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Chromatin Structure and Mobile DNA group

No loose ends: a structural and molecular investigation of retroviral integration mechanism

Retroviral replication proceeds through the integration of a DNA copy of the viral RNA genome into the host cellular genome, a process that is mediated by the viral integrase (IN) protein. IN catalyses two distinct chemical reactions: 3'-processing, whereby the viral DNA is recessed by a dinucleotide at its 3'-ends, and strand transfer, in which the processed viral DNA ends are inserted into host chromosomal DNA. Although IN has been studied since the 1980s, detailed structural understanding of its catalytic functions and mechanism awaited high resolution structures of functional IN-DNA complexes - or intasomes, initially obtained for the spumavirus prototype foamy virus (PFV) in 2010. Since then, new high-resolution structures of retroviral intasomes emerged, notably thanks to the recent advances in cryo electron microscopy technics.

Here I present the β -retrovirus mouse mammary tumor virus (MMTV) and lentivirus Maedi visna virus (MVV) intasome structures, as well as the latest simian immunodeficiency virus (SIV) intasome bound with inhibitors structure. The MMTV and MVV intasome structures revealed an unexpected octameric and hexadecameric architecture, respectively, providing new insights on the retroviral integration mechanism, while the SIV intasome structure in complex with inhibitors help us to understand the apparition of drug-resistant mutations in infected patients treated with antiretroviral therapy.

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