

Suppression of ABCG2 inhibits cancer cell proliferation

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The ATP-binding cassette efflux transporter, ABCG2, is widely expressed in a variety of normal tissues, stem cells, as well as cancer cells. Existing data suggest that ABCG2 plays an important role in the maintenance of the stem cell phenotype and multidrug resistance of cancer cells. However, the potential role of ABCG2 in other cellular processes remains speculative and poorly understood. Here, we demonstrated that ABCG2 is involved in the proliferation of cancer cells. We used RNA interference approach to efficiently and specifically down-regulate ABCG2 protein levels in MCF-7/MX and A549 cells. We showed that knockdown of ABCG2 significantly inhibited the proliferation of these cells. Suppression of ABCG2 reduced the percentage of cells in the S phase of the cell cycle and enhanced G0/G1 accumulation. The G0/G1 growth arrest was associated with down-regulation of cyclin D3 and up-regulation of p21. Furthermore, blocking of ABCG2 function by chemical inhibitor fumitremorgin C also inhibited cell proliferation via the prolonged G0/G1 interval. Taken together, these findings suggest that ABCG2 correlates with cell cycle progression, highlighting a novel function of ABCG2 in cancer cell proliferation.

ABCG2, also known as breast cancer resistance protein (BCRP)/placental ABC protein (ABCP)/mitoxantrone resistance protein (MXR), belongs to the ATP-binding cassette (ABC) transporter family.¹⁻³ To date, more than 50 ABC transporters have been described, classified, localized and functionally evaluated in diverse organisms from microbes to human beings. Most of these proteins actively transport an array of biological compounds, including peptides, steroids, ions and phospholipids, contributing to physiology, pathology, toxicology and pharmacology.

Several ABC transporters have been recognized as a source of drug resistance in the treatment of malignancies. ABCG2, the latest of drug efflux ABC transporters discovered, was first cloned by Doyle *et al.*¹ from a doxorubicin-resistant MCF-7 breast cancer cell line. Since then, the function

of ABCG2 has been studied extensively in terms of multidrug resistance. Nowadays, ABCG2 has been considered as 1 of the major transporters causing drug resistance in cancer cells. Actually, ABCG2 is expressed not only in some cancer cells, but also in a variety of normal tissues. For instance, ABCG2 is present in the apical membrane of placental syncytiotrophoblasts, in the endocrine cells of the pancreas, in the luminal membranes of villous epithelial cells in the small intestine and colon, in the bile canalicular membrane of hepatocytes, in ducts and lobules of the breast and in venous and capillary endothelial cells of almost all tissues.⁴⁻⁶ The functional characteristics and the distribution of ABCG2 suggest that this transporter may play an important role in protecting sensitive body compartments from potentially harmful xenobiotics.

Furthermore, ABCG2 has been demonstrated to be expressed in a wide variety of stem cells and to be a molecular determinant of the side-population phenotype. The sharp down-regulation of ABCG2 at the stage of lineage commitment suggests that ABCG2 might have a key role in maintaining progenitor cells in an undifferentiated state.⁷ It is worth noting that progenitor cells obtained from ABCG2 knock-out mice showed a reduced ability to form colonies under hypoxia. This phenomenon was attributed in part to the accumulation of heme (porphyrin) molecules. Because of the regulation of ABCG2 by HIF and the ability of ABCG2 to bind and interact with heme, it seems that ABCG2 permits enhanced cell survival in hypoxic conditions by reducing the accumulation of toxic heme metabolites.⁸

To date, the potential function of ABCG2 is incompletely understood and may be more complicated than we thought. Accumulating evidence suggests that alternative functions for this transporter may exist. It has been established that ABCG2 is a high-capacity efflux transporter with wide

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