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Internet resources for proteins associated with drug therapeutic effects, adverse reactions and ADME

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Drug actions and human response often involve the interaction of a drug or its metabolites with specific proteins. Knowledge about these proteins is important in facilitating the understanding of drug actions and new drug discovery. Internet resources for proteins involved in drug therapeutic effects, adverse reactions, absorption, distribution, metabolism and excretion are reviewed here.

Drug therapeutic effects, adverse reactions and pharmacokinetics often involve interaction of a drug or its metabolites with specific proteins [1–3]. Knowledge about these proteins is important in facilitating the study of the molecular mechanism of therapeutic actions, adverse reaction, disposition and individual responses of drugs. It is also useful in the development and testing of tools for drug design [1], side effect detection [4] and pharmacokinetics evaluation [5]. Several freely accessible internet databases are now available which provide useful information about these drug-associated proteins. These databases, listed in Table 1 with website addresses, are reviewed here.

Therapeutic targets

Therapeutic targets are proteins or nucleic acids used as the principal target of therapeutic action by drugs or investigative drugs. One resource for therapeutic targets is the Therapeutic Target Database (Chen, X., *et al.*, National University of Singapore, Singapore), which contains information on 433 therapeutic targets, covering 125 disease conditions along with 809 drugs/ligands directed at each of these targets. Each entry can be retrieved through multiple methods including target name, disease name, drug/ligand name, drug/ligand function and drug therapeutic classification.

Guanine nucleotide-binding protein (G protein)-coupled receptors (GPCR), ion channels, nuclear receptors, protein kinases, phosphatases, proteases and phosphodiesterases constitute the majority of known therapeutic targets [1]. Information about these proteins can thus be obtained from databases specialized in each of these protein classes.

The Receptor Database (Nakata, K., *et al.*, National Institute of Health Sciences, Tokyo, Japan) is a useful resource for different types of receptors. Information System for GPCR (Horn, F., *et al.*, University of Nijmegen, Netherlands) provides information or hyperlinks about sequence, fragments, ligand-binding data and other aspects of GPCRs. G-protein coupled receptors mutant database (GRAP mutant databases, Edvarson, O., *et al.* University of Tromso, Norway) provides relevant information on sequence alignment, mutant and binding assay. The G-protein Coupled Receptors page of the Kyoto Encyclopedia of Genes and Genomes (Kanehisa, M., *et al.* Bioinformatics Center, Institute for Chemical Research, Kyoto University, Japan) lists GPCRs in different organisms. An automated system is provided in the SEVENS database (Suwa, M., *et al.*, Computational Biology Research Center, National Institute of Advanced Industrial Science and Technology, Japan) for discovering 7-transmembrane helix receptors in the human genome sequence. Information about the structure, function and classification of glutamate receptors can be obtained from the Tools for the Glutamate Receptor Research database (Center for Synaptic Plasticity, Medical Research Center, University of Bristol, UK).

NucleaRDB: An Information System for Nuclear Receptors (Horn, F., *et al.*, University of Nijmegen, Netherlands) contains information about sequence, sequence-derived data, multiple sequence alignment, phylogenetic relations, structural data, related genes and chromosomal locations of nuclear receptors. Nuclear Protein Database (NPD) (Dellaire, G., *et al.*, Medical Research Council Human Genetics Unit, Edinburgh, UK) includes >1000 vertebrate proteins localized inside the cell nucleus. Other related sites for nuclear receptors are Nuclear Receptor Resource (McAdara, J., *et al.*, Georgetown University, Washington, DC, USA), nuclear receptors page of the Collecting Duct database (NIH, MD, USA) and Nuclear Receptors Database (Duarte, J., *et al.*, Laboratoire de Biologie Moleculaire et Cellulaire, Lyon, France).

