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SAMHD1 enzymatic activity toward non-canonical nucleotides

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Macrophages are able to maintain a long-lived viral reservoir of HIV. Although HIV-1 is able to infect macrophages, it does so at a much slower rate compared to $CD4^+$ T cells. This is due to their low dNTP pools, which are needed as substrates for HIV reverse transcriptase (RT) to synthesize viral DNA. It has recently been shown that the low dNTP levels found in macrophages are not just the result of maintaining a static lifecycle, but the result of a newly discovered myeloid specific host restriction factor, SAMHD1, which is able to hydrolyze dNTPs into nucleosides. Another mechanism of host restriction in macrophages is the high level of dUTP (58 fold higher than TTP), which is frequently misincorporated by RT; however HIV-1 has evolved to package host nuclear uracil DNA glycosylase (UNG2) to remove dUMPs from its genome. This mechanism was not adopted by HIV-2. Instead, HIV-2 has a separate anti-restriction capability, which allows it to replicate efficiently in macrophages. HIV-2 evolved the accessory protein Vpx to direct proteasomal degradation of SAMHD1 thereby increasing dNTP pools. We hypothesize that degradation of SAMHD1 will reduce the concentration disparity of dUTP and TTP during viral replication. Therefore, we predict that SAMHD1, which is only present in macrophages infected by HIV-1, is able to selectively decrease the levels of canonical dNTPs and not non-canonical dUTP resulting in the virus to evolve separate antiviral activities from HIV-2 to counteract uracilation of its' genome.

Biography

Sarah Amie is in the process of completing her PhD at the University of Rochester. She is in the Microbiology Immunology department under the advisement of Dr. Baek Kim. Her research has focused on the incorporation of ribonucleotides by HIV-1 reverse transcriptase in macrophages and the implications of their persistence in viral DNA. She also has been trying to elucidate the activity of SAMHD1, an HIV-1 host restriction factor in myeloid cells, on non-canonical nucleotides.

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