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Understanding the dynamics of reactivation from latency in macaques infected with tagged simian immunodeficiency virus

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Modern anti-retroviral therapy can effectively control HIV. However, the virus cannot be eradicated due to the presence of latently infected CD4+ cells that cause the reactivation of virus when a patient stops anti-retroviral treatment.

There is a lack of knowledge about the basic dynamics of reactivation of latently infected cells and the interaction of virus with immunity. We combined mathematical modelling with a novel experimental method of 'barcoded' viruses to quantify the contribution of individual latently infected cells.

Rhesus macaques were infected intravenously with a sequence-tagged SIV-M virus with ~10,000 different barcodes. Animals were treated with antiretroviral therapy for various times prior to treatment interruption. After interruption serum samples were subjected to gene sequencing in order to identify the frequency of individual barcoded viruses.

We developed a mathematical model of growth of virus from different latently infected cells. Applying this model to experimental data we estimate that the frequency of reactivation from latency ranges from around 20 reactivations per day to 0.5 reactivations per day, depending on the timing and duration of treatment. A single reactivated latent cell can produce an average viral load equivalent to ~0.1-0.5 viral copies/ml of virus, depending on assumptions about duration of drug action.

We have also studied the virological parameters that may predict reactivation rate. When comparing animals treated starting on day 4 and day 27 post-infection and find that monkeys treated on day 4 have 40-fold higher reactivation rate per SIV DNA copy then monkeys treated on day 27. This difference cannot be simply explained by differences in immune activation or immune response. We analyse this by modelling the dynamics of DNA accumulation and viral-immune interactions.

The combination of mathematical modelling of viral dynamics of barcoded virus provides a powerful tool to understand latency formation, maintenance and reactivation in SIV / HIV.

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