MBG FOCUS TALK

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SAM lyases – small, divergent and multifunctional proteins in bacteriophage counter defence

S-adenosyl methionine (SAM) is an essential metabolite that is used as methyl donor and for biosynthesis of polyamines. In the arms race between bacteriophage and bacteria, many bacterial defence systems have evolved where DNA methylation is used for self-nonself recognition. In turn, bacteriophage have evolved a range of counter-defence systems, one of them involving SAM degradation. A bacteriophage T3-encoded SAMase was identified already in the 1960s. We identified novel SAMases encoded in environmental phage DNA based on their ability to rescue an ilvA knockout. Using X-ray crystallography, microbiology, biochemistry and computational biology we could show that this family of enzymes are SAM lyases, not SAM hydrolases, warranting a new EC code 4.4.1.42 (S-adenosyl-L-methionine lyase). The trimeric Svi3-3 structure shows three active sites at the intersubunit interfaces, where the enzyme stabilizes a reactive conformation of SAM for an intramolecular lyase reaction producing L-homoserine lactone and methyl-thioadenosine. To learn more about the function of SAM lyases in bacteriophage, we had to turn to a system from a known phage with a known bacterial host. T3 SAMase was known to provide anti-restriction activity against the SAM-dependent Type I Restriction-Modification defence of the host bacterium Escherichia coli, but was also shown to protect phage against BREX defence. The anti-BREX activity of the T3 SAMase is mediated by two independent mechanisms: enzymatic degradation of SAM and inhibition of SAM synthesis through direct interaction with the host SAM synthase MetK.
We purified the native octameric complex of T3 SAMase with E. coli MetK and determined a 2.8 Å cryo-EM structure. The complex stoichiometry was confirmed with mass photometry and small-angle X-ray scattering. Structure guided mutagenesis of the SAMase-MetK interface revealed that the interaction with MetK stabilizes the T3 SAMase in vivo, thus further contributing to its counter-defence activity. Phage-encoded SAMases belong to a family of small proteins with extremely low sequence conservation, different oligomeric states and different interaction partners. They mediate bacteriophage counter-defence with different mechanisms and show the importance of SAM as cofactor of diverse bacterial phage-defence systems.

All welcome