM1015
Thrombin and Factor Xa Inhibitor oxazolopyridines
Thrombin and Factor Xa Inhibitor**Scheme 1.**

Chemical structures of known representative inhibitors (designed by using different strategies) that are potent toward WT and many drug-resistant mutants

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Table 1

Computational drug resistance prediction capability

Year	method	Target	Reported prediction accuracy ^a			
			Criterion 1	Criterion 2	Criterion 3	Criterion 4
Phenotypic predictions						
2008 [12]	Molecular Dynamics	HIV protease				< 1.5 kcal/mol
2008 [8]	Molecular Modeling Protocols	HIV protease			R ² =0.61	
2008 [43]	Vitality value calculation	HIV protease				< 1.2 kcal/mol
2008 [44]	Molecular Dynamics with free energy/variability value	HIV protease	88%			
2009 [45]	Molecular Dynamics	EGFR			R ² =0.84	
2009 [46]	Molecular Dynamics	ACCase			R ² =0.74	
2009 [13]	Molecular Dynamics	PPO			R ² =0.84	
2009 [47]	Proteochemometric Modeling	HIV protease			R ² =0.92	
2009 [17]	Molecular interaction energy components and support vector machine	HIV protease		86–93%	R ² =0.81–0.92	
2010 [15]	Computational Mutation Scanning	HIV protease	96%	82%	R ² =0.75	
Genotypic predictions						
2006 [48]	Decision trees, neural networks, support vector regression, least-squares regression, and least angle regression	HIV protease and reverse transcriptase		80.1%		
2006 [49]	Recurrent Neural Networks	HIV protease	81.4–94.7%			
2007 [50]	Itemset boosting	HIV reverse transcriptase			R ² =0.55–0.94	
2008 [51]	Support Vector machine, the Radial Basis Function Network, and k-Nearest Neighbor	HIV protease and reverse transcriptase	88.0%			
2009 [52]	Artificial neural network, random forest, and support vector machine committee	HIV reverse transcriptase			R ² =0.73	
The consensus predictions						
2008 [53]	Multivariate statistical procedures	HIV reverse transcriptase and protease	65–80%			
2008 [54]	fitness landscape	HIV protease			R ² =0.47–0.84	

^aVarious criteria used to represent the prediction accuracy in the references cited:

Criterion 1 – Percentage of the correctly predicted resistance and non-resistance mutations.

Criterion 2 – Percentage of the correctly predicted drug-resistance levels (high, middle, low, and no resistance) in which the low resistance level means less than 10-fold resistance (in terms of the IC₅₀ value increase), the middle resistance level means less than 100-fold but higher than 10-fold resistance, and the high resistance level means higher than 100-fold resistance.

Criterion 3 – Correlation coefficient (R²) for the linear correction between the computational binding free energy changes and the corresponding experimentally-derived binding free energy changes.

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Criterion 4 – Standard deviation of the computational binding free energies from the corresponding experimentally-derived binding free energies