Coadaptive Stability of Interfering Particles with HIV-1 When There Is an Evolutionary Conflict

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HIV-1 evolution is a fundamental challenge for any therapeutic intervention. Rouzine and Weinberger (1) presented a mathematical analysis of the evolutionary stability of proposed therapies that would use engineered defective interfering particles (DIPs) to treat HIV-1 patients. Their analyses are illuminating, particularly in highlighting the importance of multiple DIP infections of a cell and the possible role of “capsid sealing” by the DIPs. However, they state that the coevolution of HIV-1 and DIPs has not been explored previously while simultaneously raising “doubts regarding the validity” of our recent study of this problem (2). We wish to clarify two key issues and broaden the discussion.

First, the authors’ doubts about our work are based on their conclusion that DIP interference by “genome stealing” (i.e., formation of nonviable HIV-DIP heterodimers) is evolutionarily unstable, because HIV-1 cannot mutate its dimerization initiation signal (DIS) to escape. This finding arises from the assumption that mutations away from the wild-type DIS sequence bear no fitness cost for HIV-1, which is based on the observation that different HIV-1 subtypes have different DIS sequences (3). However, the fact that the DIS sequence is strongly conserved within each subtype suggests that mutations in the DIS induce significant fitness costs in vivo (4). Furthermore, in vitro studies have shown that mutated DIS sequences substantially decrease the efficiency of HIV-1 packaging and/or cellular infectivity (at least for the subset of mutations that have been studied) (5–8). Our recent work integrated these factors and showed that a genome-stealing strategy can be coevolutionarily stable, though we emphasized that experimental confirmation will be needed for particular DIP constructs (2).

Second, Rouzine and Weinberger (1) do not consider the evolutionary pressure on a crucial parameter—the intracellular production asymmetry between DIPs and HIV-1, denoted P. Changes in the value of P have opposing effects on the fitness of HIV-1 and DIPs, leading to a potential evolutionary conflict. The value of P is partly determined by DIS and genome architecture (9), which is not directly altered by HIV-1 evolution. However, because DIS genomes must be rescued by HIV-1 trans elements to become mature particles, the production rate of DIPs is influenced by factors encoded by HIV-1. Thus, mutations in HIV-1 could reduce the value of P, enabling evolutionary escape from the parasitism of DIPs (2, 9, 10).

We explored the coevolutionary dynamics arising from this conflict and identified a characteristic three-phase pattern (2). Initially, the DIP treatment is effective in suppressing HIV-1, but then HIV-1 evolves to escape DIPs by reducing P. Under some circumstances, DIPs then evolve to catch up with HIV-1 and establish a set point phase characterized by sustained suppression of HIV-1 viral load and “Red Queen” coevolutionary dynamics. Importantly, these qualitative dynamics are robust to different mechanisms of interaction between DIP and HIV-1 (including the “capsid-stealing” strategy explored by Rouzine and Weinberger [1]), so long as the evolutionary conflict exists at the host level (2). Therefore, measures to maintain the production asymmetry between DIPs and HIV-1, by inhibiting HIV-1 escape or facilitating the catch-up by DIPs, are crucial design principles for all DIP-based antiretroviral therapies.

REFERENCES