SFB 35 Colloquia in Membrane Transport

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"ABC transporters in Cancer drug resistance and ADME-tox"

Chemotherapy resistance is a recurrent problem, and the mechanism of resistance should be clarified in order to help further drug development. The active extrusion of several therapeutic agents by the MDR-ABC transporters should be considered as a potential cause of clinical resistance. The three major types of multidrug resistance (MDR) transporter proteins in humans include members of the ABCB, the ABCC, and the ABCG subfamily. These pumps recognize a wide range of drug substrates, mostly hydrophobic compounds, but also a variety of amphipathic anions and cations. MDR-ABC proteins play an important role in cancer drug resistance, but also in the absorption, distribution, metabolism and toxicity (ADME-tox) of several pharmaceutical agents. This concept is summarized as a "chemoimmunity" network, protecting our body against hydrophobic toxic agents.

This talk will discuss the role of MDR-ABC transporters in ADME-Tox and in drug resistance phenomena, focusing on the potential role of the ABCG2 transporter. This protein provides tissue protection against numerous toxic compounds and accounts for multidrug-resistant phenotype in various cancer cells.

Selective tyrosine kinase inhibitors (TKI) are key agents in modern cancer chemotherapy, and combination of TKIs with classical chemotherapeutic drugs may help to overcome currently untreatable metastatic cancers. However, ABCG2 displays a high affinity interaction with several clinically effective small molecule tyrosine kinase inhibitors, including Iressa (Gefitinib), an inhibitor of EGF-receptor dependent signaling, or Imatinib (Glivec) that inhibits the Bcr-Abl fusion protein, the molecular basis of chronic myeloid leukemia (CML). Recently we investigated the interaction of ABCG2 with several second generation Bcr-Abl inhibitors, already in clinical trials. Our data suggest that TKI interactions with ABC transporters may modulate drug metabolism, including the fate of diverse, chemically or target-wise unrelated drugs. These effects are based on multiple forms of MDR-ABC transporter interactions with TKIs, as these compounds may be both substrates and/or inhibitors of an ABC transporter. These interactions

should be carefully considered in clinical application. Also, a combined MDR-ABC transporter and TKI effect may bring an advantage in future drug development.