Abstract

Acinetobacter baumannii is a pleomorphic, aerobic, rod-shaped Gram-negative bacterium that belongs to family Moraxellaceae in class Gammaproteobacteria, and *A. baumannii* belongs to 'ACB' species and is held responsible for causing mild to severe infections in immunocompromised patients. It has emerged as a predominant pathogen due to its unique propensity to acquire versatile resistance determinants, resist sterilization procedures and capability to stay on abiotic surfaces for long periods of time. Thus continued occurrence of MDR *A. baumannii* infections worldwide is a serious threat to available limited therapeutic options. Researchers worldwide have proven the genetic plasticity of *A. baumannii*, and the added trait of it being natural competent makes this is the hospital superbug raising alarm on the pressing need to develop new antibacterial agents. As therapeutic options remain critical, search for new anti-infectives are imperative, and currently signalling proteins are considered to be the promising drug targets. According to the NCBI database, as of July, 2018, it contained 2710 *Acinetobacter baumannii* genomes. The MDR *A. baumannii* strain AYE genome is approximately 4-Mb long with 39.3% GC content and contains 3,712 proteins (www.mistdb.com). Around 298 proteins found in its genome are involved in signal transduction of which 39 belong to TCS proteins (Fournier et al., 2006) and function of only a few has been elucidated so far. The bioinformatic analysis helped us identify an OmpR-type signaling pair BaeSR (ABAYE0599/ABAYE0600). Though few studies have explained the role of BaeRS in physiology; however its novel contribution regulating stress response, oxidative assails and antimicrobial susceptibility in a multidrug resistant clonal strain AYE remained enigmatic so far. Given the dearth of the situation, a systematic study with a hypothesis as described before was initiated with the following objectives:

1) Elucidating molecular mechanisms of drug resistance in Indian clinical isolates with a prime focus on multidrug efflux pumps and outer membrane porins.
2) Role of two component signaling system *baeRS* in mediating antimicrobial resistance in *Acinetobacter baumannii.*
3) Role of *baeRS* in regulating the expression of multidrug efflux pumps in MDR *A. baumannii*

To begin with, our temporal analysis revealed that the strains in our collection were multidrug resistant and had a diverse resistome which included the presence of β-lactamases, aminoglycoside modifying enzymes and active efflux. The *baeR* expression level was noticed in all the MDR isolates and it was ~5.5-fold greater compared to sensitive strain. Genetic studies through knock out and complementation, revealed the role of *baeR-baeS* in stress response and antimicrobial resistance for the first time in *A. baumannii*. Inactivation of

Abstract

ompR-envZ led to decreased expression of a promiscuous outer membrane TolC like efflux protein. The role of TolC like protein, named AbuO has been experimentally characterized in our lab previously. However to decode the unanimous functions of AbuO like homologs, efforts were focussed further to delineate the functions of this OM protein in three resistant Indian isolates. **Conclusively, this thesis provides novel experimental findings where the role and regulatory importance of BaeRS on TolC like protein has been demonstrated for the very first time, an unprecedented observation which remained masked so far. Decoding this linear cascade marks just the beginning**. Further experimental strategies to identify key players/network are highly warranted and remain the focus of our lab in future.