The Ligand-gated Ion Channel Database (Novère, N. Le, *et al.*, Institute Pasteur, Paris, France) contains 420 entries of ligand-activated ion channel

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Table 1. Summary of targets related databases and their websites

Databases	Proteins contained[a]	Website address
48 Human ATP-Binding Cassette Transporters (48ABC)	ADME	http://nutrigene.4t.com/humanabc.htm
ABC Permease Database (ABCdb)	ADME	http://ir2lcb.cnrs-mrs.fr/abcdb/
ADME-Associated Protein database (ADME-AP)	ADME	http://xin.cz3.nus.edu.sg/group/admeap/admeap.asp
Cytochrome P450 Homepage of Nelson's	ADR, ADME	http://drnelson.utmem.edu/cytochromep450.html
Cyclic Nucleotide Phosphodiesterases page on CCDB	TT, ADR	http://mrb.niddk.nih.gov/cddb/display.php?section=4
Cytochrome P450 Drug Interaction Table	ADR, ADME	http://medicine.iupui.edu/flockhart/
Directory of P450-containing Systems	ADR, ADME	http://www.icgeb.trieste.it/~p450srv/
Drug Adverse Reaction Target Database (DART)	ADR	http://xin.cz3.nus.edu.sg/group/dart/dart.asp
Endogenous G-Protein-Coupled Receptor List	TT, ADR	http://www.tumor-gene.org/gpcr/gpcr.html
GRAP Mutant Databases	TT, ADR	http://tinygrap.uit.no/grap/homepage.html
G Protein-Coupled page of Kyoto Encyclopedia of Genes and Genomes	TT, ADR	http://www.genome.ad.jp/kegg/ortholog/tab04030.html
Glutamate Receptor Research	TT, ADR	http://www.bris.ac.uk/synaptic/info/tools.html
HIV Protease Database	TT	http://srdata.nist.gov/hivdb/
Human Intestinal Transport System	ADME	http://bigfoot.med.unc.edu/watkinslab
Human Membrane Transporter Database (HMTD)	ADR, ADME	http://laboratory.digibench.net/transporter/
Human Olfactory Receptor Data Exploratorium (HORDE)	TT, ADR	http://bioinfo.weizmann.ac.il/horde/
Human P450 database	ADR, ADME	http://www.gentest.com/human_p450_database/
Information System for G Protein-Coupled Receptors (GPCRDB)	TT, ADR	http://www.gpcr.org/7tm/
Information System for Nuclear Receptors (NucleaRDB)	TT	http://receptors.ucsf.edu/nr/
Ion Channel Network (ICN)	TT	http://www.pain.med.umn.edu/csn/
Ligand-gated Ion Channel Database (LGIC)	TT	http://www.pasteur.fr/recherche/banques/lgic/lgic.html
Mendelian Inheritance and the Mitochondrion (MitoDat) database	ADR	http://www-lecb.ncifcrf.gov/mitodat/
MEROPS, the Proteases Databases	TT	http://www.merops.ac.uk/merops/merops.htm
Mitochondria Project database (MITOP)	ADR	http://www.mips.biochem.mpg.de/proj/medgen/mitop/
Nuclear Protein Database (NPD)	TT	http://npd.hgu.mrc.ac.uk/
Nuclear Receptor Resource (NRR)	TT	http://bc.georgetown.edu/nrr/nrr.html
Nuclear Receptors database (NuReBase)	TT	http://www.ens-lyon.fr/lbmc/laudet/nurebase/access/access.html
Nuclear Receptors page on CDDB	TT	http://mrb.niddk.nih.gov/cddb/display.php?section=16
Olfactory Receptor DataBase (ORDB)	TT	http://senselab.med.yale.edu/senselab/ordb/default.asp
Peptaibol Database	TT	http://www.cryst.bbk.ac.uk/peptaibol
Phosphodiesterases Page of the Collecting Duct Database	TT	http://mrb.niddk.nih.gov/cddb/
Phosphoprotein Database (PPDB)	TT	http://www-lecb.ncifcrf.gov/phosphodb/
PhosphoBase	TT	http://www.cbs.dtu.dk/databases/phosphobase/
PROLYSIS (Protease database)	TT	http://delphi.phys.univ-tours.fr/prolysis/
Protease/ExPASy	TT	http://www.expasy.org/cgi-bin/lists?peptidas.txt
Proteases of *E. coli*	TT	http://www.cf.ac.uk/biosi/staff/ehrmann/tools/proteases.index.html

