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Understanding of human ATP binding cassette superfamily and novel multidrug resistance modulators to overcome MDR

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ABSTRACT

Indeed, multi-drug resistance (MDR) is a significant obstacle to effective chemotherapy. The overexpression of ATP-binding cassette (ABC) membrane transporters is a principal cause of enhanced cytotoxic drug efflux and treatment failure in various types of cancers. At cellular level, the pumps of ABC family regulate the transportation of numerous substances including drugs in and out of the cells. In past, the overexpression of ABC pumps suggested a well-known mechanism of drug resistance in cancers as well as infectious diseases. In oncology, the search for new compounds for the inhibition of these hyperactive ABC pumps either genetically or functionally, growing interest to reverse multi-drug resistance and increase chemotherapeutic effects. Several ABC pump inhibitor/modulators has been explored to address the cancer associated MDR. However, the clinical results are still disappointing and conventional chemotherapies are constantly failed in successful eradication of MDR tumors. In this context, the structural and functional understanding of different ATP pumps is most important. In this concise review, we elaborated basic crystal structure of ABC transporter proteins as well as its critical elements such as different domains, motifs as well as some important amino acids which are responsible for ATP binding and drug efflux as well as demonstrated an ATP-switch model employed by various ABC membrane transporters. Furthermore, we briefly summarized different newly identified MDR inhibitors/modulators, deployed alone or in combination with cytotoxic agents to deal with MDR in different types of cancers.

1. Introduction

Cancer is still a leading cause of mortalities with a figure of about 21% (2.8 million) and 9.5% (4.8 million) of all deaths in developed and developing countries, respectively, and increasing every year. The world health organization (WHO) expected 17.5 million cancer associated deaths and 27 million new cancer cases every year, by the year 2050. On the other hand, multidrug resistance (MDR) is a major cause of treatment failure in various cancers. In MDR, whereby cancer cells exposed to a cytotoxic agent induces cross-resistance against several functionally and structurally unrelated compounds. Usually, in tumor cells, MDR is the upregulation of cell membrane associated drug transporters. P-glycoprotein also refers as (P-gp, MDR-1, ABCB-1), indeed a well-studied drug efflux transporters and it belong to the adenosine triphosphate binding cassette (ABC) superfamily [1–3]. There are several other drug efflux transporters such as, multidrug resistance protein-1 (MRP-1, ABCC1), breast cancer resistant protein (BRCP, MXR, ABCP, ABCG-2), cystic fibrosis transmembrane regulator (CFTR) and sulphonyl urea receptor (SUR) [4–9]. Infect, ABC transporter proteins are important cell surface proteins, present ubiquitous on the cell membrane and responsible for the transportation of different ligands across physiological membranes, which is essential for the normal cellular function. Any modulation in the level of these efflux proteins could results into drug resistance as well as genetic diseases because of the inherent drug pumping ability associated with these efflux proteins. Recent studies demonstrated an ATP switch model, including ATP dependent closed conformation nucleotide-binding domain (NBD) and a nucleotide free, open structure to translocate ligands across the cell membrane into the extracellular space [10].

ABCs, the pumps of ABC superfamily are the largest group of cell membrane proteins. There are 49 ABCs which are distributed on the cell membrane [11–14] and on the basis of their abundance they are characterized into seven subfamilies (A–G). Importantly, ABCs are responsible for the efflux of various endogenous ligands such as proteins, lipids, metabolic products and drugs such as, cytotoxic and antibiotics [15] by using energy produced from the hydrolysis of ATP. It was found

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that ABCs are abundantly present in central nervous system [16,17], lung, liver, pancreas, kidney, stomach 7, intestine [18] and various autonomic barriers [18–20]. Furthermore, the expression levels of ABCs regulate the drug concentration inside the cells and overexpression of ABCs leads to MDR in cancer [21,22], HIV [23,24] and hepatitis-B. Thus, the interaction process between ABCs and drugs must be critically observed. On the other hands, in some cases one therapeutic agent could be a substrate of more than one efflux pump such as, nucleoside reverse transcriptase inhibitors (NRTIs) are the substrate of BCRP [25] but abacvir (NRTI) concentration in brain is also reduced by P-gp [26]. In this respect, search of new potent ABCs inhibitors/modulators and use them in an adjuvant therapy with therapeutic drugs gain interest in MDR related cancer [27] and various infectious diseases.

Some cancer cells own intrinsically higher expression of drug efflux transporters even without the exposure of cytotoxic drugs. This phenomenon termed as “intrinsic resistance” of tumor cells against cytostatic drugs. Many factors such as genetic mutation, tumor microenvironment and most important nature of the tissues, could be responsible for this intrinsic resistance of tumor cells against variety of chemotherapeutics [28]. However, an upregulation of drug efflux pumps was observed in response of antitumor drug exposure. This upregulation could be due to the mutation or modulation of the expression of MDR gene [27]. A study on patients with metastatic lung cancer revealed that a 20-min exposure of cytotoxic drug (Doxorubicin) could enhance 6-7-fold MDR-1 gene expression [28]. This could be referred as “acquired resistance”. Later, it was found that P-gp expression moves from higher expressing cells to the cells have low expression of P-gp in a wave and step-wise manner. Consequently, the sensitive cells with low expression of drug transporter turned into resistance ones [29].

