Abstract

Curing infections by HIV and hepatitis C virus (HCV) have remained a challenge for a long time due to their efficient ways of evading host immune responses and therapies. They do so by rapidly mutating their genomes, which prevents their identification by the immune system and compromises the action of drugs and vaccines. In this thesis, we construct mathematical models that help optimize novel intervention strategies that are designed not to succumb to viral mutation-driven failure. In the first part of the thesis, we developed a mathematical model to understand HCV evolution that underlies treatment failure due to the development of drug resistance. Mutant strains resistant to drugs can exist in individuals before the start of therapy but may lie below current assay detection limits. Mathematical models have been developed therefore to estimate the frequencies of such mutants. Current models build on models of HIV infection, which do not accurately capture the evolution of HCV. In particular, unlike HIV, HCV evolution is a multiscale phenomenon, with selection at the intracellular and extracellular levels. The few hundred genomes in each cell and the relatively short infected cell lifespan make intracellular evolution stochastic and subject to strong founder effects. In contrast, the large populations of target cells and free virions render extracellular dynamics deterministic. We developed a novel strategy to bridge these scales. Using a codon-level description of amino acids and the known replicative fitness landscape, we identified the mutational pathways connecting all non-lethal mutations at a chosen locus. Using every codon in these pathways, one at a time, as the codon in the infecting strain, we performed stochastic simulations of intracellular replication, mutation, and selection, and quantified the likelihood of the cell being productively infected and, once infected, the distribution of mutants produced by the cell. Using these quantities as inputs to a deterministic viral kinetics model, we estimated the steady state frequencies of all possible mutants at the chosen locus in an infected individual. Our model yielded the frequency of the mutant RI55K, resistant to the drug telaprevir, in close agreement with experiment. Importantly, our model estimated the frequencies of all the other mutations at the locus, not previously estimated, defining the mutant spectrum. Mutant frequencies below assay detection limits, such as for Y93H, mark hidden escape pathways which our model unravelled. We expect our approach to improve treatment optimization and vaccine design strategies. In the second part, we discuss the role of interferon in improving the current treatments for HCV infection. Previously, a combination of pegylated interferon and ribavirin was used as treatment for 24-48 weeks and cured ~50% of the patients treated. Current treatments with direct acting antivirals (DAAs) cure nearly all patients with 8- 12 weeks of treatment. Significant efforts are now being made to optimize treatments with DAAs so that cure can be achieved with the least drug exposure and in the shortest possible time. We believe that interferon may have a new role here. Clinical studies present compelling evidence that DAAs perform better in treatment-naive individuals than in individuals who previously failed treatment with interferon, a surprising correlation because interferon and DAAs are thought to act independently. We developed a mathematical model to explore a mechanistic hypothesis underlying this correlation. The hypothesis invokes the action of interferon at the cellular, the individual and the population level. Strong interferon responses prevent the productive infection of cells, reduce viral replication and impede the development of resistance to DAAs in infected individuals, and improve cure rates elicited by DAAs in treated populations. The model develops descriptions of these processes, integrates them into a comprehensive framework, and captures clinical data quantitatively, providing a successful test of the hypothesis. Individuals with strong endogenous interferon responses thus present a promising subpopulation for reducing DAA treatment durations. In the last part, we developed a mathematical model for passive immunization with broadly neutralizing antibodies (bNAbs) during HIV infection. Current antiretroviral therapies (ART) for HIV-1 infection control viremia in infected individuals but

are unable to eradicate it or achieve sterilizing cure. bNAbs are antibodies (Abs) capable of neutralizing a diverse spectrum of viral variants, rendering immune escape by mutation difficult for HIV-1. They emerge naturally in 10-30 % of HIV-1 infected individuals, but after 2-4 years of infection. When spontaneous Ab generation is inefficient, exogenous Abs can be administered for immediate, but usually temporary, clearance of antigen (Ag). Passive immunization with bNAbs of HIV-1 early in infection was shown recently to elicit long-term viremic control in most SHIV-infected macaques treated, raising hopes of a functional cure of HIV-1 infection. The mechanisms with which short-term exposure to bNAbs resulted in lasting viremic control remained elusive, precluding the rational design of bNAb-based interventions. Here, we employed mathematical modelling coupled with analysis of recent in vivo data to elucidate the underlying mechanisms. We found that bNAbs acted via multiple mechanisms: They enhanced antigen uptake, stimulating cytotoxic T lymphocytes (CTLs), and suppressed viremia, limiting CTL exhaustion. When bNAbs were cleared from circulation, viremia rose but in the presence of a primed CTL population, which eventually controlled the infection. Our model fit data quantitatively only when all these effects of bNAbs were considered. Our model identifies optimal bNAb-based interventions and predicts that bNAbs combined with antiretroviral therapy would elicit functional cure also of chronic HIV-1 infection.