Table continued overleaf

Table 1. Continued

Databases	Proteins contained[a]	Website address
Protein Kinase Resource (PKR)	TT, ADR	http://pkr.sdsc.edu/html/index.shtml
Proteinase Inhibitor Database	TT	http://www.ysbl.york.ac.uk/~proteinase/
Receptor Database	TT, ADR	http://impact.nihs.go.jp/rdb.html
SEVENS database (7-Transmembrane helix proteins database)	TT, ADR	http://sevens.cbrc.jp/
Serine proteases	TT	http://biochem.wustl.edu/~protease/ser_pro_link.html
Therapeutic Target Database (TTD)	TT	http://xin.cz3.nus.edu.sg/group/ttd/ttd.asp
Transporter Page of University Hospital Groningen	ADR, ADME	http://www.med.rug.nl/mdl/english/tab3.htm
Voltage-gated Potassium Channel Database (VICDB)	TT	http://vkcdb.biology.ualberta.ca/

[a]Abbreviations: ADME, absorption, distribution, metabolism and excretion-associated proteins; ADR, Adverse drug reaction; TT, therapeutic target.

subunits with information about sequence, structure, multiple sequence alignment, phylogenetic relations, and gene sequence of subunits or portions of subunits of ligand-gated ion channels. Voltage-gated Potassium Channel Database (Li, B., *et al.*, University of Alberta, Canada) provides information about sequence, references, and functional data of voltage-gated potassium channels. The Ion Channel Network (Conley, E.D., *et al.*, University of Leicester, UK) is a pilot website for information on nomenclature and expression data of different types of ion channels. Peptaibol Database (Chugh, J., and Wallace, B., Birkbeck College, University of London, UK) provides the sequence of >200 membrane-active polypeptides, their alignment and derived common features for ion channel formation.

Information about protein kinases can be retrieved from Protein Kinase Resource (Smith, C.M., *et al.*, University of California San Diego, USA), which contains integrated data about classification, disease, sequence, proteomic and tools for structural and computational analyses. PhosphoBase (Kreegipuu, A., *et al.* University of Tartu, Estonia) gives phosphorylation sites of protein kinases. The Phosphoprotein Database (Hornbeck, P., NIH, USA, under construction) is intended to provide information about phosphatases, as well as kinases. The phosphodiesterases page of the Collecting Duct Database (NIH, USA) is useful for direct search of phosphodiesterase-related information from PubMed and Online Mendelian Inheritance in Man (OMIM) databases.

MEROPS, the Protease Database (Wellcome Trust Sanger Institute, Cambridge, UK), contains entries for several hundred proteases searchable by enzyme name, identifier, organism and family. 3D structure of some proteases and their inhibitors are also provided. Protease/ExPASy (Rawlings, N., *et al.*, The Babraham Institute, Cambridge, UK) gives classification of peptidases and hyperlinks to SWISS-PROT and PROSITE databases. Serine Proteases Database (Rose, T., and Cera, E.D., Washington University School of Medicine, MO, USA) provides information about sequence, structure, function, mutations and phylogeny of serine proteases. Protease and inhibitor web server PROLYSIS (Moreau, T., University of Tours, France) is a resource for proteases and their natural or synthetic inhibitors. Proteinase Inhibitor Database (Bray, J., University of York, UK) gives information about proteinases and their inhibitor/drugs. Other protease websites are HIV Protease Database (Vondrasek, J., Macromolecular Crystallography Laboratory, National Cancer Institute, NIH, MD, USA), and Proteases of *E. coli* (Ehrmann, M., Laboratory, Cardiff University, UK).

Adverse drug reaction targets

Adverse drug reaction (ADR) targets refer to proteins or nucleic acids to which drug binding induces adverse reactions. One useful website for ADR targets is Drug Adverse Reaction Target Database (Ji, Z.L., *et al.*, National University of Singapore, Singapore), which contains entries for 282 adverse reaction targets, covering 187 adverse reaction conditions along with 257 drugs, and 1080 ligands known to bind to each of these targets. It also provides information about the corresponding agonists, antagonists, activators and/or inhibitors, IC_{50} values of the inhibitors, synonym, Chemical Abstracts Service (CAS) number, molecular formula, chemical classification, and the toxic effect or side effect resulting from the binding of a drug or ligand.

Several mitochondrial proteins are known to be ADR targets as a result of their crucial role in ATP synthesis [6]. Information about these proteins can be retrieved from the Mitochondria Project database (Scharfe, C., *et al.*, Ludwig-Maximilians-Universitat Munchen, Germany) which describes the function, protein class, protein complexes, subcellular location, EC number, related motifs and the corresponding gene. The Mendelian Inheritance and the

Mitochondrion database (Lemkin, P.F., *et al.*, NCI-FCRDC, NIH, USA) contains data on human mitochondrial proteins.

