BioISI - Biosystems & Integrative Sciences Institute

BioISI Research Seminar

ABC Transporters in Health and Disease: Multidrug Resistance and Cystic Fibrosis

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When: April 4 - 11h30

Where: Building C1, Amphitheatre

ATP-binding cassette (ABC) proteins are ubiquitous super-family of membrane transporters present in all phyla with 7 sub-families (A-G) playing central roles in drug disposition, metabolism and pharmacokinetics. They are flexible transporters that act with the membrane environment to efflux undesirable metabolites or xenobiotic drugs from inside the cell providing this way a highly relevant protective role. At least 11 transporters of the ABC family have well characterized roles in human diseases while others are expressed in many tissues and appear to be particularly related with multidrug resistance (MDR) in cancer.

Although multifactorial in nature, multidrug resistance to chemotherapy regimens can be achieved by selecting phenotypes that over-express ABC transporters. The over-expression of P-glycoprotein (Pgp/ABCB1), multidrug resistance protein 1 (MRP1/ABCC1) or breast cancer resistance protein (BCRP/ABCG2) were found to be markers of overall poor chemotherapy response and prognosis in various cancers. For instance, Pgp is a single polypeptide of ~170 kDa and effluxes a wide-range of substrates through an ATP-dependent mechanism and is found at the apical surface of kidney proximal tubule cells, canalicular membrane of hepatocytes, pancreas, villous intestinal cells, and blood–tissue barriers (e.g., brain, placenta, testis).

We developed a new research line to discover the main physicochemical features responsible for modulation through a new pharmacophore/QSAR with a better classification capability and, with the appearance in 2009 of the murine P-gp structure, this structural information was used through molecular simulations to study the dynamics of the transporter, how drug efflux occurs and how drug adsorption may affect P-gp activity. The characterization of three drug binding sites was achieved by matching experimental information with extensive docking results to unravel elusive drug/Pgp recognition, interactions and modulation mechanisms. A computational classification scheme was proposed to organize molecules in different class types (modulators, substrates, non-substrates). The access of drugs to the drug-binding pocket through a hypothesized gate was also investigated.

Unfortunately, all Pgp modulators entering phase III clinical trials failed by showing a dramatic increase in cellular toxicity (tariquidar) or reduced in vivo effectiveness (zosuquidar, laniquidar). Thus, the problem resides elsewhere, namely in the polyspecificity of the binding sites. All these findings will be reviewed, discussed and linked with very recent findings as new emerging strategy to overcome the problems found in clinical trials. Finally, applications and relevance to other efflux pumps of the same familly, e.g. ABCC7 misfolding responsible for cystic fibrosis will be presented and discussed.

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