Math Model Demonstrates Unexpected Feature of HIV Infection

February 17, 2014

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A large determinant of the eventual fate of untreated HIV-infected individuals is the degree to which their T cell population declines during infection. A large proportion of the $CD4^+$ T cells that become infected are killed directly by the virus or by host $CD8^+$ T-cells. However, virus-induced killing of infected cells is not sufficient by itself to explain the full depletion of T cells. Indirect killing of bystander T cells also occurs, which can be caused by such things as inflammation or proapoptotic (leading to programmed cell death) responses to viral products. Thus far it has been difficult to distinguish between infected and uninfected cells within this pool of lost cells in a way that would allow for the quantification of these two effects. However, a 2013 study carried out by the Dr. Hans-Peter Kiem Lab (Clinical Research Division) provided experimental data that allowed for a collaboration with members of Dr. Joshua Schiffer's group (Vaccine and Infectious Disease Division) to separate these two causes of cell death via the use of mathematical modeling. By being able to clearly distinguish between cells that were either susceptible or resistant to infection, the researchers calculated rates of T cell depletion from either virus-induced direct killing or indirect killing, and found that indirect killing accounts for a prominent proportion of total T cell depletion during the course of infection.

The initial study by Younan *et al*. incorporated a nonhuman primate AIDS model that involved the genetic modification of macaque hematopoietic stem cells in order to make them resistant to SHIV infection (Younan *et al*., 2013). As we reported in July 2013, autologous transplant of modified stem cells into five pigtail macaques followed by viral challenge resulted in a pool of infection-resistant cells and a much-improved antiviral immune response. One caveat of the experimental design that proved exceptionally helpful to Dr. Schiffer's Group was the inclusion of a green fluorescent protein cassette in the genetically modified stem cells, so that the researchers were able to distinguish between infection-resistant and infection-susceptible cells following transplantation. Data from that study indicated that both infected cells and uninfected cells were depleted during the initial phases of SHIV infection.

To explain the depletion in infection-resistant cells, the researchers proposed two hypotheses and designed a separate model to test each one. One potential explanation was that the genetic modification that made the cells resistant was less than 100% effective allowing for some of those modified cells to become infected and succumb to direct virus-induced killing. The second hypothesis was that of a bystander effect killing uninfected cells, or an 'indirect effects' model. Upon supplying the models with the experimental data from the animals, the incomplete efficacy model failed to reproduce key elements of the data, while the indirect effects model correctly produced sharp declines in the modified target cells.

When the researchers used data from only one of the monkeys to provide the parameters for the indirect effects model, the model was able to predict the viral load and $CD4^+$ T cell dynamics of the other four monkeys. This gave better confidence to the validity of the model in spite of the very small sample size. This predictive capability of the model worked regardless of which of the monkeys were used to supply data for the model in order to predict the outcomes for the remaining monkeys.

The most interesting results were obtained when the indirect effects model was used to directly calculate the amount of T cell death caused by indirect effects. Simply by providing the model with the dynamics of viral load and modified (infection-resistant), and unmodified (infection-susceptible) T cell populations (see figure), the model was able to quantify the depletion in T cell populations due to indirect effects. Surprisingly, indirect effects were responsible for at least 60% of all T cell death during the acute phase and 99% during established infection.

Dr. Laura Matrajt, lead author of the study, explains, "by using mathematical models, we were able to provide the first quantification of the loss of $CD4^+$ T-cells during an acute SHIV infection, and showed that the vast majority of cell death during infection is in uninfected cells." The fact that the indirect killing of T cells far outpaces direct virus-induced killing highlights the importance of studying the complete immunological system during HIV infection. "Our results suggest that a therapy targeting the loss of uninfected cells could result in immune preservation and improved long-term survival," Dr. Matrajt said.

Matrajt L, Younan PM, Kiem HP, and Schiffer JT. 2014. The majority of CD4+ T-cell depletion during acute SHIV89.6P infection occurs in uninfected cells. *Journal of Virology*. Epub ahead of print; doi: 10.1128/jvi.03428-13

See also: Younan PM, Polacino P, Kowalski JP, Peterson CW, Maurice NJ, Williams NP, Ho O, Trobridge GD, Von Laer D, Prlic M, Beard BC, Derosa S, Hu SL, Kiem HP. 2013. Positive selection of mC46-expressing CD4+ T cells and maintenance of virus specific immunity in a primate AIDS model. *Blood*. 122:179-87.

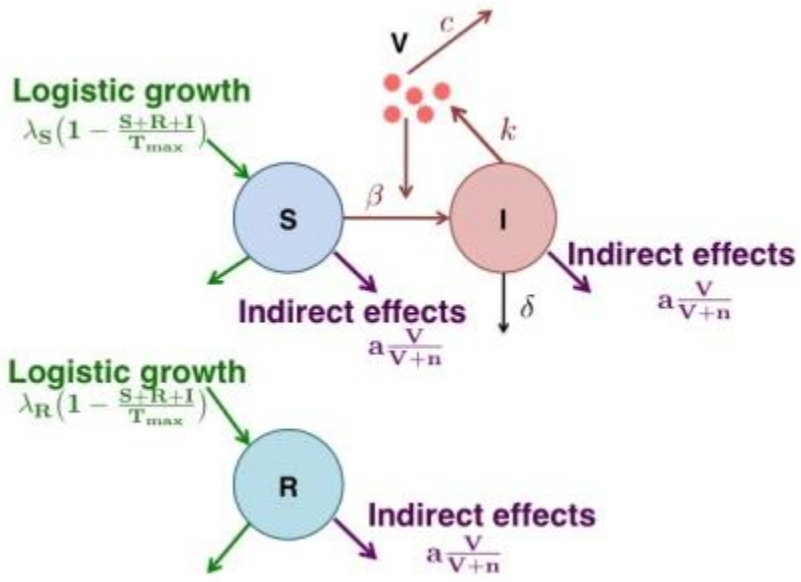

Image provided by Dr. Laura Matrajt.

Schematic diagram of the mathematical model used. Virus (V) infects susceptible cells (S) and converts them into infected cells (I), which can be depleted by direct virus-induced killing (δ), while resistant cells (R) do not suffer this fate. Indirect effects contribute to the depletion of all three cell types.