THE CRYSTAL STRUCTURE OF THE NATIVE CAPSID FROM BOVINE LEUKEMIA VIRUS: RETROVIRAL CAPSIDS ARE PLASTIC

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Retroviruses undergo an obligatory maturation step in the formation of infectious particles. The cleavage of Gag generates several mature proteins, including capsid (CA), which self-assembles into a fullerene-like core, enclosing the RNA genome. Revealing the molecular features of the retroviral mature core and its assembly mechanism is important for understanding retrovirus biology and developing novel antiretroviral drugs. Despite the essential role of the retroviral core, its high polymorphism has hindered high-resolution structural analyses. We now report the crystal structure of the native, mature CA protein from bovine leukemia virus (BLV) at 2.75 Å resolution [1]. The structures of the individual NTD and CTD subdomains of BLV CA were determined, respectively to 1.44 and 2.45 Å resolution, which was instrumental in the structure determination process. This structure represents the first X-ray structure of a native retroviral capsid protein (i.e. containing no mutations). BLV is a tumorigenic B-lymphotropic delta-retrovirus that infects cattle worldwide, closely related to human T-lymphotropic viruses (HTLV). The BLV CA crystals contain one CA hexamer in the asymmetric unit, which pack laterally forming planar layers. CA hexamers deviate significantly from 6-fold symmetry, yet adjust to make two-dimensional pseudo-hexagonal arrays that mimic mature retroviral cores. Intra- and inter-hexameric quasi-equivalent contacts are uncovered, with flexible trimeric lateral contacts among hexamers, yet preserving very similar dimeric interfaces making the lattice. The conformation of each capsid subunit in the hexamer is therefore dictated by long-range interactions, revealing how the hexamers can also assemble into closed core particles, a relevant feature of retrovirus biology. This model of capsid plasticity contributes with a novel framework to develop more accurate hypotheses of capsid self-assembly and uncoating. Implications of this mechanism seem relevant for the discovery of allosteric effectors with novel antiretroviral properties.