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# IN BRIEF

## STRUCTURAL BIOLOGY

### High-order integration

To establish a lasting infection, lentiviruses, such as HIV-1, stably integrate their DNA into the chromatin of host cells. Integration is mediated by the viral integrase enzyme in a multimeric nucleoprotein complex called the intasome, which assembles onto viral DNA ends to form the strand transfer complex that mediates 3′-end processing and the strand transfer reaction. Structural studies of the architecture of the intasome have been hindered by the tendency of the integrase and intasomes to aggregate *in vitro*; however, Passos *et al.* and Ballandras-Colas *et al.* now provide high-resolution models of the HIV-1 and Maedi-Visna virus (MVV) intasomes, respectively, using cryo-electron microscopy. Structural studies of the HIV-1 intasome were facilitated by fusing the HIV-1 integrase to a DNA-binding protein to improve solubility, and MMV integrase was chosen because it does not aggregate in solution. Previous studies had found that several retroviral integrases form dimers and that the HIV-1 integrase forms tetramers; however, both HIV-1 and MMV integrases formed higher-order assemblies of 16 protomers, constituting a hexadecamer, or tetramer of tetramers. Thus, lentiviral intasomes are more intricate and complex than those of other retroviruses. Mutagenesis experiments that blocked the assembly of large integrase assemblies affected strand catalytic activity and virus replication, which suggests that higher-order intasomes are important for efficient DNA integration. Together, these studies provide novel insights into lentiviral integration and a platform for the development of HIV-1 integrase inhibitors.

**ORIGINAL ARTICLES** Passos, D. O. *et al.* Cryo-EM structures and atomic model of the HIV-1 strand transfer complex intasome. *Science* **355**, 89–92 (2017) | Ballandras-Colas, A. *et al.* A supramolecular assembly mediates lentiviral DNA integration. *Science* **355**, 93–95 (2017)

## METAGENOMICS

### Mining for CRISPR–Cas

CRISPR–Cas systems confer adaptive immunity against exogenic elements in bacteria and archaea, and provide unprecedented potential for genome editing that is revolutionizing biological and clinical research. Current CRISPR–Cas systems are based on enzymes that were identified in isolated bacteria, thus excluding the majority of enzymes from organisms that have not been cultured in the laboratory. Using metagenomics, Burstein *et al.* uncovered novel CRISPR–Cas systems in uncultured microbial communities, including samples from the infant gut, soil and groundwater. Their analysis focused on identifying uncharacterized genes that were proximal to CRISPR arrays and CRISPR-associated protein 1 (*cas1*), which is the conserved CRISPR integrase. They analysed 155 million proteins and identified the first Cas9 (type II) system in archaea. Previously, archaea were known to use class I systems, and class II systems had only been found in bacteria. In addition, the authors identified two new compact CRISPR–Cas systems in uncultured bacteria that they named CRISPR–CasX and CRISPR–CasY. All of the functional components of these two systems were identified using metagenomics, which enabled the expression of these systems in *Escherichia coli*, leading to robust RNA-guided DNA interference of a plasmid that contained target sequences. As the newly identified DNA-interference systems contain a small number of proteins, they are particularly valuable for the development of new gene-editing tools for biological and clinical research.

**ORIGINAL ARTICLE** Burstein, D. *et al.* New CRISPR–Cas systems from uncultivated microbes. *Nature* http://dx.doi.org/10.1038/nature21059 (2016)