Structure of the Human T cell Leukaemia Virus capsid protein – a new drug target

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Human T cell leukaemia virus 1 (HTLV-1) is a retrovirus belonging to the family of Retroviridae and causes adult T cell leukaemia (ATL) and HTLV-1-associated myelopathy (HAM). HTLV-1 subtype C is highly prevalent in the indigenous peoples of central Australia with over 40% adults were testing seropositive in 2018[1]. The viral capsid is essential for the maturation of virions and protects the RNA genome from hydrolysis by cytosolic enzymes. Here, we report novel structural information of HTLV-1 capsid protein (CA) by crystallising the N-terminal domain (NTD), C-terminal domain (CTD) and full-length, respectively. Intriguingly, three crystal forms with different space groups of NTD were obtained: 1) triclinic P 1 with an ultra-high resolution of 0.87 Å that offers unambiguous atomic information of each residue, including the N-terminus β-hairpin which is important in HIV-1 CA for nucleotides transport[2]; 2) hexagonal P 6 2 2 which diffracted to 2.05 Å showing that crystallographic six-fold symmetry appears in the hexagonal capsid lattice, indicating HTLV-1 CA could potentially assemble to a hexameric conformation that is canonical in HIV-1 CA hexamer; 3) orthorhombic P 2 1 2 1 diffracted to 1.47 Å displaying that a sulfate occupies the positively charged pocket, enclosed by H71/72, R98 and W117, implying HTLV-1 CA might interplay with new cellular factors that are different from the cofactors interacting with the HIV-1 capsid. The HTLV-1 CA-CTD was also solved to 1.47 Å and reveals the dimerisation packing of the capsid lattice. The crystal of HTLV-1 CA-full-length diffracted to 2.25 Å belonging to the F 2 2 2 space group, which also contains a six-fold crystallographic symmetry to generate a hexameric lattice. With the insight these structures have given us, we can predict how the HTLV-1 CA protein self-assembles and begin exploring how to disrupt the capsid pharmacologically.