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The first structural observations of an XerCD-dif DNA recombinase complex

Xer recombination is a ubiquitous process which enables the resolution of bacterial chromosome dimers at cell division. The Xer system of most bacterial species is composed of two related proteins, XerC and XerD, which are part of the wider tyrosine recombinase family with well-known enzymes such as Cre and Flp. An active Xer recombinase complex is heterotetrameric, containing two XerC units, two XerD units, and two DNA duplexes, which are subsequently recombined through a Holliday-Junction intermediate.

The Xer system is also commonly hijacked by mobile genetic elements to drive their integration into a host chromosome. These elements are termed IMEX (Integrative Mobile Elements exploiting Xer) and have evolved diverse specialized accessory proteins and/or accessory DNA sequences to circumvent the strict spatio-temporal control of typical Xer recombination. The IMEX bacteriophages of *Vibrio cholerae* are central to the transmission of the pandemic disease Cholera, as the Cholera toxin genes are encoded within the lysogenic phage CTXΦ genome.

Structural studies of XerCD have been attempted mostly without success since the discovery of the system over 30 years ago. Practical difficulties surrounded the highly recalcitrant nature of XerC, with problems of purification, solubility, and aggregation. Our recent work has developed simple methodological advances that have enabled the purification of homogeneous *V. cholerae* XerCD-DNA complexes at high concentrations. We believe our new methods should be applicable to a wide array of insoluble DNA-binding proteins.

For the first time we have been able to produce XerCD-DNA crystal structures and cryo-EM reconstructions, and we have begun to answer biological questions about assembly, interactions, and regulation of the recombinase complex. Through specific DNA substrates, and/or the use of certain protein mutants, we can force the complex to adopt different conformational states to gain specific insights. In combination with our long-running molecular-genetic research into the Xer of chromosome segregation, our new structural viewpoint will shed light on how this system is hijacked by IMEX such as *V. cholerae* CTXΦ. In particular we wish to understand why certain closely related bacterial species may have, or may lack, IMEX elements.

Auteur principal: PROVAN, James (I2BC - CNRS UMR9198)

Co-auteurs: BALANEC, Mael (I2BC - CEA); VITARD, Arthur (I2BC - CEA); Dr OCHSENBIEN, Françoise (I2BC - CEA); Dr BARRE, Francois-Xavier (I2BC - CNRS)

Orateur: PROVAN, James (I2BC - CNRS UMR9198)