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Databases and ontologies

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IntSide: a web server for the chemical and biological examination of drug side effects

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ABSTRACT

Summary: Drug side effects are one of the main health threats worldwide, and an important obstacle in drug development. Understanding how adverse reactions occur requires knowledge on drug mechanisms at the molecular level. Despite recent advances, the need for tools and methods that facilitate side effect anticipation still remains. Here, we present IntSide, a web server that integrates chemical and biological information to elucidate the molecular mechanisms underlying drug side effects. IntSide currently catalogs 1175 side effects caused by 996 drugs, associated with drug features divided into eight categories, belonging to either biology or chemistry. On the biological side, IntSide reports drug targets and off-targets, pathways, molecular functions and biological processes. From a chemical viewpoint, it includes molecular fingerprints, scaffolds and chemical entities. Finally, we also integrate additional biological data, such as protein interactions and disease-related genes, to facilitate mechanistic interpretations.

Availability and implementation: Our data and web resource are available online (http://intside.irbbarcelona.org/).

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

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1 INTRODUCTION

Side effects (SEs) are defined as non-therapeutic, generally undesired, phenotypic responses to drug treatment. They affect around 2 million patients per year in the USA, ranking the fourth cause of death (Giacomini *et al.*, 2007). Anticipating SEs before launching a drug to the market is crucial for reducing health risks, as well as costs and time during drug development. To address this issue, many databases and tools have flourished. For instance, the Food and Drug Administration developed the Adverse Event Reporting System (FAERS) that contains adverse reactions and medication error reports. Another major SEs repository is Side Effect Resource (SIDER) (Kuhn *et al.*, 2010), which collects information on marketed medicines and their SEs recorded in package labels.

The wealth of information in these repositories has enabled systematic studies on SEs permitting, for instance, the computational inference of unknown drug targets (Campillos *et al.*, 2008; Cheng *et al.*, 2013). However, most studies are not able to capture complex or unspecific events, which are often directly related to the drug structure and reactivity (Williams and Park, 2003). The association between drug structure and its activity has indeed been used in predictive toxicology (Sushko *et al.*, 2012). Yet, available resources offer very broad phenotypic categories and are not able to discriminate among the great variety of SEs.

The emerging picture is that drug SEs are the result of the interaction of small molecules with complex biological systems (Bai and Abernethy, 2013), requiring an integration of chemical and biological details that, unfortunately, is not conducted in most studies. Very recently, we presented a top-down approach to identify chemical and biological drug features that might be involved in the development of adverse drug reactions (Duran-Frigola and Aloy, 2013). We delimited the chemical and biological space for each compound by gathering molecular properties from major biomedical resources, and carried out an enrichment analysis associating more than 1000 SEs with molecular features. Here, we present a web server, named IntSide, which automates this analysis and enables a quick and easy access to our findings. Moreover, we further integrate additional biological information, such as protein interactions and disease-related genes, to facilitate mechanistic interpretations. As a result, IntSide provides a complete catalog of proteins, cellular processes and chemical structures that may lead to undesired responses to drug treatments.

2 IntSide DESCRIPTION

IntSide contains drug traits classified into eight groups representing different levels of biological and chemical details (Fig. 1A). Within the biological features, we consider therapeutic drug targets, protein interactors (i.e. drug targets and off-targets), pathways, biological processes and molecular functions. In addition, we represent drug chemical traits such as small molecular descriptors, scaffolds and structural terms. We applied the strategy presented in Duran-Frigola and Aloy (2013) to identify over-represented molecular features among drugs causing an SE. We defined as 'over-represented' a feature significantly more present in drugs causing the SE compared with the background set of drugs (see Supplementary Material). In an updated dataset, we detected enrichment signals for 1175 SEs. For 56% of the SEs, we found both biological and chemical traits, while 38% and 6% were only associated with biological or chemical characteristics, respectively. In addition, using protein networks,

