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Review

Development of efflux pump inhibitors in antituberculosis therapy

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ABSTRACT

Resistance and tolerance to antituberculosis (anti-TB) drugs, especially the first-line drugs, has become a serious problem in anti-TB therapy. Efflux of antimicrobial agents via bacterial efflux pumps is one of the main reasons for drug resistance. Efflux pump inhibitors (EPIs) bind to efflux pumps to inhibit drug efflux and thus enhance the drug effect and reduce drug resistance. Studies on EPIs targeting the efflux pumps of *Mycobacterium tuberculosis* (Mtb) help to understand Mtb resistance and to identify the potential drug target and are of significance in guiding the development of new anti-TB drugs and optimal combinations. Currently, there are many potential EPIs under study, but none of them has been used clinically for anti-TB therapy. In this article, we will provide an overview on the current development of EPIs targeting the efflux pumps of Mtb and discuss their potential clinical applications.

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1. Introduction

Resistance of *Mycobacterium tuberculosis* (Mtb) to antituberculosis (anti-TB) drugs is one of the intractable problems of anti-TB therapy. The mechanisms of resistance have not yet been fully understood and several possible mechanisms are currently under investigation, including (i) mutations in Mtb drug resistance-associated genes encoding key enzymes or transcription factors; (ii) overexpression of Mtb efflux pumps; (iii) changes in Mtb cell wall permeability; and (iv) high expression of the Mtb two-component system that regulates Mtb adaptation to intracellular and extracellular environments [1–3]. This review will focus on the effects and therapeutic potential of efflux pump inhibitors (EPIs) targeting various Mtb efflux pumps.

Efflux is a self-protection phenomenon that exists widely in prokaryotic and eukaryotic cells. It is a physiological process extruding endogenous metabolic waste and exogenous chemicals to maintain normal cell function [4–8]. Efflux pumps are key membrane structures responsible for efflux and play crucial roles in maintaining intracellular and extracellular material exchange and cellular homeostasis [7,8]. They can recognise a variety of substances with a wide range of physical and chemical properties, which is the cellular basis of multidrug resistance [8]. Bacterial efflux pumps are divided into six categories, including major facilitator superfamily (MFS), ATP-binding cassette (ABC) family, small multidrug resistance (SMR) family, resistance–nodulation–division (RND) family, multidrug and toxic compound extrusion (MATE) family and drug metabolite transporter (DMT) superfamily [7,9]. Efflux pumps of the MFS, ABC, RND and SMR families have been found in Mtb.

Drug resistance can be divided into two types, comprising intrinsic resistance and acquired resistance. Intrinsic resistance refers to efflux of antibiotics or toxic substances by induced expression of intrinsic efflux pumps coded by bacterial genes or plasmids. Intrinsic resistance is species-specific and allows bacterial cells to evade adverse environments [10,11]. In contrast, acquired resistance can develop by mutations that lead to high expression of efflux pump genes or by the spread of plasmids carrying drug resistance genes. As drug resistance is beneficial to bacterial survival, resistance will spread in the population and will eventually become intrinsic resistance. The expression of a variety of efflux pumps in a bacterial population can lead to drug resistance to a broad spectrum of antimicrobial agents, leading to multidrug resistance [10,11].

EPIs are a type of molecule that binds to bacterial efflux pumps to inhibit their efflux function. EPIs binding to Mtb efflux pumps were shown to inhibit efflux of anti-TB drugs, to enhance Mtb killing, to reverse Mtb drug resistance and to produce synergistic effects with first-line anti-TB drugs [12,13]. Anti-Mtb EPIs can also reduce the Mtb load, the dosage of chemotherapy drugs, and the time and relapse rate of TB treatment in animal models [12,13]. In this article, the effects of potential EPIs and their combined use with first-line anti-TB drugs are reviewed, and the prospects of EPIs in anti-TB therapy are discussed.

2. Major bacterial efflux pumps

Bacterial efflux pumps can be divided into two classes based on their structure, energy source and substrate types. The first class

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is the ABC transporters, which use the free energy of ATP hydrolysis to extrude drugs, whilst the second class is the secondary drug transporters utilising the transmembrane electrochemical gradient of protons or sodium ions to extrude drugs. Based on size and similarities in the primary and secondary structure, the secondary drug transporters can be subdivided into several distinct families, including the MFS, SMR, RND and MATE families [9]. Efflux pumps belonging to ABC, MFS, RND and SMR families have been found in Mtb. Some of them have been confirmed to be functional membrane proteins by multiple studies, whilst others appeared to be putative Mtb efflux pumps suggested by comparative genomic studies [8]. The major Mtb efflux pumps will be introduced in detail in this section.

2.1. The ATP-binding cassette (ABC) family

The ABC efflux pump family is a group of transmembrane proteins with a channel structure and cytosolic ATP-binding sites. ATP hydrolysis provides energy for transport in the presence of magnesium. P-glycoprotein (P-gp) is the most representative efflux pump in the family. As shown in Fig. 1, P-gp is composed of two hydrophobic transmembrane domains (TMD1 and TMD2) and two nucleotide-binding domains (NBD1 and NBD2) [14,15]. The TMD contains six hydrophobic α-helices and forms the substrate recognition sites and transport duct. The DrrABC complex (gene name Rv2936/2937/2938) is one of the confirmed ABC family transporters in Mtb. DrrA contains two NBDs, and DrrB contains six α-helices that are structurally and functionally homological to P-gp [16]. The Rv2686c-Rv2687c-Rv2688c and Rv1456c-Rv1457c-Rv1458c transport systems are two ABC family efflux pumps identified recently in Mtb H37Rv. High expression of the two pumps was observed in the presence of first-line anti-TB drugs, leading to resistance of H37Rv strain to at least one of the drugs from isoniazid (INH), rifampicin (RIF), streptomycin (STM) and ethambutol (EMB) [17].

