LEADING ARTICLE

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Drug Adverse Reaction Target Database (DART)

Proteins Related to Adverse Drug Reactions

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Abstract

An adverse drug reaction (ADR) often results from interaction of a drug or its metabolites with specific protein targets important in normal cellular function. Knowledge about these targets is both important in facilitating the study of the mechanisms of ADRs and in new drug discovery. It is also useful in the development and testing of rational drug design and safety evaluation tools. The Drug Adverse Reaction Database (DART) is intended to provide comprehensive information about adverse effect targets of drugs described in the literature. Moreover, proteins involved in adverse effect targets of chemicals not yet confirmed as ADR targets are also included as potential targets. This database gives physiological function of each target, binding drugs/agonists/antagonists/activators/inhibitors, IC_{50} values of the inhibitors, corresponding adverse effects, and type of ADR induced by drug binding to a target. Cross-links to other databases are also introduced to facilitate the access of information about the sequence, 3-dimensional structure, function, and nomenclature of each target along with drug/ligand binding properties, and related literature. The database currently contains entries for 147 ADR targets and 89 potential targets. A total of 187 adverse reaction conditions, 257 drugs, and 1080 ligands known to bind to each of these targets are also currently described. Each entry can be retrieved through multiple search methods including target name, target physiological function, adverse effect, ligand name, and biological pathways. A special page is provided for contribution of new or additional information. This database can be accessed at http://xin.cz3.nus.edu.sg/group/drt/dart.asp.

All drugs can produce harmful as well as therapeutic effects. Adverse drug reactions (ADRs) often result from interaction of a drug or its metabolites with either its main therapeutic target or other protein and nucleic acid targets important in the normal cellular functions.[1-6] Identification and characterisation of these adverse effect-related protein or other molecular targets constitutes a major focus of pharmacology and toxicology research.[5,7,8]

Knowledge about these targets not only facilitates the study of the mechanisms behind ADRs, but it has also been widely used in the development of experimental techniques and computer tools for molecular analysis and high-throughput screening of ADRs as an early risk assessment tool.[9-12] Rapid advance in genetic,[13] structural[14] and functional[15] genomics is providing increasingly more comprehensive information about adverse effect related

genes, proteins and pathways. This helps to broaden the scope of drug safety evaluation research and development to include such tasks as analysis of pharmacogenetic implication of sequence variation or expression pattern alterations of adverse effect targets.[16-18]

Traditionally, knowledge about known ADR targets is acquired from literature searching, which can be time consuming and difficult particularly for those not working in a specific field. Therefore, a publicly accessible database that provides comprehensive information about these targets provides a convenient and useful platform for obtaining relevant information. The information of particular interest includes the functional aspects of ADR targets, mode of interaction of a target with its binding drugs and ligands, as well as the adverse effect due to the binding of a drug or a chemical to each target. To the best of the authors' knowledge, such a publicly accessible database is not yet available. We introduce the Drug Adverse Reaction Target (DART) database, which contains information about the literature-described known targets related to adverse effects of drugs. In addition to ADR targets, literature-described proteins involved in adverse effect of a chemical are also included in our database and marked as potential ADR targets. Although these potential targets are not yet qualified as ADR targets, they are included in the database based on the consideration that they can potentially become ADR targets for new drugs structurally and chemically similar to the adverse effect inducing chemicals directed at the same target. A disclaimer about this is given in the database.

Other information in DART includes the molecular properties of each target such as its synonym, name of corresponding gene, physiological function, tissue distribution, and sub-cellular location as well as the adverse effect resulting from the binding of a drug or a chemical to the target. For each ADR target, the type of ADR induced by the binding of a drug is also given. To give a comprehensive perspective about adverse effect targets, more information is provided which includes the diseases in which each target may play an important role, agonists/antagonists/activators/inhibitors that bind to each target, the related biological pathway (enzyme only) and possible mechanisms of related adverse effect. Cross-links to other databases are also introduced to facilitate the access of information about the function, sequence, 3-dimensional structure, nomenclature, and related toxicity literature of each target.

The targets collected in DART were obtained from a comprehensive search of available literature from sources including Medline,[19] review articles and books.[1-6] A target is included in DART if it has been reported that an adverse effect results from direct disturbance of the normal function of the target. Adverse effects are either related (type A) or unrelated (type B) to the principal pharmacological action of a drug.[4] Approximately 75% of ADRs belong to the type A group, and are primarily induced by affecting exactly the same target as is affected to achieve the therapeutic response. In most cases type A effects are reversible and can be reduced by lowering the drug dose or, in some cases, by changing to a different drug combination. Although the interaction of any drug with its main therapeutic target can potentially induce a type A ADR, only those with well-characterised adverse effects are included in our database at this stage. Type B effects often involve a chemically reactive metabolite of a drug and the effects can also be induced by different kinds of chemicals. Thus type B effects and associated targets are main subjects of study in toxicology.[5] Some of the mechanisms of type B effects discussed in the literature include dysregulation of gene expression, dysregulation of ongoing cell activity, impairment of internal cellular maintenance and impairment of external cellular maintenance.[5] In the database, the type of ADR resulting from the binding of a drug to an ADR target is provided. The letter A or B in the bracket before each drug name indicates its binding to the corresponding ADR target induces type A or type B ADR.

