Human Genetics and HIV Pathogenesis

In our efforts to extend the HARC Systems to Structure pipeline using genetic information, we are presently collaborating with Steve Wolinsky and the MACS (Multicenter AIDS Cohort Study; http://aidscohortstudy.org [1]) group to help identify mutations from a group of long-term non-progressors that confer resistance to developing AIDS.

The discovery of putative host mutations that lend protection from HIV has accelerated in recent years. These include the well-characterized CCR5?32 mutation as well as a number of other variants that remain to be characterized. Understanding the mechanisms of natural immunity to HIV would be an important step in HIV prevention, however functional analysis of these variants has been impossible until recently, as there has been no way to mutate the endogenous proteins in primary human T cells.

The HIV Accessory and Regulatory Complex (HARC) Center, in close collaboration between the Krogan and Marson laboratories is working to leverage our ability to create such mutants to validate and fully characterize proposed HIV resistance variants. This is made possible by our collaboration with Dr. Steven Wolinsky and the Multicenter AIDS Cohort Study (MACS). They have generated exome sequencing data on a cohort of HIV-exposed seronegative individuals and have already identified candidate mutations that may be responsible for resistance to HIV infection. Notably, several mutations occur at the structural interfaces of macromolecular complexes comprised of HIV and host proteins. Now it is critical that we confirm the causal functions of these host genetic variants.

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