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Exploring the Role of DCAF1 in HIV Replication: A 2-Hybrid Screen in Yeast

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Viral proteins x and r (Vpx and Vpr) are members of the lentiviral accessory protein family, which function to manipulate native cell machinery and enhance viral replication in differentiated immune cells, including monocyte-derived macrophages. Macrophages, along with CD4+ T cells, are primary targets of HIV infection and crucially important in *in vivo* virus proliferation. Vpr is ubiquitous across all primate lentiviruses, but Vpx is unique to HIV-2 and some Simian Immunodeficiency Viruses (SIVs). Vpr and Vpx both associate with the CRL4 E3 ubiquitin ligase complex via binding to Cul4-associated factor 1 (DCAF1), the complex's substrate receptor. E3 ubiquitin ligases identify target proteins for degradation, and catalyze the transfer of ubiquitin from an E2 enzyme; they are frequent targets of viral infections and cancers, as they control the final step in the ubiquitination pathway. Vpx uses the CRL4 E3 ligase complex to target the restriction factor SAMHD1, which hydrolyzes dNTPs to maintain a cellular concentration below the functioning capacity of HIV-2 reverse transcriptase, for degradation. Vpx-controlled degradation of SAMHD1 removes this block, and allows for viral replication in HIV-2/SIV. Vpr is needed to induce G2 cell cycle arrest, but the exact mechanism and scope of Vpr-mediated inhibition is poorly understood.

We use a yeast 2-hybrid screen to identify DCAF1-interacting proteins, which could provide vital insight into the mechanism of Vpx and Vpr function and inform novel HIV therapies. Our ongoing screen has revealed several interesting candidate DCAF1 interactions, and, we hope, will reveal several more within the semester.