MOLECULAR MEDICINE PROGRAM, SICKKIDS
&
BHT ORGANIZATION SPECIAL SEMINAR

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CRYO-EM STRUCTURES OF HUMAN MULTIDRUG ABC TRANSPORTERS PROVIDE INSIGHT INTO DRUG TRANSPORT AND SMALL-MOLECULE INHIBITION

The multidrug transporters ABCB1 (P-glycoprotein) and ABCG2 (BCRP) are expressed in many tissues and mediate the translocation of a wide array of endogenous or exogenous compounds across cellular membranes. Both transporters have a protective role against xenobiotics and simultaneously affect the pharmacokinetics of commonly used drugs. Their overexpression in certain tumor cells correlates with a poor prognosis and treatment outcome.
To understand their broad substrate specificity, their ATP-driven transport mechanisms, and the inhibition of ABCB1 and ABCG2 by small-molecule compounds and externally binding antibodies, we determined high-resolution structures using single particle cryo-electron microscopy. The structures revealed distinct architectures and identified hydrophobic cavities in ABCB1 and ABCG2 that differ in size and shape, which can explain their overlapping, but non-identical substrate specificities. Combined with functional studies, transport mechanisms can be formulated for ABCB1 and ABCG2. In both cases, conformational "clamping" allows externally binding antibodies to inhibit transport activity. Bound inhibitors block the central drug-binding cavities of the transporters and prevent a full closing of the cytoplasmic ends of the transmembrane domains and of the nucleotide-binding domain interface, which would be needed for ATP hydrolysis. Chemical modification of specific compounds allows the SAR of inhibitory compounds to be studied and may provide a rational basis for the future design of ABCG2 inhibitors.

HOSTS: DRS. JEAN-PHILIPPE JULIEN & JEFF LEE

THURSDAY NOVEMBER 1, 2018
2:00-3:00 PM
MSB 2170 (MEDICAL SCIENCES BUILDING)
UNIVERSITY OF TORONTO, 1 KING'S COLLEGE CIRCLE

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