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Mini-review

Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: A review of the past decade

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ABSTRACT

Multidrug resistance (MDR) is a serious phenomenon employed by cancer cells which hampers the success of cancer pharmacotherapy. One of the common mechanisms of MDR is the overexpression of ATP-binding cassette (ABC) efflux transporters in cancer cells such as P-glycoprotein (P-gp/ABCB1), multidrug resistance-associated protein 2 (MRP2/ABCC2), and breast cancer resistance protein (BCRP/ABCG2) that limits the prolonged and effective use of chemotherapeutic drugs. Researchers have found that developing inhibitors of ABC efflux transporters as chemosensitizers could overcome MDR. But the clinical trials have shown that most of these chemosensitizers are merely toxic and only show limited or no benefits to cancer patients, thus new inhibitors are being explored. Recent findings also suggest that efflux pumps of the ABC transporter family are subject to epigenetic gene regulation. In this review, we summarize recent findings of the role of ABC efflux transporters in MDR.

Introduction

Despite significant advances in the area of chemotherapy which have led to decreased mortality rate in cancer patients, 5-year survival rates remain dismal, largely due to the resistance to antineoplastic drugs by either intrinsic or acquired mechanisms [1,2]. Chemoresistance, or multidrug resistance (MDR), describes a phenomenon whereby cancer cell's resistance to one drug is accompanied by resistance to pharmacologically and structurally distinct class of drugs [3].

Even the mechanisms of anticancer drug resistance appear to be complex; the most common mechanisms are categorized into drug dependent, target-dependent and drug/target-independent. Drug dependent MDR is mainly attributable to the overexpression of efflux drug transporters and detoxifying enzymes which reduced uptake or enhanced efflux of drugs in cancer cells. Target-dependent MDR is caused by factors influencing drug targeting such as translocation, deletion, mutation, and amplification of the target. Drug/target-independent MDR is due to the desensitization of drug targeting by alternation of cell signaling pathways genetically or epigenetically [4–8]. Among these, one of the most important mechanisms underlying MDR is the overexpression of adenosine triphosphate (ATP)-binding cassette (ABC) super-family of transporters, which efflux both cytotoxic agents and targeted anticancer drugs using ATP driven energy [9–11].

The purpose of this review is to discuss and highlight the role of the ABC transporters in mediating MDR in cancer cells and the development of ABC efflux transporter inhibitors which could restore the sensitivity of chemotherapy, as well as the epigenetic gene regulation in the control of MDR.

General properties of ABC transporters

The human ATP-binding cassette (ABC) transporters, a large group of membrane protein complexes, consist of 48 members that are

Abbreviations: 3′-UTR, 3′-untranslated region; ABC, ATP-binding cassette; ATP, adenosine triphosphate; BCR-ABL, breakpoint cluster region-Abelson; BCRP/ABCG2, breast cancer resistance protein; BMP4, bone morphogenetic protein 4; BrTet, 5-bromotetrandrine; cMOAT, canalicular multispecific organic anion transporter; COX-2, cyclo-oxygenase-2; DNMT, DNA methyltransferase; DVL1, dishevelled-1; EGCG, (−)-epigallocatechin-3-gallate; EGFR, epidermal growth factor receptor; EZH2, histone-lysine N-methyltransferase; FZD1, Frizzled-1; FZD7, Frizzled-7; HDAC, histone deacetylase; lncRNAs, long non-coding RNAs; MDR, multidrug resistance; miRNAs, microRNAs; MRP2/ABCC2, multidrug resistance-associated protein 2; NBDs, nucleotide-binding domains; NRF2, NF-E2-related factor 2; PDT, photodynamic therapy; P-gp/ABCB1, P-glycoprotein; RNAi, RNA interference; RUNX3, Runt-related transcription factor 3; SFRP5, secreted frizzle-related protein 5; shRNA, short hairpin RNA; siRNA, small interfering RNA; TKIs, tyrosine kinase inhibitors; TMD0, terminal transmembrane domain; TMDs, transmembrane domains; VEGFR, vascular endothelial growth factor receptor; YC-1, 3-(5′-hydroxymethyl-2′-furyl)-1-benzylindazole.

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classified into seven subfamilies from ABC-A through to ABC-G based on their sequence similarities [12]. Among the 48 ABC transporters identified in humans, those primarily located on the plasma membrane significantly reduced the intracellular concentration of a variety of diverse drugs, drug conjugates and metabolites by export [12,13]. Of them the major ABC superfamily transporters involved in MDR development are P-glycoprotein (P-gp/ABCB1), multidrug resistance-associated protein 2 (MRP2/ABCC2), and breast cancer resistance protein (BCRP/ABCG2) [14,15].

