Structure and Function of ABC Transporters in Health and Disease

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Clinical Pharmacology, January 13, 2011

Drug Resistance in Cancer

1. May affect multiple drugs used simultaneously: known as multidrug resistance (MDR)
2. Affects all classes of drugs, including newly designed targeted drugs
3. Just as oncogene targets have been catalogued, we need to enumerate all mechanisms of drug resistance in cancer to solve this problem and circumvent resistance

Ultimate Goals

1. Molecular analysis of human cancers to predict response to therapy
2. Use this information to develop novel drugs to treat cancer and new imaging modalities for cancer
3. To learn more about cellular pharmacology and pharmacokinetics of drugs

Mechanisms of resistance to anti-cancer drugs

Decreased Uptake-- 100's of Solute carriers

➔ Reduced apoptosis

Altered cell cycle checkpoints and/or growth pathways
Increased metabolism of drugs
Increased or altered targets
Increased repair of damage
Compartmentalization

➔ Increased Efflux--48 ABC transporters

Why study multidrug transporters?

- Important role in multidrug resistance in cancer and in pathogens
- Important role in drug pharmacokinetics (uptake, distribution, and excretion)
- Important role in drug toxicity
- Key role in development (stem cells, morphogenesis)
- To learn about the biology of all transport systems

ATP-Binding Cassette (ABC) Transporter Superfamily

- One of the largest family of transport proteins known. Currently, more than 2000 members have been identified.
- Transport substrates include-- ions, sugars, glycans, phospholipids, cholesterol, peptides, proteins, toxins, antibiotics, and hydrophobic natural product anticancer drugs.
- Structurally, consist of various combinations of ATP-binding cassettes and segments with 6 trans-membrane domains.

The Eukaryotic ABCome
57 ABC-family genes

Graphic From M. Dean

48 Human ABC Genes

Graphic

The Clustal W program was used to make the alignment of the NBDs
and the tree was built by using the MEGA program -- By Mike Dean, NCI

ABC transporters determine oral bioavailability, excretion, penetration and protect the organism against airborne xenobiotics

Graphic

Human diseases associated with an ABC Transporter

Disease	Transporter
Cancer	ABCB1, ABCC1, ABCG2
Cystic fibrosis	ABCC7 (CFTR)
Stargardt disease & AMD	ABCA4 (ABCR)
Tangier Disease (HDL deficiency)	ABCA1 (ABC1)
Progressive familial intrahepatic cholestasis	ABCB11(SPGP), ABCB4 (MDR2)
Dubin-Johnson syndrome	ABCC2 (MRP2)
Pseudoxanthoma elasticum	ABCC6 (MRP6)
Persistent hypoglycemia of infancy, neonatal diabetes	ABCC8 (SUR1), ABCC9 (SUR2)
Sideroblastic anemia and ataxia	ABCB7 (ABC7)
Adrenoleukodystrophy	ABCD1 (ALD)
Sitosterolemia	ABCG5, ABCG8
Immune deficiency	ABCB2 (Tap1), ABCB3 (Tap2)

ABC transporters that confer MDR: Domain organization

Image of the domain organization of ABCB1
Image of the domain organization of ABCC1
Image of the domain organization of ABCG2

Overlapping substrate specificity of ABCB1, ABCG2 and ABCC1

Image of 3 overlapping ovals showing the similarities and differences of ABCB1, ABCC1, and ABCG2

Multiple ABC Transporters Confer Resistance to Anti-Cancer Drugs

Graph of ABC transporters confer resistance

Hypothetical Model of Human P-glycoprotein

Image of model

P-glycoprotein removes hydrophobic substrates directly from the plasma membrane

Image

Atomic models of the structures of P-gp

Mouse P-gp at 3.8Å (Aller and Chang)
Human P-gp model based on Sav1866 (Xia)

Physiologic Role of P-glycoprotein

Oral Intake -> Intestine -> Fecal Excretion
IV -> Vascular space -> Urinary Excretion
Interstitial space

Role of P-glycoprotein in cancer

- Approximately 50% of human cancers express P-glycoprotein at levels sufficient to confer MDR
- Cancers which acquire expression of P-gp following treatment of the patient include leukemias, myeloma, lymphomas, breast, ovarian cancer; preliminary results with P-gp inhibitors suggest improved response to chemotherapy in some of these patients
- Cancers which express P-gp at time of diagnosis include colon, kidney, pancreas, liver; these do not respond to P-gp inhibitors alone and have other mechanisms of resistance
- Animal models with human cancer xenografts and BRCA1-driven mouse mammary cancers show role for P-gp in MDR

(Pajic et al., Cancer Res. 69, 6396-6404, 2009)