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Title:STRUCTURAL BASIS OF STABILITY OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) CAPSID

Human immunodeficiency virus type 1 (HIV-1) is the etiologic agent of acquired immunodeficiency syndrome (AIDS). Since its discovery in early 1980, many advances have been made in the prevention and management of HIV/AIDS. However, there is no cure and infection can eventually lead to fatal results. Hence, there is a need for new antivirals with novel mechanisms of action, favorable resistance, and low toxicity profiles, which will offer more therapeutic options in the clinic.
The HIV-1 capsid protein (CA) has been increasingly viewed as an attractive therapeutic target as it plays a critical role in multiple steps of the virus life cycle. Over the past 25 years, several X-ray, nuclear magnetic resonance (NMR) and cryo-electron microscopy (cryo-EM) structures of HIV-1 CA fragments or engineered variants have been solved. However, none of these provide the complete set of molecular details of the critical CA-CA contacts that govern capsid stability, which is at the heart of its biological functions.
In this study, we aimed to solve crystal structures of HIV-1 CA, including the elusive structure of the native full-length HIV-1 CA, in the space group P6, which allows the building of the hexameric biological unit. Our findings describe novel interactions between CA monomers related by 6-fold symmetry within a hexamer (intra-hexamer) and by 3-fold and 2-fold symmetry between neighboring hexamers (inter-hexamer). These structures help elucidate how CA builds a hexagonal lattice, the foundation of the mature capsid. Moreover, they demonstrate that the intra- and inter-hexamer interfaces are malleable and can change through an adaptable hydration layer. Disruption of this layer by crystal dehydration treatment alters inter-hexamer interfaces and condenses CA packing. The structures reveal a remarkable plasticity which explains the polymorphism observed in virions. They also establish our experimental system to be the most relevant for the study of CA interactions in a native context. Moreover, they provide unique information on how CA structure controls interactions with host factors and small molecule CA-targeting antivirals.