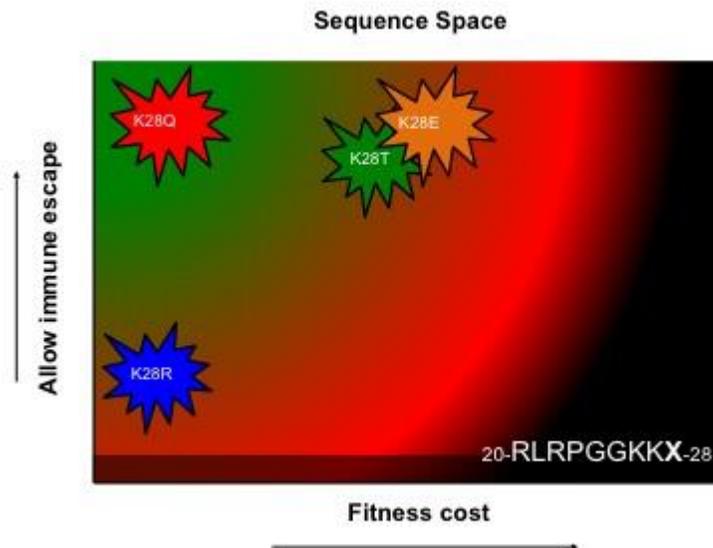


Escape strategies: how HIV evades immune control

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Graphic representation highlighting that the selection of fitness-balanced mutations leads to the resolution of dynamic escape processes.

Image provided by Dr. Justine Sunshine.

Cytotoxic T lymphocytes (CTL) are a powerful tool used by the immune system to detect and remove infected cells. CTL recognize non-self peptides presented by MHC-I (a class of molecules the function of which is to display peptides on the surface of cells) through their T-cell receptor, and eliminate the cell recognized as infected by secreting cytotoxic molecules such as perforin and granzymes. In HIV infection, CTL have been identified as responsible for the decrease in viral load two weeks after infection. Therefore, from the virus' prospective, to elude this control benefits its 'survival'. HIV utilizes its capacity to mutate to avoid CTL recognition and destruction of infected cells.

Understanding the process that leads from a founder virus to the establishment of escape variants is best studied with samples obtained at the time of transmission from both the transmitting partner (TP) and the seroconverting partner (SP). Dr. Justine Sunshine from the Vaccine and Infectious Disease Division at Fred Hutch analyzed the mechanisms of HIV escape by analyzing viral RNA samples from 6 transmission pairs, TP at a time close and subsequent to the transmission and of the SP at different time points after viral acquisition. The results of this study have been published in the August issue of *Journal of Virology*.

The sequences of HIV RNA extracted from TP and SP sera were compared with those able to generate a CTL response, measured as the secretion of IFN- γ and IL-2, at a specific time point, in order to evaluate whether a particular sequence can be detected by CTL or is an escape mutant. Frequent sampling of the viral population revealed that many escape processes are complex and characterized by the emergence of multiple, near-simultaneous mutations. These processes resolve with the selection of a particular variant that is able to achieve optimal balance between escaping CTL recognition without losing viral fitness. Even a small loss in fitness results in the failure of a variant fixation. This evolutionary process, being so strict, requires a long time to be established (an average of over 500 days). The study also documents a correlation between epitope entropy and its capability to originate multiple escape variants. This observation may represent a predictor of the escape potential of a certain peptide.

"What was interesting in this study for me was focusing on these dynamic escape processes and combining phylogenetics, immunology, and viral fitness assays in order to better understand the selective forces leading to one variant being selected over another and why mutations were restricted to certain sites within the epitope" said Dr. Sunshine. Indeed, this study certainly identifies a pattern of mutations and highlights the requirement for a variant to maintain its fitness in order to be fixed in the population.

[Sunshine JE, Larsen BB, Maust B, Casey E, Deng W, Chen L, Westfall DH, Kim M, Zhao H, Ghorai S, Lanxon-Cookson E, Rolland M, Collier AC, Maenza J, Mullins JI, Frahm N.](#) 2015. Fitness-balanced escape determines resolution of dynamic founder virus escape processes in HIV-1 infection. *J Virol*. [Epub ahead of print]

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