A variety of enzymes are ADR targets, which include metabolizing enzyme cytochrome P450 subtypes, proteases and kinases. The Human P450 Metabolism Database (Rendic, S., and di Carlo, F.J., University of Zagreb, Croatia) contains information about human P450 metabolism, which is organized by enzyme, therapeutic area, chemical substance, reaction and ligand type. The Cytochrome P450 Homepage of Nelson's laboratory (Nelson, D., University of Tennessee, USA) includes 2383 P450s from different species. It provides sequences, phylogenetic trees and hyperlinks to other databases. The Cytochrome P450 Drug Interaction Table (Flockhart, D.A., Indiana University, USA) contains relevant information and links to related literatures about substrates and drugs known to interact with various P450 enzyme subtypes. Another useful P450 site is the Directory of P450-containing Systems (Degtyarenko, K.N., *et al.,* International Centre for Genetic Engineering and Biotechnology, Trieste, Italy), which provides access to internet resources of P450 proteins, P450-containing systems, steroid ligands known to bind to P450, and cross-links to several sequence, structure and function databases.

Certain members/subtypes in GPCR family and glutamate receptor family have been identified as ADR targets. Some transporters and carriers are also ADR targets, based on the observation that their inhibition or activation lead to specific adverse reactions. Useful information about these transporters and carriers can be found in the Human Membrane Transporter Database (Yan, Q., *et al.*, University of California San Francisco, USA), which include >250 human membrane transporters with information about sequence, gene family, structure, function, substrate, tissue distribution, and genetic disorders associated with transporter polymorphisms.

Absorption, distribution, metabolism and excretion-associated proteins

While passive diffusion plays important role in pharmacokinetics of many drugs, drug absorption, distribution, metabolism and excretion-associated proteins (ADME) is also known to involve interaction of a drug or its metabolites with various proteins. The ADME Protein Database (Sun, L.Z., *et al.*, National University of Singapore, Singapore) contains entries for 331 proteins involved or potentially involved in drug ADME, as described in the literature. It describes physiological function of each protein, pharmacokinetic effect, ADME classification, direction of ligand transport (e.g. into or out of cell) and driving force (e.g. ion-dependent or voltage-dependent) of disposition, location and tissue distribution, protein substrates, synonyms and gene name.

Drug metabolism is associated with interaction of a drug with specific metabolizing enzymes [7]. In certain cases, drug ADME is facilitated by drug binding to transporters and carriers [8]. Information about ADME-associated proteins can thus be obtained from specialized databases and websites focusing on specific class or group of transporters, carriers and metabolizing enzymes.

The Transporter Page (Muller, M., *et al.*, University Hospital Groningen, The Netherlands) provides information on family classification, gene sequence, homology, expression level and localization of transporters in liver and intestine. A website of the 48 human ATP-binding cassette (ABC) transporters for the P-glycoprotein nomenclature (Allikmets, R., *et al.*, Frederick Cancer Research and Development Center, Bethesda, MD, USA) includes information about related genetic diseases, tissue distribution and substrates. The ABC Permease Database (Quentin, Y., *et al.*, Institut de Biologie Structurale et Microbiologie, Marseille, France) contains information about ABC transporters, protein partners, classification, evolutionary trees and taxonomy. The Human Intestinal Transport System website (Watkins Laboratory, University of North Carolina at Chapel Hill, NC, USA) provides substrates, activators and inhibitors of P-glycoprotein and hOATP and other transporters in epithelial cells.

Conclusion

The databases surveyed in this article are useful resources for accessing proteins associated with drug therapeutic effects, adverse reaction and ADME. With the rapid development of pharmacology, toxicology and pharmacokinetics, more information of related targets will become available. Moreover, progress in the study of proteomics and pathways related to potential therapeutics, adverse effects and drug disposition will further facilitate our understanding of the mechanism of drug action and human response. It is hoped that more information or public databases will be made available that include additional proteins, pharmacological role of related proteins (therapeutic, ADR or ADME), structural data, protein–protein interaction, binding/reaction kinetics data and related pathways.

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