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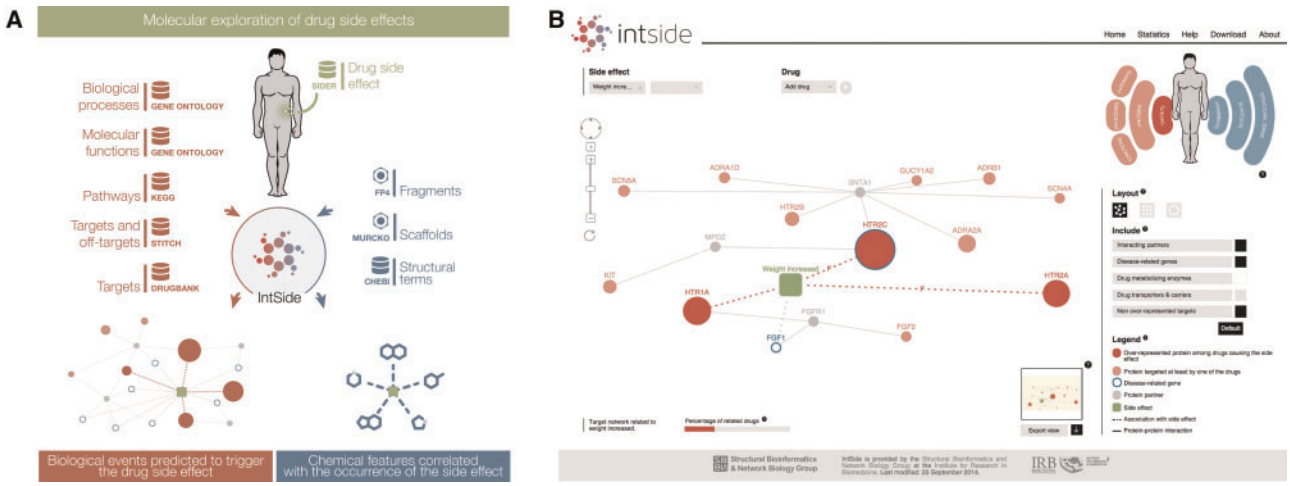

Fig. 1. (**A**) IntSide work flow. Biological and chemical drug characteristics are integrated from distinct resources and connected to SEs by performing an enrichment analysis. (**B**) The target network page for 'weight increased'. Users can modify the query by specifying a drug or by adding SE(s). Characteristics of drugs with over-represented features can be explored through the top-right panel. The 'Include' section enables the filtering of nodes. The 'Percentage of related drugs' bar indicates the number of SE-related drugs annotated with features in the network over the total number of SE-related drugs

we connected drug receptors with disease-related genes by mapping SEs to diseases based on common phenotypes.

We designed a web server interface that allows a quick and intuitive access to our data and results. Users can explore up to three SEs at the same time and, as output, the server produces different networks displaying the common significant biological and chemical features associated to each SE (Fig. 1B). In the case of 'targets' and 'proteins' networks, non-associated proteins (target proteins without strong statistical association with the SE) and disease-related genes are also included, provided they are connected to an associated protein by a path ≤ 2 in the binary interactome (Fig. 1B). Users can also specify a drug that causes the SE(s) of interest, reducing the network to features belonging to that drug.

These networks allow for inferring complex mechanisms responsible for an SE, which is valuable since drugs rarely disturb a single target. They interact, intendedly or not, with a set of proteins involved in diverse biological pathways and physiological functions, which are eventually related.

3 CONCLUSIONS

IntSide provides information to unravel the molecular mechanisms underlying drug SEs. Compared with other resources, our web server offers faster and more straightforward access to biological and chemical features that are likely related to SEs of interest. In particular, IntSide includes the human interactome and disease-related genes, facilitating the conception of mechanistic hypotheses. As SEs may be caused by several factors, network integration and visualization allow for the identification of complex mechanisms.

Unfortunately, the applicability of IntSide is currently limited by data availability in public repositories. We anticipate that ongoing efforts to increment clinical and pharmacological reports will improve the coverage and accuracy of our results.

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