Furthermore, intracellular detoxification process could also be a reason of acquiring drug resistance of tumor cells. Modulation of cellular detoxification such as glutathione conjugation, enables cells to eliminate drugs faster leaving intracellular low drug concentration thereby reduced therapeutic effects [30]. It was reported that, a continuous exposure of cisplatin for 18 months to ovarian cancer cells derived from an untreated patient represent a higher level of glutathione, which in turn decreased the sensitivity of tumor cells against cisplatin as well as potently inhibit the intracellular cisplatin accumulation [31].

In past numerous ABC inhibitors has been discovered to deal with MDR associated cancers [29,32].The first generation of ABCs inhibitors include repurpose drugs with established pharmacokinetic profiles such as cyclosporine-A, quinidine and verapamil [33]. While, the second (valspodar) [30] and third generation (tariquidar [34], zosuquidar) [31] of ABCs blocker were specifically design to reverse MDR with no other uncertain pharmacokinetics effects. Recently several natural compounds (curcumin, Neochamaejasmin-B [35] and small molecules (VX710, PSC833) [36] also studied in this context. Unfortunately, the clinical results were disappointing due to unsatisfactory outcomes, inadequate toxicity and absence of reproducible, validated and high-throughput analysis techniques to observe the accurate level of ABC in MDR tumors, tissues and organs as well as co-existence of other non-ABC efflux pumps, which also manipulate the actual assessment [22,37,38]. In this review, we briefly demonstrated the structure and functions of different ABC drug efflux transporters as well as different MDR modulators employed to overcome cancer associated drug resistance.

2. Classification, structure and functions of ATP-binding cassette superfamily

ATP-binding cassette (ABC) family is a group of most ancient and largest family of transmembrane proteins, which consume the energy of ATP in order to transport numerous substances across an extra and intracellular membrane such as metabolic products, sterols, lipids and drugs and non-transport procedures as translocation of RNA and DNA renovation. These specific proteins are categorized as ABC transporters on the basis of their structure and sequence ABC domain(s).

In humans, it was estimated that there are 49 ABCs [39,40] which are ubiquitously distributed on the central nervous system [19], lung, liver, pancreas, stomach, intestine and kidney and several anatomical cellular barriers [18,41]. Since ABCs are the transmembrane regulatory proteins and their upregulation is a principle mechanism associated with MDR in many cancers [42], HIV and hepatitis [43]. Furthermore, the overexpression of ABCs also lead to the insufficient therapeutic level and bioavailability of different drugs as well as their metabolites. With the advancement in science, P-glycoprotein (P-gp), a product of MDR-1 gene, was the first efflux transmembrane protein [44] and the polymorphism of MDR-1 gene could affect the biodistribution and pharmacokinetics of different drugs including chemotherapeutics, followed by multidrug resistance protein-1 (ABCC-1 or MRP-1) [45] and breast cancer resistance protein (ABCG-2 or BRCP) [46]. In pharmacological point of view, the drug molecules and ABCs interaction are very specific and one drug moiety could be a substrate of more than one drug efflux ABC pump [47], thus there is a need to explore them individually. On the basis of genome sequence and organization, these 49 ABCs are further subdivided into 7 subfamilies from ABCA to ABCG and their summary is presented in Table 1. The ABCs comprises of two domains, one is the cytosolic and the other is membrane domain. The cytosolic nucleotide binding domain (NBD) is sealed and all the members of a specific sub-family share about 30–40% of residue [48]. More precisely, each NBD contains almost three basic elements; Walker-A, Walker-B, and C or ABC signature motifs [49]. The Walker-A and Walker-B are separated by approximately 120 amino acids while the third motif-C, is a unique signature for each ABC [50], showed in Fig. 1.

There are four to eight transmembrane α-helix present in membrane domain and are responsible for the exchange of various substrates across the membrane. It was noticed that some ABCs co-transport several substances synergistically at the same time. Such as, in the presence of low concentration of glutathione MRP1 extrude vincristine and etoposide, simultaneously [51] and in case of fluorescence dyes like Hoechst 33,342 and rhodamine 123, the P-gp pump plays the same role [52]. These observations explore that there must be two binding sites with differential affinity are present in ABCs pump, which is responsible for this co-transport. In this case, it could be hypothesized that both sites of drug efflux pump are occupied with their respective substrates, which result in co-transportation of these substances [53]. Interestingly, a third binding site of P-gp was also discovered by Shapiro et al. [54]. The ABC subfamilies with emphasis on their association with drug resistance are described here and more detail on each one could be seen in Table 1.

2.1. ABCA

These are the subfamily of ABC which are present in different cells and organs and are mainly responsible for the exchange of lipids, including phospholipids and cholesterol, especially from the peripheral cells. The ABCA3 discovered in acute myeloid leukemia in childhood [52], both ABCA3 and ABCA6 are responsible for a poor chemotherapeutic response. While N-retinylidene-phosphatidylethanolamine is specific to ABCA4. Furthermore, ABCA8 involved in the regulation of cholesterol efflux and high-density lipoprotein cholesterol level [55].

2.2. ABCB

The most renowned drug efflux and principle MDR associated protein “P-gp” first identified by Juliano and Ling 1976 are belong to this class [56]. Among other proteins, P-gp remains most investigated protein in past because of its accountable MDR potential to various chemotherapeutics. Its over-expression in intestinal epithelium resulted in a considerable low bioavailability of different protease inhibitors (PI),

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