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Structural studies of dynamic CD4 changes relevant to HIV infection

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Cluster of differentiation 4 (CD4) plays an important role in the adaptive immune response. It acts co-operatively with the T-cell receptor (TCR) to bind the Major Histocompatibility Complex Class 2 (MHC2) on antigen-presenting cells (APCs) to effect down-stream immune responses. However, it is also the primary receptor for the Human Immunodeficiency Virus-1 (HIV-1) which binds to human CD4+ cells via the surface glycoprotein gp120. CD4 has 4 ectodomains (D1-4) of which domains D1, D2 and D4 contain disulphide bonds. The second domain disulphide bond is classed as an allosteric disulphide, of the configuration "–RHStaple", which has unusually high dihedral energy, resulting in its relatively facile reduction and potential structural realignment.

Biochemical analyses have shown that gp120 can only bind to a monomeric form of CD4 in which its second domain allosteric disulphide bond is reduced [1,2]. However, until recently, there has been no biophysical or structural data published that can explain why CD4's redox state is essential for gp120 binding, during HIV-1 infection.

Through a collaboration, between the HIV Pathogenesis Research Unit (HPRU), South Africa, the Insitute Laue-Langevin (ILL), the European Synchrotron (ESRF) and Synthelis, France, biophysical analyses of two-domain CD4 (2dCD4) wild-type and disulphide knock-out mutant proteins has shown that ablation of the allosteric disulphide bond in domain 2 causes an energetically favorable, domain collapse, resulting in increased 2dCD4 stability. Conversely ablation of the structural disulphide bond in domain 1 causes destabilisation of 2dCD4 [3].

Small-angle neutron scattering experiments, exploiting deuterium contrast variation, have allowed low resolution structural analysis of the redox isoform of 2dCD4 bound to gp120. In addition, small-angle X-ray scattering has been used to compare and contrast the size and shape of wild-type 2dCD4 to a panel of 2dCD4 disulphide-bond knock-outs, which mimic the various redox states of 2dCD4-WT.

This novel structural data can help us to understand why gp120 binds this specific, partially reduced form of 2dCD4 and we anticipate that this information will inform the structure based design of future HIV anti-viral treatments and, hopefully, a prophylactic HIV vaccine.

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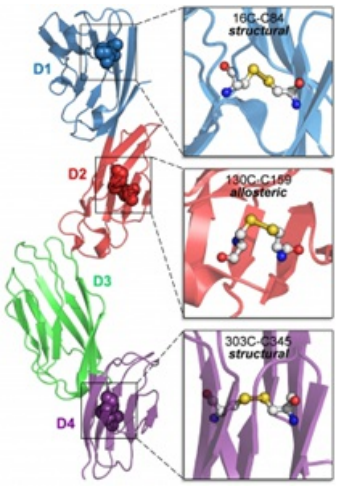

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