

8.1.2 Secondary Active Drug Transporters

The second active drug efflux system is commonly called secondary active transport. These secondary active drug transporters utilize the biological energy inherent within ion motive forces to transport inhibitory agents across the membrane to reduce their cellular concentrations, providing resistance multiple drugs. Such secondary transporters have been referred to as antiporters and exchangers. Currently, several secondary active drug transporter families have been established. These include the major facilitator superfamily (MFS) (Saier et al. 1999), the resistance-nodulation-cell division (RND) superfamily (Ruggerone et al. 2013), the multidrug and toxic compound extrusion (MATE) superfamily (Kuroda and Tsuchiya 2009), the small multidrug resistance (SMR) superfamily (Chung and Saier. 2001), and the recently described proteobacterial antimicrobial compound efflux (PACE) family (Hassan et al. 2018). Important key members within each of these secondary active efflux pump families are considered below.

8.1.2.1 Bacterial MFS Drug Efflux Pumps

The MFS of solute transporters is currently composed of tens of thousands of members from across all living taxa (Pao et al. 1998). In general, these MFS transport systems harbor 12 or 14 transmembrane domains and consist of both passive and secondary active transporters with diverse substrates and highly conserved structures and sequence motifs (Law et al. 2008; Ranaweera et al. 2015; Kumar et al. 2016b; Kakarla et al. 2017b). Because many of the MFS proteins function to extrude antimicrobial agents from microbial pathogens (Saidijam et al. 2006), these drug and multidrug efflux pumps are considered good targets for modulation (Kumar et al. 2013, 2016a).

The first MFS drug efflux pump to be discovered occurred in the laboratory of Levy in which they had found active bacterial efflux of the tetracyclines from *E. coli* (Levy 2002). Another drug efflux pump from *E. coli* called MdfA (previously known as CmlA) confers multiple drug efflux and has been intensively studied, especially at the structural level (Nagarathinam et al. 2017; Yardeni et al. 2017). Together, with the structural features of MdfA, along with the crystal structure for the *E. coli* YajR, which was also solved to high resolution (Jiang et al. 2013), these known transporter structures have served to help demonstrate the functional importance of highly conserved sequence motifs that are found in many members of the MFS (Kakarla et al. 2017b). A related efflux pump, CraA, from *Acinetobacter baumannii* confers resistance to the chloramphenicols in this bacterium (Roca et al. 2009). In *S. aureus*, NorA, QacA, and LmrS were all demonstrated at the physiological level to be effective in conferring multidrug efflux of a variety of structurally unrelated antimicrobial agents (Brown and Skurray 2001; Floyd et al. 2010; Schindler and Kaatz 2016). In particular, NorA has been shown to be an excellent target for modulation by efflux pump inhibitors (Zhang and Ma 2010). In our laboratory, we