

Role of ABCG2 in Multi Drug Resistance and Cancer Stem Cell



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Opinion

Multidrug drug resistance (MDR) is the single most common reason for cancer treatment failures and relapse [1]. For overcoming these problems, new approaches of treatment like immunotherapy, targeted therapy, hormone therapy and enzyme pro drug therapy and modified chemotherapeutics has been devised [2]. Some of these approaches also reached the clinical trials or being used in clinics but it hardly improved the relapse free survival or overall survival of cancer patients. During decades of research, different mechanisms for MDR was discovered such as drug inactivation, drug target alteration, epithelial mesenchymal transition, DNA damage repair, cell death inhibition and efflux pump/ drug transporters activation or over expression [2,3]. MDR phenomenon is shown to be often associated with cancer stem cells in GBM, leukemia, breast- and ovarian- cancer but thorough investigations are required regarding its role in cancer stem-ness.

In simple word, MDR is the resistance phenomenon developed by cancer cells to counter various chemotherapeutic agents that have different structure and mode of action [4]. There are multiple path ways that can cause MDR such as, reduced cellular activity of topoisomerase II, resistance to apoptosis induction and the drug efflux activity of group of proteins called ATP binding cassette (ABC) transporters [5,6]. ABC transporters consist of more than 48 proteins that are divided into seven distinct subfamilies (ABCA-ABCG) based on their sequence homology and domain organization [7]. Among them, the classical MDR is attributed mainly to ABCB1 (P-glycoprotein), ABCC1 (multidrug resistance protein 1; MRP1) and ABCG2 (breast cancer resistance protein, BCRP) [8] that were also studied intensively. ABCG2 was first discovered simultaneously by three different groups in 1998 and because of its identification in human placenta, its isolation from the breast cancer cell line MCF-7/AdrVp, and its identification in the mitoxantrone (MX) resistant colon carcinoma cell line S1-M1-80, it is known as ABCP, BCRP and also MXR respectively [9,10].

ABCG2 is a half transporter that consist of one Nucleotide-binding domain (NBD), one membrane-spanning domain (MSD) and six transmembrane (TM) segments. It was shown that, in plasma membranes, the major oligomeric unit of human ABCG2 is a homo-dodecamer with a minimum stable unit of homo-tetramer [11]. Although the mechanism of substrate translocation/ disposition by ABC transporters are not completely understood but the evidences and mutational studies suggest the role of two amino acids (R⁴⁸² and P⁴⁸⁵) lying in TM3 region in drug selectivity [12]. There are also other amino acids lying in the TM region that plays role in either dimerization or helical interactions and also in ATPase activity. More mutational studies and functional studies should be carried out to know the detailed mechanism of ABCG2 in substrate selectivity and translocation.

ABCG2 is widely distributed in the plasma membrane of intestine, liver, kidney, and brain and it contributes to the absorption, distribution, and elimination of endogenous compounds as well as tissue protection against toxic xenobiotics exposure [13]. Another interesting aspect of ABCG2 is its potential role in protecting cancer cells or developing drug resistance. The commonly used drugs in clinics for the treatment of cancer was found to be the substrate of BCRP [12]. ABCG2/BCRP was now considered as key ingredient molecule for disposition of clinically relevant drugs in cancer treatment. Apart from drug resistance, its' expression was found to play role in cancer stemness, adding further complexities in cancer treatment and evolution of therapy resistant cancer stem cells [11].

Cancer stem cells are group of immortal cells within a tumor that asymmetrically divide into self-renewal stem cell and differentiated non-stem cells that constitute the heterogenous tumor [14]. After exposure to cytotoxic drugs that specifically targets fast growing proliferating cells, slow-growing or quiescent cells has the intrinsic advantage in escaping the

therapy. These rare quiescent cells also over express anti-apoptotic proteins for their survival against the cytotoxic insults. Interesting hypoxic tumor niche also plays a pivotal role in up regulation of cis-acting transcription factors that ultimately contributes to BCRP over-expression and hematopoietic stem cell (HSC) regulation [15]. One of the classical substrate of BCRP is the DNA binding fluorescent Hoechst 33242. This property or concept 'rare cells that efflux DNA binding dye Hoechst-3342 or Side population (SP)' is originally applied in murine bone marrow cells to isolate HSC [16]. Since then it has been applied in other cancers to identify cancer stem cells. Although ABCG2 over expression may confer SP cells to selectively protect themselves against chemotherapeutics e.g. mitoxantrone, camptothecins, anthracyclines, etc., but at the same time, the lack or the absence of ABCG2 doesn't have any adverse effect in hematopoiesis and transplantation studies [17] conducted using knockout ABCG2 transgenic mouse. Hence, reflecting the insignificant role of ABCG2 in stem cell regulation [17,18]. In fact human embryonic stem cells lack ABCG2 and the expression of ABCG2 is inversely correlated with pluripotent stem cell genes [19]. There are numerous studies suggesting that ABCG2 is more involved in therapy resistance as it showed wide range of substrates selectivity including anti-cancer agents. Promoter studies also indicated the involvement of different intracellular detoxification enzymes in influencing cis-acting transcription factors in ABCG2 expression [20]. In conclusion, ABCG2 without any doubt play an important role as cytoprotectant in cells irrespective of differentiated and non-differentiated cancer stem cell nature, whereas the involvement of ABCG2 in cancer stem cell regulation required further investigations.

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