IMOL SCIENCE CLUB

THE INTERNATIONAL INSTITUTE
OF MOLECULAR MECHANISMS AND MACHINES
POLISH ACADEMY OF SCIENCES

ONLINE SEMINAR

Michal Barski

ILLUMINATING HTLV INTEGRATION AND ITS INHIBITION AT THE ATOMIC SCALE WITH CRYO-EM.

October 20th, 2021, 2 pm (CET)
Online seminar via ZOOM

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Illuminating HTLV integration and its inhibition at the atomic scale with cryo-EM

SPEAKER

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ABSTRACT:

The human T-cell lymphotropic virus type 1 (HTLV-1) is a deltaretrovirus and one of the most oncogenic human viruses. It is the causative agent of a severe form of blood cancer called adult T-cell leukaemia/lymphoma (ATLL) and a range of debilitating neuromuscular disorders – HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) which often lead to paralysis. Despite that, there is still no therapeutic regimen for this deltaretrovirus.

Integration of a DNA copy of the viral genome is an essential step in the replication of all retroviruses and is catalysed by the viral enzyme integrase (IN). Integrase strand transfer inhibitors (INSTIs) are among the most effective anti-HIV drugs. Similarly, understanding the IN enzyme of HTLV, and its inhibition, will be a critical part of the effort to control HTLV infections.

Using cryoelectron microscopy in conjunction with X-ray crystallography we solved the supramolecular structure of IN in complex with its viral dsDNA and bound to the B56 subunit of the PP2A phosphatase. PP2A is one of the most abundant proteins in the human cell and a host factor for HTLV-1 IN. The structure reveals how the virus mimics an endogenous motif to bind to PP2A. It is also the first report of a "promiscuous motif" shown in action.

Also, through further high-resolution cryo-EM complex structures as well as infection experiments we have proven that INSTIs of HIV-1 IN are just as effective against HTLV-1 and have the same binding mode. These findings have important implications for establishing therapies targeted at HTLV-1 and provide a framework for understanding the mechanism of INSTI action on the HTLV-1 intasome at the atomic scale.

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