Targeting efflux transporters in multidrug resistant cancer: an unfinished business

Gergely Szakács

Institute of Enzymology, Research Centre of Natural Sciences, Eötvös Loránd Research Network, Budapest, Hungary.

Institute of Cancer Research, Medical University of Vienna, Borschkegasse, Vienna, Austria.

Clinical evidence shows that, following initial response to treatment, drug-resistant cancer cells frequently evolve, and eventually most tumors become resistant to all available therapies. The most straightforward cause of therapy resistance is linked to cellular alterations that prevent drugs to act on their target. Upregulation of cell membrane efflux transporters of the ATP-binding cassette (ABC) superfamily leads to simultaneous resistance against structurally and functionally unrelated chemotherapeutic agents. In particular, P-glycoprotein (Pgp, MDR1), the product of ABCB1 gene, was shown to be expressed in several drug resistant malignancies. Based on the correlation of P-glycoprotein expression and function with unfavorable treatment response, it is universally accepted that pharmacological modulation of the MDR phenotype has the potential to significantly increase the efficacy of currently available anticancer therapies. Unfortunately, despite a few early successes, clinical trials conducted with Pgp inhibitors did not fulfill this expectation, failing to confirm clinical benefit. Failure of the trials led to a setback in research, and the shutdown of the pharmaceutical development of transporter inhibitors for the improvement of anticancer therapy. Yet the “transporter problem” has not vanished, as evidenced by new studies supporting the relevance and benefit of research on the role of ABC transporters in clinical drug resistance. Failure of the inhibitors has boosted research in other directions, exploring the possibility to evade efflux, or to exploit the paradoxical sensitivity associated with efflux-based drug resistance mechanisms. In this talk I will describe new approaches to combating multidrug-resistant cancer, including the development of drugs that engage, evade or exploit efflux by P-glycoprotein.