It is worth noting that the mechanism reported in some literature may be postulated and thus the related targets require further validation. A disclaimer

about this is given in our database. The coverage in DART is incomplete. It is not expected that all the ADR targets have been found by experiments. In some cases, experimental evidence is not specific enough to point to a particular protein or molecule as an ADR target. Rapid advances in research and development from both academia and pharmaceutical industry are leading to the discovery of new knowledge about adverse effect targets. In addition to our continued effort for mining the relevant information, it is hoped that new knowledge or existing information missing in this database can be made available by other researchers.

1. Data Collection and Mechanism Analysis

DART has a web interface at http://xin.cz3.nus.edu.sg/Group/dart/dart.asp. The entries in this database are generated from a search of Medline,[19] pharmacology and toxicology textbooks,[4-6] review articles[1-3,7,20,21] and a number of other publications.[22-24] It is known that deficiency and inhibition of some proteins important in normal cellular function may result in adverse effects. Examples of these proteins are those involved in key cellular metabolism processes, for instance, gastric mucosal cyclo-oxygenase is irreversibly inhibited by anti-inflammatory drug aspirin (acetylsalicylic acid), which leads to gastritis with focal erosions and bleeding.[25] Another example is the inhibition of phosphodiesterase by theophylline, which results in emetic responses such as nausea and vomiting.[26] Some drugs can be transformed into toxic agents by metabolising enzymes such as cytochrome P450.[27] Adverse reactions to drugs may also result from an immune mechanism.[21] In addition, drug interaction with some proteins involved in signalling pathways may also produce toxic as well as anticancer effect.[7]

Adverse effects may also be produced by dysregulation of gene expression, dysregulation of ongoing cell activity, impairment of internal cellular maintenance and impairment of external cellular maintenance. An example is ubiquinol-cytochrome C reductase (complex III), which is part of the mitochondrial respiratory chain. This enzyme oxidises the reduced ubiquinol, generates the proton gradient and reduces cytochrome C. High doses of antimycin A, an antibiotic, can inhibit the electron transfer from heme b_H to a quinone or semiquinone molecule bound to the centre Q_1.[2] The inhibition of the electron transporting complex can cause symptoms such as muscle weakness, easy fatigability, hypertension, headache, facial flushing, nausea, confusion and aggravation of latent myocardial angina.

Based on their respective role, the targets are grouped into four categories: receptors, transporters, enzymes and other proteins. This database currently contains 147 entries for protein targets found from the literature. The information about each target including physiological function, synonym, name of corresponding gene, tissue distribution, and subcellular location is generated from multiple sources such as literature and bioinformatics databases. For each enzyme target, its nomenclature class, catalytic abilities and pathway information is also searched and included in the database. Currently, 187 different adverse reaction conditions are described in the database and it also lists a total of 1337 different ligands. These ligands are drugs, drug candidates or leading compounds, natural substrates, and synthesised chemicals. They are categorised into agonists/

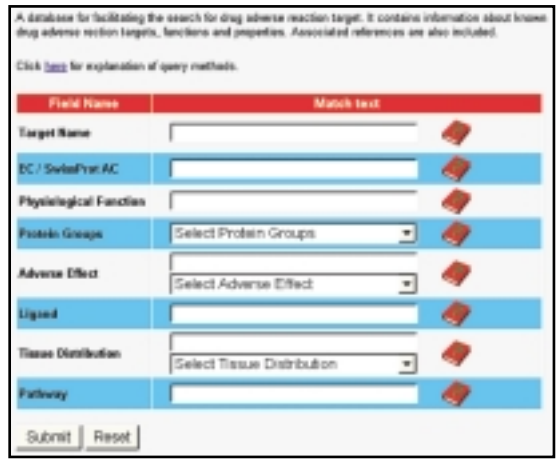

Fig. 1. The search interface of the Drug Adverse Reaction Database (DART).

activators and antagonists/inhibitors of the target molecules.

2. Database Access

The DART database web interface is shown in figure 1. This database is searchable by target name or ligand name. It can also be easily accessed by keyword full text search such as adverse reaction, physiological function, or biological pathways. An exact search method through the EC access number of enzymes (Enzyme Data Bank access number, http://www.expasy.org/enzyme/), and SwissProt access number is available also. Searches involving any combination of these search or selection fields are also supported.