Structurally, all ABC transporters have two transmembrane domains (TMDs) and two nucleotide-binding domains (NBDs) [16]. They show a common structural fold that is composed of a core of six TM helices per TMD. The hydrophobic TMDs are structurally diverse, which alternately recognize and translocate various substrates upon conformational changes. So the TMDs which span the membrane and form channels could determine the transport characteristics of substrates [17,18]. ABC transporters can be classified on the basis of the structure and sequence of the NBDs, also known as ABC domains [19,20]. The NBDs are highly conserved proteins consisting of conserved ABC that is responsible for binding and hydrolyzing ATP via an ATPase, thus providing energy for translocation or efflux of physiological and xenobiotic substrates from the cytoplasm to the extracellular space. In addition, the NBDs also contain Walker A and B motifs as well as a signature motif which play a vital role in the hydrolysis of ATP to ADP + P and energy collecting [16,21]. A functional ABC transporter often requires two core units, forming a TMD1–NBD1–TMD2–NBD2 single polypeptide assembly such as ABCB1 (Fig. 1A), but there will be quite a bit difference in the molecular structure of other MDR proteins [22]. ABCC2 protein contains an N-terminal extension consisting of five helical transmembrane fragments as so called terminal transmembrane domain (TMD_0), which linked to the core of the molecule by a L_0 loop (Fig. 1B) [23]. By contrast, ABCG2 protein is a half-transporter, composed of one TMD and one NBD domain, but in reverse order (i.e. TMD is the C-terminal domain; see Fig. 1C) [24]. Unlike the above-mentioned transports, which function as monomers, ABCG2 forms a homodimer through the disulfide bonds thereby extruding its substrates [25]. Although changes of the transporter structures at different stages are not elucidated exclusively, substrates seem to be bound at the high-affinity site within the TMDs.

The physicochemical interactions responsible for substrate binding and mechanisms of ABC efflux transporter-mediated substrate translocation are still incompletely understood. Yet, it is widely assumed that the ATP switch plays an important role in the extraction of their substrates [26]. Generally, binding of two ATPs at the dimer interface could induce changes in TMD conformation, thus leading to the dimerization and configuration of a sandwich-like NBD. When a substrate binds to the TMD, it could induce a decrease in the activation energy for NBD dimerization. The bound ATP molecule is hydrolyzed to ADP and Pi, which separates the NBDs, then substrate is released into the extracellular space and restores the stable conformational state of the NBD which is ready for binding and transporting of another substrate (Fig. 2). Moreover, ABC transport systems can be viewed as catalytic systems or enzymes [27]. Then subsequently, a very recent article stated by Brian H. Shilton shows that active transport can use the well-established energetic framework consisting of low-energy and high-energy conformation for enzyme-mediated catalysis. The transport process involves binding interactions that selectively stabilize the higher-energy intermediate conformations, and thus promote conformational changes in the system that are coupled to decreases in free energy and substrate translocation [28].

P-gp/ABCB1 (P-gp/MDR1)

The first member of ABC transporters, ABCB1 (P-gp/MDR1), was identified in 1976 by Ling et al. as a 170-kDa membrane glycoprotein overexpressed in colchicine resistant cell lines and was referred to as a glycoprotein that reduces drug permeability [29]. P-gp is an apical membrane transporter that is abundantly expressed on the intestine mucosal membrane, kidney proximal tubule epithelia, liver, placenta, and luminal blood–brain barrier, where it functions to protect against xenobiotics and cellular toxicants [30]. As seen in Table 1, P-gp has a very wide substrate spectrum mediating the export of a variety of drugs from different drug classes. These substrates include chemotherapeutic drugs, HIV-protease inhibitors, immunosuppressive agents, antiarrhythmics, calcium-channel blockers, analgesics, antihistamines, antibiotics, natural products, fluorescent dyes and pesticides, among many others [31–38]. And most of the substrates are weakly amphipathic and relatively

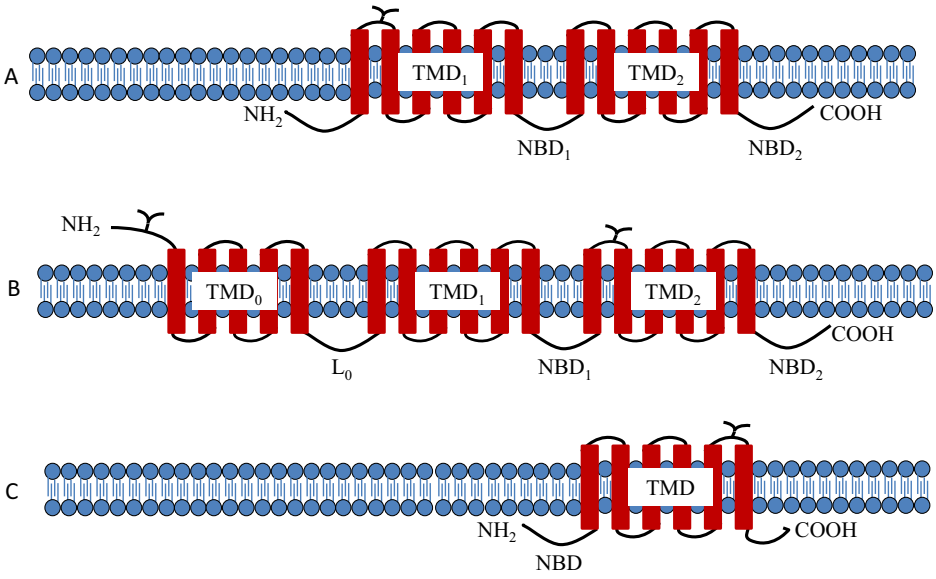

Fig. 1. Secondary structure models of drug efflux transporters of the ATP-binding cassette family. (A) P-gp/ABCB1, (B) MRP2/ABCC2, (C) BCRP/ABCG2. TMD – transmembrane domain; NBD – nucleotide-binding domain; L0 – loop 0.