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Understanding transport through pharmacological barriers — are we there yet?

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Recently, three papers have been published in *Nature Reviews Drug Discovery* that deal with the concepts, problems and regulatory aspects of drug transport across biological membranes (*Nature Rev. Drug Discov.* **9**, 597–614 (2010); *Nature Rev. Drug Discov.* **9**, 215–236 (2010); *Nature Rev. Drug Discov.* **7**, 205–220 (2008))[1–3]. The articles emphasize different aspects of drug permeation across pharmacological barriers, concentrating either on the role of carrier proteins (such as ATP-binding cassette (ABC) transporters and solute carrier proteins)[3] or on the relevance of passive diffusion and its coexistence with carrier-mediated pathways[1]. More importantly, these papers direct the limelight to a field that has been long characterized by confusion and neglect.

The classical approach of membrane biophysics and membrane biochemistry regarded the cell membrane as an efficient barrier for hydrophilic compounds (especially those that are ionized), whereas a rapid passive permeation was granted for hydrophobic compounds. Accordingly, basic textbook terms such as 'semi-permeability', 'diffusion' and 'reflection coefficient', as well as the properties of carriers and transporters, were defined as if they existed in water-based solutions. However, following the discovery of ABC multidrug transporters, it was recognized that laws governing drug permeation across the lipid phase of the membrane are more complex and that these laws could not be analysed using the classical approach.

ABC proteins transport an extremely large variety of — mostly hydrophobic — compounds, which are mainly recognized by these transport proteins in the lipid phase of the membrane[4]. However, in the hydrophobic environment of the membrane lipids and proteins, all the basic concepts of chemistry (including pH, molecular charge, intracellular or extracellular membrane localization of compounds) cannot be readily applied. With the discovery of more and more transporters that carry readily lipid-soluble hydrophobic or amphipathic compounds with high passive permeation, it has become increasingly evident that there is no proper scheme of drug permeation through cellular barrier membranes. It is now understood that, in addition to basic physical characteristics (such as the simple 'rule of five', suggested by Lipinski[5]) required by a drug to cross pharmacological barriers, drug interactions with membrane transporters are key determinants. In fact, the second article outlines a practical approach for evaluating these processes, providing a basis for the work of the major regulatory agencies supervising drug development[2].

From a pharmacological perspective, a major goal is to fully understand the interactions between transporters and drugs to predict general absorption, distribution, metabolism, elimination and toxicity properties, and individual variations for personalized therapy. Unfortunately, the hundreds of relevant transporters cannot be easily surveyed, especially considering the varying levels of their site-specific and localized expression, their apparent affinities for the various compounds and the wide, overlapping specificities for substrates and inhibitors. Clearly, a major effort is needed to develop and to establish a physiologically and pharmacologically relevant, systems-biology and computer-based support system. As a framework for this effort we propose the use of the concept called 'chemoimmunity' and its practical application to generate a useful database and exploratory tool.

In this concept we have suggested that the coordinated action of drug transporters and enzymes implicated in xenobiotic metabolism form an innate defence system, which recognizes and eliminates hydrophobic or amphipathic agents that are not handled by the classical immune response[6]. The chemoimmunity network has several features reminiscent of classical immunology. The innate form is based on the balance of passive drug permeation and the involvement of transporters and metabolic enzymes that recognize an extremely wide range of foreign hydrophobic or amphipathic compounds. The adaptive form involves the complex and interrelated regulation of numerous transporters and metabolic enzymes, especially in response to stress and to toxin exposure. Interestingly, transporters are coordinately regulated with metabolic enzymes. As a general rule, multidrug-resistant ABC (efflux) transporters are regulated in a positive correlation with the key Phase I and Phase II metabolic enzymes, whereas solute carrier proteins (uptake) transporters, which in most cases accelerate cellular drug or toxin exposure, are coordinately downregulated[7–9].

We suggest that a new attempt, based on the concept of the chemoimmunity network, which can be used to integrate data on how pharmacological barriers are functioning and maintained, is needed to help drug research and development. This should be a scientific community effort that integrates results of wet experiments and bioinformatical modelling with data obtained in clinical studies throughout the drug development process. Thus, in parallel to research elucidating mechanistic details and determinants of passive permeability and drug transport, existing information on large inventories of pharmacological agents (including compounds that were excluded during preclinical or clinical phases of drug development) should be collected and organized to interlink knowledge domains. It is especially important that transporter expression, localization in respective tissue barriers, polymorphisms and regulatory modulation for relevant protein expression should also be included. The enormous amount of currently non-standardized data should be assayed using a systems-biology approach in a newly defined network representation and data analysis.

Such a support system would greatly facilitate the work of drug developers and provide a rational basis for clinical studies. In addition, because membrane transporters are themselves drug targets, the above system would also prove beneficial in specific areas, such as cancer therapy. Cancer pharmacologists have worked in vain to develop drugs to counter the activity of ABC transporters that expel (mostly amphipathic) cytotoxic agents from multidrug-resistant cancer cells. Progress in this area has been slow, mostly because of the unexplored transporter–drug and drug–drug interactions[10].

Development based on open access information and data sharing may be too much to ask from the pharmaceutical industry. However, there is little chance that any company may be able to reach this goal alone. A reliable prediction of absorption,

distribution, metabolism, elimination and toxicity properties on the basis of membrane transporter and metabolic enzyme interactions of drugs and natural compounds would be of tremendous importance. A cooperative approach would serve the interest of drug companies, health-care providers and the general public.

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