Editorial

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Multidrug Resistance Transporters and Implications on Drug Development

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Editorial

Multidrug resistance caused a disaster on the effective treatment of cancers and infectious diseases [1,2]. It is appalling that the current pace of drug development still could not overcome this problem, so we will continuous to lose the war on combatting cancers and infectious disease [2]. The solution may be to fully understand the molecular mechanisms of multidrug resistance and how they can be handled. There are many mechanisms involving in multidrug resistance, but multidrug transporters which are integral transmembrane proteins play a major role to medicate multidrug resistance [2]. Multidrug transporters can transport cytotoxic chemicals and compounds from cells can confer multidrug resistance. In other words, it is easy to remove drugs which are uptake into cells and drugs could not exhibit their functions.

According to their characteristics, multidrug resistance transporters are classified into five categories including ATP binding cassette (ABC) family, the resistance-nodulation-division (RND) family, the small multidrug resistance (SMR) family, and the multidrug and toxic compound extrusion (MATE) family. Based on energy source, they are divided into two groups called primary transporter and second transporter [3,4]. ATP binding cassette (ABC) family uses ATP as an energy source and other four families use electrochemical gradients such as Na+ and H+. The structures of those five-distinct superfamilies have obtained, however, the detailed transport mechanism such as coupling, and substrate recognition still maintains unclear.

Most of multidrug transporters are multispecific for different substrates, which means multidrug transporter can export several functionally and structurally unrelated compounds. To gain a deep insight into how to prevent drugs or toxic compounds are expelled from cells, it is important to figure out the molecular transport mechanism of the multidrug transporter and how to recognize substrates with different structures. In the past two decades many atomic structures of multidrug transporters bound with/without substrates or inhibitors were determined to provide the detailed molecular structure [5]. That means that there are mechanistic knowledge gaps to understand the transport cycle of compounds and drugs.

Recently, the Cryo-EM technique is improved, and the resolution could reach up to around 2 angstroms [6,7]. It sheds some light to under the deep molecular mechanism of multidrug resistance transporters by determining their atomic structures from distinct states during the transport cycle from human transporters. Besides, biochemical and biophysical approaches can be employing to support and evaluate the transport mechanism. Given those information, we have a greater understanding of drug recognition of drug recognition and transport mechanism. Two threads emerge to overcome drug resistance problem based on a prevention of drug extrusion via multidrug resistance transporters. One is to develop clinically useful inhibitors which can block transport activity of multidrug resistance pumps. The other one is to design cancer drugs or antibiotics which could not expel from cells. The concept is to increase the time for drugs existing in the cells and then drugs can exhibit their weapons and functions. Scientists can use structural information and computational approaches to explore new and effective classes of inhibitors and drugs which can treat diseases. Although it still has a long way to go, I believe that it is a correct direction for fighting drug resistance threats.

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