Drug Development

Technological developments in areas such as genomics, proteomics and high-throughput screening are also beginning to impact significantly upon the early stages of drug development. For example, by linking changes in gene/protein expression to various disease states, these technologies will identify new **drug targets** for such diseases. Most such targets will themselves be proteins, and drugs will be designed/developed specifically to interact with them. It has been estimated that all drugs on the market target one (or more) of a maximum of 500 targets. The majority of such targets are proteins (mainly enzymes, hormones, ion channels and nuclear receptors). Hidden in the human genome sequence data is believed to be anywhere between 3000 and 10,000 new protein based drug targets. Additionally, present in the sequence data of many human pathogens (e.g. *Helicobacter pylori*, *Mycobacterium tuberculosis* and *Vibrio cholerae*) is sequence data of hundreds, perhaps thousands, of pathogen proteins that could serve as drug targets against those pathogens (e.g. gene products essential for pathogen viability or infectivity).

While genome sequence data undoubtedly harbors new drug leads/drug targets, the problem now has become one of specifically identifying such genes (Walsh, 2003).

PHARMACOGENOMICS (Pharmacogenetics**)**

Pharmacogenetics is the study of the roles of genetic variations in the responses to drugs. As a result of the progress made in sequencing the human genome, a new field of study—**pharmacogenomics**— has developed recently. Information from genomics, proteomics, bioinformatics, and other disciplines such as biochemistry and toxicology will be integrated to make possible the synthesis of newer and safer drugs (Murray *et al.,* 2003).

Different people respond differently to any given drug, even if they present with essentially identical disease symptoms, e.g. optimum dose requirements can vary significantly. While the basis of such differential responses can sometimes be non-genetic (e.g. general state of health, etc), genetic variation amongst individuals remains the predominant factor. While all humans display almost identical genome sequences, some differences are evident. The most prominent widespread-type variations amongst individuals are known as **single nucleotide polymorphisms** (SNPs, sometimes pronounced 'snips'). SNPs occur in the general population at an average incidence of one in every 1000 nucleotide bases and hence the entire human genome harbours 3 million or so. SNPs are not mutations; the latter arise more infrequently, are more diverse and are generally caused by spontaneous/mutagen-induced mistakes in DNA repair/ replication. SNPs occurring in structural genes/gene regulatory sequences can alter amino acid sequence/expression levels of a protein and hence affect its functional attributes. SNPs largely account for natural physical variations evident in the human population (e.g. height, color of eyes, etc.). The presence of a SNP within the regulatory or structural regions of a gene coding for a protein which interacts with a drug could obviously influence the effect of the drug on the body. A (distant) futuristic scenario could be visualized where all individuals could carry chips encoded with SNP details relating to their specific genome, allowing medical staff to choose the most appropriate drugs to prescribe in any given circumstance.

Classical Multidrug Resistance

One of the best-investigated mechanisms of drug resistance is the phenomenon of drug efflux with a non-specific carrier, such as the P-glycoprotein, called classical multidrug resistance. It occurs because of the overexpression of P-glycoprotein (Pgp), a transmembrane protein with a molecular weight of 170 kDa. Pgp is coded by the *mdr-1* gene on chromosome 7q21 and belongs to the ATP binding cassette (ABC) transporter family. Synonyms for Pgp are MDR-1, PGY1, and is also called ABCB1. ABC transporters are a large superfamily of integral membrane proteins involved in ATP-dependent transport of chemotherapeutic drugs across biological membranes. Most ABC transporters consist of four domains – two membrane-spanning domains and two cytoplasmic domains. The latter contain conserved nucleotide-binding motifs. Chemoresistance caused by the overexpression of Pgp exhibits a typical resistance pattern towards anthracyclins, epipodophyllotoxins, vinca alkaloids, and taxol (**Sanchez, Corthals, and Hochstrasser, 2004**).

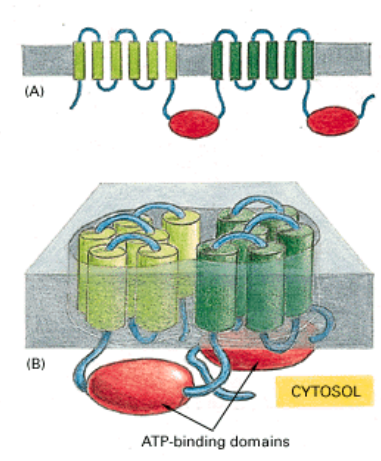

Figure 11-16. A schematic drawing of a typical ABC transporter. (A) Topology diagram. (B) Hypothetical arrangement of the polypeptide chain in the membrane.
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