Molecular mechanism and evolutionary impact of a prokaryotic epigenetic-targeted immune system

Supervisory team:
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Project description:
Interactions between bacteria and their viruses (bacteriophages) over billions of years have led to the evolution of a wide range of bacterial mechanisms to resist viral infection. The exploitation of such systems has produced true revolutions in biotechnology; firstly, the restriction enzymes for genetic engineering, and secondly, CRISPR-Cas9 for gene editing. This project aims to unravel the mechanisms and consequences of another class of bacterial immune system, the Type IV restriction endonuclease SauUSI. This enzyme cuts covalently-modified bacteriophage DNA, specifically targeting 5-methylcytosine and 5-hydroxymethylcytosine. Very little is known about Type IV restriction enzymes at a mechanistic level, or about their importance to the coevolution of prokaryotic-phage communities. SauUSI has domains for DNA modification recognition and cleavage but in addition has an ATPase domain. DNA cleavage appears to be activated when there are two modified sites on the DNA, which can be distant from one another, and is dependent upon ATP hydrolysis. This interdisciplinary project will combine biophysical and single molecule microscopy analysis in the Szczelkun lab to determine how the SauUSI ATPase activity is coupled to motion along the DNA between modified sites. Our experiments will be informed by structural data that is being collected by the Saikrishnan lab in Pune , India. A better understanding of the SauUSI mechanism will help in the development of Type IV restriction enzymes as tools for the study of innate and pathological changes in human epigenomes. To address the role of SauUSI for bacteria, the project will also involve evolutionary ecology experiments in collaboration with the Westra lab (Exeter). These will determine the fitness costs of encoding SauUSI for individual cells and for cell populations. This will add to our understanding of how bacteria influence the acquisition of traits such as virulence or antibiotic resistance.