Predicted Confounding Effect of Weakly Immunogenic Long-Lived Infected Cells on Vaccination against Simian Immunodeficiency Virus

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Abstract

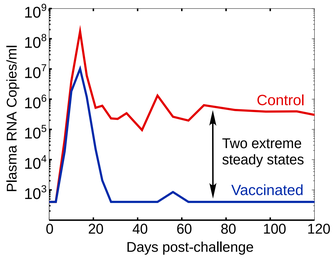
Although vaccination with SIVmac251 is unable to prevent chronic infection upon challenge with the same virus, a representative vaccinated macaque establishes a lower steady-state virus level (~ 30 fold on average), higher CTL frequencies (~ 10-fold), and much higher (a few orders of magnitude) helper cell frequencies, than a representative control animal.

Our previous model, selected to match several important features of cytotoxic immune response to various viruses including HIV, predicted the existence of two steady states with the described properties: Unvaccinated animals end up in the high-virus state, and vaccination, at high initial levels of memory cells, forces the system after challenge into the low-virus state. However, if we try to apply this prediction to vaccinated animals, we conclude that the level of viremia in the low-virus state is surprisingly high (e.g. as compared to animals challenged with SHIV) and strongly variable among individual animals (3-4 orders of magnitude). Our general aim is to understand why the virus load required to maintain a constant helper response in the "low-virus" state in vaccinated animals is so large and variable. There are two major possibilities: Either the dominant infected cells are weakly immunogenic, or the helper cells have very low sensitivity to antigen.

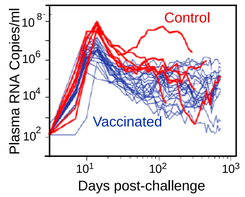
Here we investigate the first scenario. In addition to the short-lived (~ 1day) infected cells featuring in the previous model, we introduce a second infected cell type, which is longer-lived, produces less virus, and, hence, has less of an impact on the immune system. These cells are predicted to dominate the steady state infection in vaccinated animals, when highly productive cells are rapidly eliminated by fast activation of memory CTL produced by vaccination. We link this hypothetical cell type to the second, slow phase of viremia decay under ART (Perelson et al 1997) and the infected cells with low HIV RNA content observed in the lymphoid tissue (Cavert et al 1997; Zhang et al, 1999). Experiments are proposed to confirm or refute the importance of long-lived infected cells in vaccinated animals.

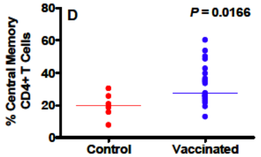
Vaccination trials: SHIV vs SIV

SHIV challenge (Barouch et al 2000)

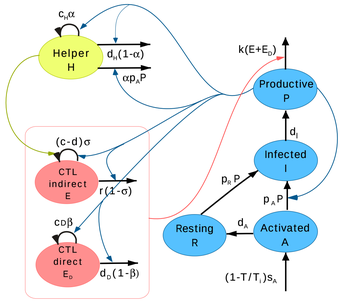


SIV challenge (Letvin et al 2006): High and variable viremia





Model 1 : Short-lived infected cells (SHIV vaccination trials)



Control functions:

$\alpha = 1 - \exp(-P/P_{H0})$

$\sigma = 1 - \exp(-\alpha H/H_0)$

$\beta = 1 - \exp(-P/P_0)$

Thresholds in antigen:

P_{H0}, H_0, P_0

$$dH/dt = [\alpha c_H - (1-\alpha)d_H - \alpha p_A P_V]\,H$$

$$dE_D/dt = [\beta c_D - (1-\beta)d_D]\,E_D$$

$$dE/dt = [\sigma\,(c-d) - (1-\sigma)\,r]\,E$$

$$dA/dt = (1-T/T_i)\,s_A - (d_A + p_A P)\,A$$

$$dR/dt = d_A A - p_R P R$$

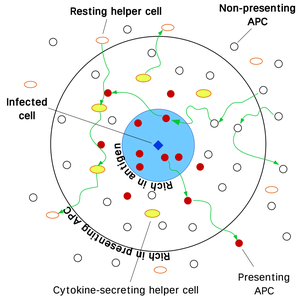
$$dI/dt = (p_R R + p_A A)P - d_I I$$

$$dP/dt = d_I I - k(E+E_D)P$$

Prediction: 2 steady states (SHIV vaccination trials)

