RCB-Colloquium

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H 53

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Combatting Ribosomal Methylation Based Antibiotic Resistance: A war at the microscopic level

Antibiotic resistance is a global pandemic that has emerged as a silent killer. Bacteria have harnessed several mechanisms to evade the effect of antibiotics with drug target modification being a highly efficient strategy utilized by pathogenic systems to render themselves resistant to antibiotics. The ribosome owing to its integral role as the protein synthesis machinery of the cell is a prime target for several antibiotics. Here, we unravel the mechanism of post-transcriptional ribosomal methylation which renders the macrolide lincosamide and streptogramin B ((MLS$_B$) class of antibiotics ineffective. The enzyme Erythromycin-resistance methyltransferases (Erms),[1] exclusively harboured by several multi-drug resistant (MDR) pathogens can site specifically methylate a ribosomal base (A2058, *E.coli* numbering) in the nascent peptide exit tunnel of the 50S ribosomal subunit which then renders the MDRs resistant to MLS$_B$ class of drugs. Interestingly, we show that Erm is an opportunistic enzyme that exclusively targets ribosomal precursors. Using Cryogenic Electron Microscopy (Cryo-EM) we have trapped the Erm-precursor complex and showed how in a complex environment, during ribosomal biogenesis, Erm can methylate its substrate selectively. Moreover, corroborating single molecule FRET measurements were performed to understand the dynamic nature of these interactions and decipher states that the enzyme charters to achieve catalysis. Our work dwells into the unique dual base flipping mechanism employed by Erms to achieve catalysis and its evolutionary implications in the design of these enzymes that induce resistance in pathogenic strains.[3] Furthermore, the findings help in the identification of allosteric sites distal from the catalytic site of Erm which can serve as druggable targets. Subsequently, we have ongoing efforts towards AI-based drug design to specifically target Erm-based resistance thereby, facilitating ways of reversal of resistance. Overall, we draw a holistic picture of Erm's action and delineate methods of curbing its pathogenic function.

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