Databases and ontologies

DCDB: Drug combination database

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ABSTRACT

Summary: Rapid advances in pharmaceutical sciences have brought ever-increasing interests in combined therapies for better clinical efficacy and safety, especially in cases of complicated and refractory diseases. Innovative experimental technologies and theoretical frameworks are being actively developed for multicomponent drug research. In this work, we present the Drug Combination Database, with aims to facilitate analyses of known drug combinations, to summarize patterns of beneficial drug interactions, and to provide a basis for theoretical modeling and simulation of such drug interactions. Its current version (1.0) collected 499 approved or investigational drug combinations, including 40 unsuccessful drug combinations, involving 485 individual drugs, from >6000 references.

Availability: http://www.cls.zju.edu.cn/dcdb/.
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Supplementary information: Supplementary data are available at the database website and Bioinformatics online.

1 INTRODUCTION

Ever since Paul Ehrlich postulated the existence of ‘chemo-receptors’ in the 1870s, finding a bioactive compound that selectively acts on a molecular target important in disease progress has been a central paradigm in drug discovery. So far, ~1500 drugs have been found to target ~2500 macromolecules, with abundant information well collected and organized in relevant databases (Wishart, 2008). However, recent advances in pharmaceutical sciences have brought accumulating evidence that this one-drug-one-target lock and key model is limited. In many complicated and refractory diseases, hardly any single target can be found to produce satisfactory benefit. Using combinations of drugs, however, has proven more successful, e.g. in treating cancer and AIDS.

In fact, therapies based on coordinated actions of multiple compounds on multiple molecular targets have been used as early as the dawn of medicine. Traditional medicines, made of herbal extracts and other natural products, are still widely used. Clinical trials even demonstrated that some of these mixtures were capable of providing unique benefits that could not be matched in any of our modern medical systems. In these cases, synergies between compounds in recipes were shown to be critical (Xue and Roy, 2003). Pioneer scientists have already started to illustrate the molecular mechanisms enabling these synergies (Wang et al., 2008). New pharmaceutical companies also support screening for ‘effective combinations’ of known drugs (Borisy et al., 2003). Some hits with yet unclear mechanisms have already entered clinical trials. Speculative, theoretical discussions on how coordinated drug actions can be modeled, analyzed and simulated have, as well, led to a series of high-impact publications (Fitzgerald et al., 2006). Yet on the other side, efforts to develop effective drug combinations were not always successful, as in the case of torcetrapib and atorvastatin (Nissen et al., 2007).

Clearly in this direction, a database of known drug combinations will help to analyze these cases in-depth, to summarize patterns of beneficial drug interactions and to provide a basis for theoretical modeling and simulation of such drug interactions. Therefore, we present the Drug Combination Database (DCDB).

2 DATABASE CONSTRUCTION

As shown in Figure 1, the drug combinations in DCDB were manually collected from PubMed and the U.S. Food and Drug Administration (FDA) (Petrelli and Giordano, 2008) Orange-Book. The latest FDA Orange-Book contained 178 approved multicomponent drugs. Another 321 combinations in different R&D stages were extracted from PubMed articles containing keywords ‘drug combination’, ‘multi-drug’ or ‘multi-therapy’. Individual drugs, active compounds and their molecular targets were manually annotated based on the literature and relevant databases such as Drugbank (Wishart, 2008), PubMed, UniProt and Drugs.com.

3 CLASSIFICATION OF DRUG COMBINATIONS

In DCDB, a drug combination is a tested multihit formulation with explicit indications and dose ratio. A drug combination may

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have multiple drug interactions between its component drugs, which are the molecular mechanisms underlying its overall effect. Drug combinations are not always successful. Based on whether a drug combination was able to produce the expected improvements over other treatments in clinical trials or preclinical studies, a drug combination was classified as efficacious or non-eficacious.

The molecular mechanisms through which drug combinations produce their overall effects are categorized with a two level system. On the first level, drug interactions are divided into pharmacodynamic interactions and pharmacokinetic interactions. Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another at its site of action. Pharmacokinetic interactions are those where one drug can affect the processes by which another drug is absorbed, distributed, metabolized and excreted. On the second level, pharmacodynamic interactions are further grouped into five categories based on their ‘sites of actions’ (Imming et al., 2006; Zybarth and Kley, 2006). They are (i) all individual drugs act on the same target; (ii) individual drugs act on different targets in the same pathway; (iii) individual drugs act on different targets in related pathways; (iv) individual drugs act on different targets in cross-talking pathways; and (v) individual drugs act on different targets in pathways of yet unknown relations. Similarly, pharmacokinetic interactions are further grouped into four categories, i.e. (i) positive or negative regulations of drug transport or permeation; (ii) enhanced or reduced drug distributions or localizations; (iii) drug metabolism interactions; and (iv) drug elimination interactions. It shall be emphasize here that the above categories of drug interactions are not mutually exclusive. For example, a drug combination may have pharmacodynamic and pharmacokinetic interactions at the same time.

4 WEB INTERFACE

The DCDB and related documents are freely accessible at http://www.cls.zju.edu.cn/dcdb/ (the trailing slash is necessary). Its web interface allows search by drug, drug combination, disease and drug target. All text queries support the use of wild characters ‘*’ (representing a string of any length) and ‘?’ (representing a single character). Drugs can also be searched by chemical similarity. For each drug combination, its intended activity, indication, potential adverse effects, use in clinical practice, and other data are provided. The database schema and related documents are available at its website. We also provide a number of summary spreadsheets for scientists who want to develop a quick overview of the current state of the art.

5 SUMMARY AND FUTURE PROSPECTIVES

DCDB is the first database devoted to the R&D of multicomponent drug combinations. Its current version collected 499 drug combinations, involving 485 individual drugs, from >6000 references. This volume of data is expected to grow rapidly with the rising interests from both academia and commercial sectors. Therefore, DCDB will be updated twice a year, including one minor update for data only, and one major update with possible changes in database schema and potential integration of new analysis tools. The next major update has been projected to launch an integrated pathways analyzer for mining drug target connections, and a software tool to identify potential ‘off-targets’ for drugs, based on our inverse-docking strategy (Chen et al., 2003). These tools are expected to offer extra power and utility when molecular mechanisms of beneficial drug interactions are analyzed.

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