$P = P^{LVS} = P_0 \log(1+d_D/c_D) \;<<\; P^{HVS} = P_{H0} \log(1+d_H/c_H)$

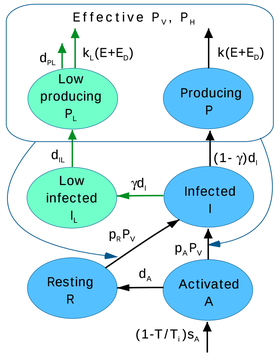
Control of helper cell: Region with APC



Tissue fraction occupied by such regions is $\alpha = 1 - \exp(-P/P_{H0})$ where P is concentration of virus-producing cells

Diffusion of soluble antigen: The region radius is proportional to the virus production rate => $1/P_{H0}$ ~ (production rate)^3

Model 2 : Adding chronically infected cells (SIV vaccination trials)



$$dA/dt = (1-T/T_i)\,s_A - (d_A + p_A P_V)\,A$$

$$dR/dt = d_A A - p_R P_V R$$

$$dI/dt = (p_R R + p_A A)P_V - d_I I$$

$$dI_L/dt = \gamma d_I I - d_{IL} I_L$$

$$dP/dt = (1-\gamma)d_I I - k(E+E_D)P$$

$$dP_L/dt = d_{IL} I - [k_L(E+E_D) + d_{PL}]P_L$$

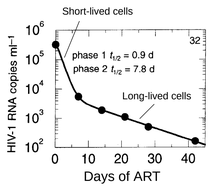
$\gamma = \gamma_0 \exp(-P_V/P_{single})$

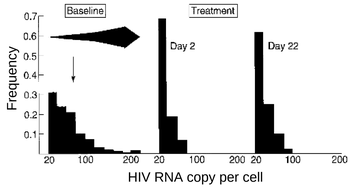
$P_V \equiv P + xP_L$

$x,\ x << 1$: Virus production ratio

Helper cell and CTL block: See Model 1

Evidence: Dynamics in antiretroviral therapy





Effective numbers of virus-producing cells

$\gamma = \gamma_0 \exp(-P_V/P_{single})$:	Fraction of infected cells on long-lived pathway
$P_V \equiv P + xP_L$:	**Effective virus-producing cell # for free virus**
$x,\ x << 1$:	Productivity ratio for two infected cell types
$\alpha = 1 - \exp(-P_H/P_{H0})$:	Fraction of cytokine-secreting helper cells
$P_H = P + x^3 P_L$:	**Effective producing cell # for soluble antigen**

Parameter estimates

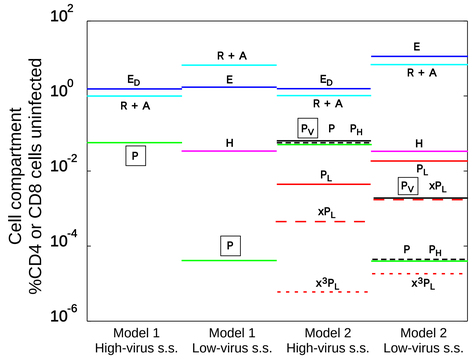
Previously, from unrelated data (Sergeev et al JTB 2009):

p_R = 0.5/(day %CD4 cell count), T_i = 7 %CD4, s_A = 0.21 %CD4 /day, d_A = 1.0/day, p_A = 120, d_I = 1.3/day, c = 2.85/day, d = 2.4/day, c_D = 1.0/day, d_D = 0.4/day, c_H = 1.7/day, d_H = 0.07/day, r = 6/day, P_0 = 0.17 %CD4, P_{H0} = $1 \cdot 10^{-3}$ %CD4

Now, from data on long-lived cells and vaccination trials:

H_0 = $5 \cdot 10^{-4}$ %CD4, x = 0.1, k = 3/(day %CD8), γ_0 = 0.8, P_{single} = $1 \cdot 10^{-2}$ %CD4, d_{IL} = 0.1/day, d_{PL} = 0.05/day, k_L = $3 \cdot 10^{-2}$

Models 1 and 2: Two steady states



Conclusions

- Interpretation of the difference in vaccination outcome between rhesus macaques challenged with SIV and SHIV is offered based on the existence of chronically infected cells with low virus production, low immunogenicity, and long life span.
- Parameter estimates and pathway of their differentiation are inferred.
- It is predicted that the long-lived cells dominate viremia in vaccinated SIV infected animals, but short-lived cells dominate the immune response.
- Multiple tests of the model are proposed (not shown in the poster).