

Role of ribosomal modifying methyltransferases in antibiotic resistance

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Modifications at various positions in ribosomes by the methyltransferases is one of the most prevalent strategy adopted by the pathogenic bacteria's to circumvent the lethal actions by plethora of antibiotics. Erythromycin resistance methyltransferase (Erm) mediate S-adenosine methionine (SAM) dependent modification at A2058 position of the 23S rRNA thereby conferring resistance against macrolide, lincosamide, streptogramin B class of antibiotics. Structurally similar methyltransferases like KsgA also catalyze analogues reaction at positions A1518 and A1519 of 16S rRNA and plays a significant role in the conferring resistance as well as in ribosome biogenesis. Over the years the mode of target modification and the molecular basis for substrate specificity remains elusive. In this work we aim to entail how these methyltransferases recognize a particular rRNA sequence and their ability to confer site specific mono and dimethylation in a precise fashion.

Towards this goal, we report the crystal structure of dimethyltransferase KsgA from gram positive species *Bacillus Subtilis* 168 in complex with its cofactor SAM to a resolution of 1.9 Å. The structure enabled identification of motifs which may be important for RNA recognition and in controlling catalysis. For example, the structure revealed that the flexible, highly conserved N-terminal region of this enzyme becomes ordered on SAM binding with a flap of around 17 amino acids enclosing the cofactor. Mutagenesis and biochemical experiments involving alternations in loop length and specific residues highlights the critical role of this flap in substrate specific methylation. Sequence analysis shows that the mono versus dimethylation determinants may also lie on this very loop. Furthermore, the N-terminal helix-loop portion of this region is highly positively charge and creates an interface which potentially serves as an entry platform for binding of the rRNA. Therefore, we conclude that the N-terminal 30 residues in this class of methyltransferases are critical and control both substrate recognition and methylation potential.

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Keywords: [methyltransferases](#), [MLS antibiotic resistance](#), [X-ray](#)