The full text search is case insensitive and wild cards supported. In a query, a user can specify full name or any part of the name in a text field. Wild characters of '?' and '*' are allowed in text field. Here, '?' represents any one character and '*' represents a string of characters of any length. For example, input of 'cholinesterase' in the target name field finds entries containing 'cholinesterase' in their name, such as cholinesterase or acetylcholinesterase. On the other hand, input of 'a*cholinesterase' finds all the cholinesterase start their names with 'a'. In this case, '*' represents 'cetyl'.

The result of a typical search is illustrated in figure 2. In this interface, all the toxicity targets that satisfy the search criteria are listed by their protein names and gene names. By clicking the target name,

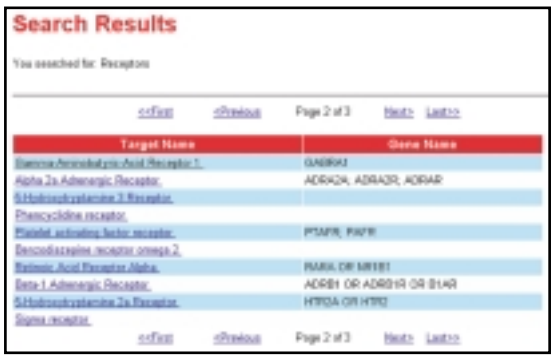

Fig. 2. A typical search result from the Drug Adverse Reaction Database (DART).

Fig. 3. The detailed information of a selected toxicity target.

a result table specific to selected target is shown (figure 3), where more comprehensive information about the target is given. The information may include: name of the target, its synonym, gene name, tissue distribution and subcellular location, if known, known agonists/activators/antagonists/inhibitors, possible adverse effect, possible toxicity mechanisms and literature reference. For an enzyme target, its EC number, corresponding biological pathways, and catalytic reaction described in chemical equation form are also provided. Additional information about a target is listed in the target prosperity item, which contains the cross-links to relevant databases such as: SwissProt database,[28] where the target sequence can be retrieved from. The available 3-dimensional structure of a target can

be accessed through cross-linking to the Protein Data Bank (PDB) database.[29] For an enzymatic target, its nomenclature can be obtained from cross-link to the Enzyme Data Bank. The related literature can be accessed from cross-link to the relevant entries in the PubMed database[19] and TOXNET (http://toxnet.nlm.nih.gov). More detailed information of ligands is also provided, when available, by clicking the ligand name, as shown in figure 4.

3. Data Submission and Updating

The database will be updated quarterly, more information will be filled in and new functions may be added. A special form is also designed for submission of new toxicity targets (figure 5); however, the new data will not be automatically integrated directly into the database. It will be validated and enriched by the curator before it can be accessed through the Internet.

4. Preliminary Analysis of Database

Currently, the database contains a total of 147 adverse effect targets, in which enzymes form the largest group with 74 members. All six classes of enzymes are found in this group including 27 hydrolases, four isomerases, two ligases, 27 oxidoreductases, nine transferases, and five lyases. The database also contains 47 receptors, 19 transporters and 17 other proteins. Of all these ADR targets, 36 proteins are also found to be the therapeutic targets, which likely lead to type A adverse effects when their therapeutic performance is significantly affected.

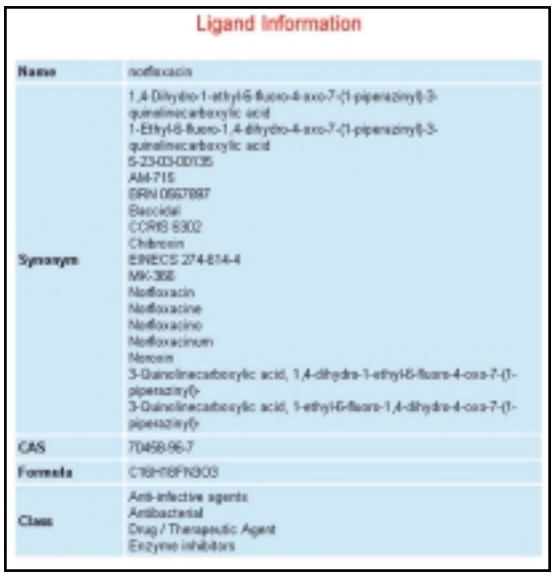

Fig. 4. The detailed information of a selected ligand.

Fig. 5. The interface of the submission form.

5. Conclusion

DART is developed from available information in the literature, which is a result of collective and persistent effort over the years. It integrates the general information of toxicity target molecule such as physiological function with its toxicity-related aspects. With the rapid development of toxicology and pharmacology, more information of toxicity and side effect targets will become available. Moreover, progress in the study of proteomics[30] and pathways[31] related to potential toxicity and adverse effects will further facilitate our understanding of the mechanisms behind ADRs. The relevant new information can be incorporated or the corresponding new databases can be cross-linked to DART to provide comprehensive description about toxicity and adverse effect targets of drug.

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