MS05.O03

Structural determinants of ssDNA- and HIV-1 Vif-binding in APOBEC3F

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The human APOBEC3 family of DNA cytosine deaminases serves as a front-line intrinsic immune response to inhibit the replication of diverse retroviruses. APOBEC3F and APOBEC3G are the most potent factors against HIV-1. As a countermeasure, HIV-1 viral infectivity factor (Vif) targets APOBEC3s for proteasomal degradation. Here, we report the crystal structure of the Vif-binding domain in APOBEC3F and a novel assay to assess Vif-APOBEC3 binding. Our results reveal a conserved, amphipathic surface in APOBEC3s that is critical for Vif binding. APOBEC3F-Vif interaction is likely mediated via electrostatic interactions. Moreover, structure-guided mutagenesis reveals a straight ssDNA-binding groove in APOBEC3F, and an 'aromatic switch' is proposed to explain the different DNA substrate specificities across the APOBEC3 family. This study opens new lines of inquiry that will further our understanding of APOBEC3-mediated retroviral restriction and provides an accurate template for structure-guided development of inhibitors targeting the APOBEC3-Vif axis.

[1] *Siu, K.K., Sultana, A., Azimi, F.C. & Lee, J.E. (2013). Nat. Comm. 4, 2593*

Keywords: APOBEC3F, HIV-1, Vif