ABCG2

ATP-binding cassette sub-family G member 2 is a protein that in humans is encoded by the ABCG2 gene.

ABCG2 has also been designated as CDw338 (cluster of differentiation w338).

The membrane-associated protein encoded by this gene is included in the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the White subfamily. Alternatively referred to as the Breast Cancer Resistance Protein, this protein functions as a xenobiotic transporter which may play a role in multi-drug resistance to chemotherapeutic agents including mitoxantrone and camptothecin analogues. Early observations of significant ABCG2-mediated resistance to anthracyclines were subsequently attributed mutations encountered in vitro but not in nature or the clinic. Significant expression of this protein has been observed in the placenta, and it has been shown to have a role in protecting the fetus from xenobiotics in the maternal circulation.

The transporter has also been shown to play protective roles in blocking absorption at the apical membrane of the intestine, and at the blood-testis barrier, the blood–brain barrier, and the membranes of hematopoietic progenitor and other stem cells. At the apical membranes of the liver and kidney, it enhances excretion of xenobiotics. In the lactating mammary gland, it has a role on excreting vitamins such as riboflavin and biotin into milk.

The ATP-binding cassette (ABC) drug transporter ABCG2 can actively efflux a wide variety of chemotherapeutic agents out of cancer cells and subsequently reduce the intracellular accumulation of these drugs. Therefore, the overexpression of ABCG2 often contributes to the development of multidrug resistance (MDR) in cancer cells, which is one of the major obstacles to successful cancer chemotherapy. Moreover, ABCG2 is highly expressed in various tissues including the intestine and blood-brain barrier (BBB), limiting the absorption and bioavailability of many therapeutic agents. For decades, the task of developing a highly effective synthetic inhibitor of ABCG2 has been hindered mostly by the intrinsic toxicity, the lack of specificity, and complex pharmacokinetics. Alternatively, considering the wide range of diversity and relatively nontoxic nature of natural products, developing potential modulators of ABCG2 from natural sources is particularly valuable. α-Mangostin is a natural xanthone derived from the pericarps of mangosteen (Garcinia mangostana L.) with various pharmacological purposes, including suppressing angiogenesis and inducing cancer cell growth arrest.

Wu et al. demonstrated that at nontoxic concentrations, α-mangostin effectively and selectively inhibits ABCG2-mediated drug transport and reverses MDR in ABCG2-overexpressing MDR cancer cells. Direct interactions between α-mangostin and the ABCG2 drug-binding site(s) were confirmed by stimulation of ATPase activity and by inhibition of photolabeling of the substrate-binding site(s) of ABCG2 with [125I]iodoarylazidoprazosin. In summary, our findings show that α-mangostin has great potential to be further developed into a promising modulator of ABCG2 for reversing MDR and for its use in combination therapy for patients with MDR tumors [1)].

1)

Wu CP, Hsiao SH, Murakami M, Lu YJ, Li YQ, Huang YH, Hung TH, Ambudkar SV, Wu YS. Alpha-Mangostin Reverses Multidrug Resistance by Attenuating the Function of the Multidrug Resistance-

Linked ABCG2 Transporter. Mol Pharm. 2017 Aug 7;14(8):2805-2814. doi: 10.1021/acs.molpharmaceut.7b00334. Epub 2017 Jul 5. PubMed PMID: 28641010.