NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

SBS Seminar Announcement

Ligand-induced structural changes in HIV-1 envelope glycoprotein and their biological effects

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Abstract:
The first step in HIV-1 entry is the interaction between viral envelope glycoprotein gp120 and CD4 receptor on permissive host cells. The interaction initiates a series of sequential conformational rearrangements that exposes epitopes involved in interaction with co-receptors. Using x-ray crystallography, the tertiary structural rearrangements may be elucidated. However, the envelope glycoprotein on the virus surface is arranged as a trimer consisting of three gp120 and three gp41 subunits (Env) and the tertiary conformational change observed in gp120 has not been characterised in the context of a quaternary structure with sufficient conformity.

Using cryo-electron microscopy we have studied the envelope glycoprotein, Env, responsible for initiating virus entry. The quaternary structure of Env, in the pre-entry and entry intermediate, provided evidence of conformational shifts upon receptor or ligand-binding. We also analysed the quaternary structure of Env when bound to another ligand, the Tat protein, since this protein has been postulated to contribute to disease progression.

Comparative analysis of the structures obtained showed that after HIV-1 binding to its receptor CD4, the tertiary conformational arrangement of gp120 is translated to the following quaternary changes: gp120 subunit tilt from the z-axis, gp120 subunit rotation along its own axis and rotation of CD4 epitopes with concomitant exposure of co-receptor epitopes. Including the Tat protein-bound Env in the comparison shows that Tat-Env has a conformation intermediate between the native and CD4-bound Env, and hence, optimal for virus entry. This structure could explain for the increased disease progression in patients with low anti-Tat antibody to viral load magnitude and slower disease progression in those patients with high anti-Tat antibody. In addition, the intermediate structure of Tat-gp120 complex could expose epitopes on gp120 that provide better immune protection in slow progressors.

We further evaluated the effect of Tat protein treatment of HIV-1 on infectivity and spread *in vitro*, and could show that the addition of Tat protein increases infection in target cells and increases spread between infected and non-infected cells through cell-cell contacts. The increased infectivity and spread is proposed to be due to interaction of Tat protein with the V3 loop of gp120, which potentially alters the co-receptor recognition. In this way, HIV-1 of a particular tropism, for example an X4-tropic HIV-1, could infect by using CCR5 as a co-receptor instead. Moreover, the low concentration of circulating Tat protein observed in the serum of HIV-1 patients could be a result of regulation by the virus as Tat protein at high concentration was found to have a negative impact on infectivity rates.

Tuesday, 06 May 2014 2pm to 3pm SBS Classroom 2 (SBS-01n-22)

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