2.2. The resistance–nodulation–division (RND) family

The RND efflux pumps are proton-dependent efflux pumps composed of an inner membrane protein, a membrane fusion protein and an outer membrane factor, as shown in Fig. 1. The most representative RND family efflux pump is the AcrAB–TolC pump in *Escherichia coli* [18], formed by AcrB (inner membrane protein), AcrA (membrane fusion protein) and TolC (outer membrane factor). AcrB is a homotrimer and each subunit is composed of a prominent cap-like structure and 12 α-helix transmembrane domains [19,20]. Drug molecules bind to AcrB and induce the formation of a complete efflux pump with AcrA and TolC [21,22]. Drug molecules are expelled by TolC through the transmembrane domains of AcrB. This process requires proton exchange to provide energy for AcrB to transfer drug molecules to TolC [22–25]. The major RND family efflux pumps in

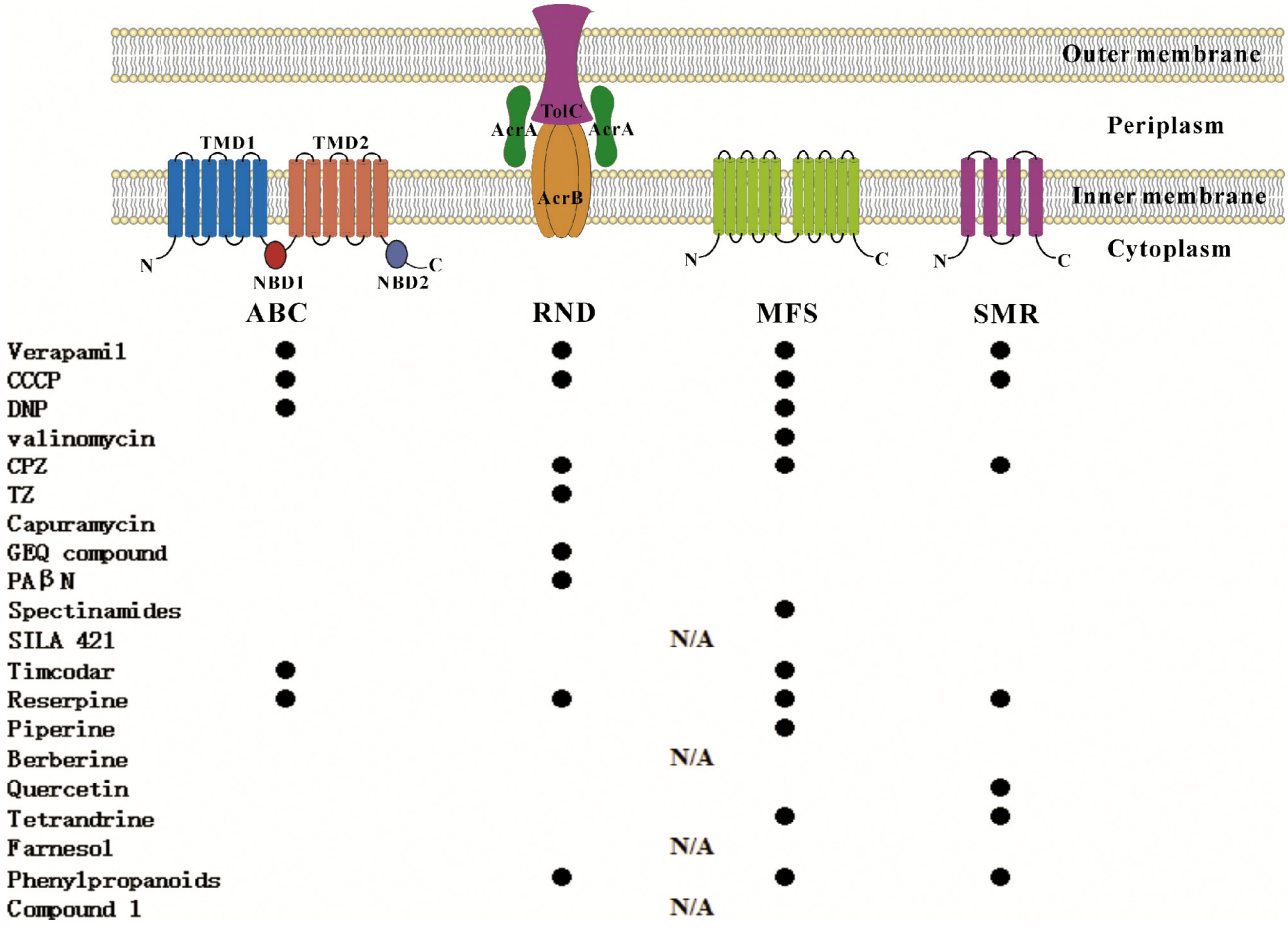

Fig. 1. Schematic structures of ATP-binding cassette (ABC), resistance–nodulation–division (RND), major facilitator superfamily (MFS) and small multidrug resistance (SMR) efflux pump systems in *Mycobacterium tuberculosis*. The structure of the P-glycoprotein (P-gp) efflux pump is used to illustrate the ABC family, and the structure of the AcrAB–TolC efflux pump is used to illustrate the RND family. A detailed description of each individual family can be found in Section 2. The binding sites for each individual drug reviewed in this article are listed under the figure. The solid circles represent binding to a certain type of efflux pump supported by the literature, whilst N/A represents that the binding site information is not available for a drug. CCCP, carbonyl cyanide *m*-chlorophenyl hydrazone; DNP, 2,4-dinitrophenol; CPZ, chlorpromazine; TZ, thioridazine; GEQ, Genz-10850.

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