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Holliday junction resolvase GEN1 functions as a versatile DNA sensor and processor

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Several DNA repair and maintenance pathways depend on the correct and efficient processing of DNA intermediates by structure-specific nucleases. Human Holliday junction resolvase GEN1 seems to be an enzyme of last resort for recognizing and cleaving a specific range of DNA structures. The crystal structure of human GEN1 in complex with Holliday junction DNA pinpointed to a crucial role of the chromodomain for efficient DNA recognition and cleavage. We further characterized different DNA-binding modes of GEN1 using biochemical methods in combination with structure-guided mutagenesis. The analysis highlights the importance of the arch region to distinguish between different DNA substrates. In addition, we identified a cluster of positive amino acids shadowing the chromodomain to assist the enzyme for robust DNA recognition. Moreover, we directly show that GEN1 operates as a monomer with 5' flap DNA and as a dimer in complex with DNA four-way junctions, which is a unique feature in the Rad2/XPG nuclease family. This linked cleavage mechanism ensures that DNA junctions are resolved in a strictly symmetric manner without altering DNA information. GEN1's DNA recognition features make it a versatile tool for DNA processing and for maintaining genome integrity.

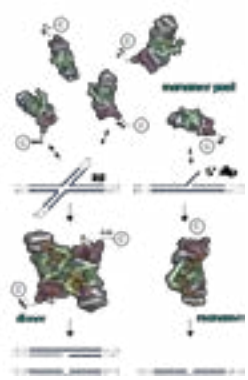

Figure1: *Holliday junction resolvase GEN1 is a monomer in solution and thus, cleavage competent for 5' flap substrates. However, it can only cleave DNA four-way junctions by forming an active nuclease dimer.*

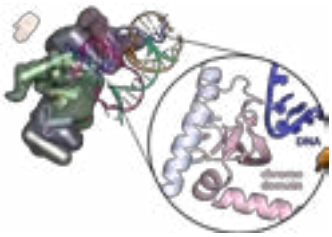

Figure2: *Structure of human Holliday junction resolvase GEN1 in complex with a DNA four-way junction. The nuclease domain is extended by a chromodomain for efficient DNA recognition and cleavage.*

Biography

Christian Biertumpfel obtained his PhD degree from the European Molecular Biology Laboratory (EMBL) and the Ruprecht Karls University of Heidelberg, Germany. His PhD research focused on the crystallization and characterization of Holliday junction resolvases. During his Postdoctoral time at the National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD, USA, he could solve a first crystal structure of a Holliday junction resolvase from T4 phages in complex with a DNA four-way junction. Furthermore, together with Wei Yang he determined the structure and mechanism of human DNA polymerase η functioning as a molecular splint. After a short period at the Vaccine Research Center, NIAID, NIH, he moved to the Max Planck Institute of Biochemistry, Martinsried, Germany as a Max Planck Research Group Leader. Recently, the Biertumpfel Lab obtained structural information on the human Holliday junction resolvase GEN1 and they found for the first time a chromodomain extending a nuclease domain.

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