ABC Transporter-mediated Porphyrin Transport and Drug-induced Photosensitivity

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Heme molecules are synthesized from glycine and succinyl Co-A via eight-stepped enzymatic reactions that are spatially shared in mitochondria and cytoplasm compartments. The transport of porphyrins across cellular membranes is crucial in metabolic compartments and cellular homeostasis of porphyrins. The ATP-binding cassette (ABC) transporter ABCB6 is considered to be responsible for import of coproporphyrinogens into mitochondria, whereas ABCG2 transports porphyrins across the plasma membrane to maintain porphyrin homeostasis in the cell. ABCG2 has been implicated to play a significant role in the response of patients to medication and/or the risk of diseases, such as porphyrin-related photosensitivity. To clarify the possible physiological or pathological relevance of ABCG2 polymorphisms with photosensitivity, we have functionally validated SNPs of ABCG2. The variants of Q126stop, F208S, S248P, E334stop, and S441N were found to be defective in porphyrin transport, whereas F489L exhibited impaired transport, about 10% of the activity observed for the wild type. Flp-In-293 cells expressing those variants were photosensitive as compared with cells expressing the wild type of ABCG2. On the other hand, inhibition of ABCG2 by certain drugs enhanced pheophorbide a-induced photosensitivity in Flp-In-293 cells expressing ABCG2. Thus, it is suggested that certain genetic polymorphisms of ABCG2 and/or its inhibition by drugs may be related to the potential risk of photosensitivity.

Reference:

Tamura A, Watanabe M, Saito H, Nakagawa H, Kamachi T, Okura I and Ishikawa T. Functional validation of the genetic polymorphisms of human ABC transporter ABCG2: Identification of alleles that are defective in porphyrin transport. *Mol Pharmacol*, 70, 287-296, 2006.