A fitness bottleneck in HIV-1 transmission

A successful infection is determined in part by how close a viral genome is to an ideal sequence

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Identifying factors that determine the successful transmission of HIV-1 may help enable the development of better prevention measures. This is what makes the findings of Carlson et al. (1) so relevant. On page 178 of this issue, the authors provide evidence for a bottleneck in HIV-1 transmission that selects for high-fitness viruses. Fitness in this analysis would be reflected either in the infectiousness of each viral particle or in the number of particles produced by an infected cell (burst size). Thus, this fitness bottleneck would act during infection of the first cell or during the first few rounds of local viral replication at the site of transmission where the infection could be extinguished.

An important feature of this study is the use of a large cohort of couples who were discordant for their HIV-1 infection (one was infected and the other was not). The authors analyzed 137 transmission events identified in the cohort over 10 years despite a two-thirds reduction in infections (the result of counseling and condom use). Comparison of the viral sequences in the chronically infected donors and their newly infected recipient partners forms the basis of the study.

HIV-1 is genetically diverse both across the epidemic and within an infected person. Yet, although its evolution on a global scale hovers around a consensus sequence that is optimal for viral gene functions, the virus never attains this idealized genome sequence. In the study of Carlson et al., differences from the consensus sequence of the cohort (“polymorphisms”) are assumed to reduce viral fitness. Each viral genome contains multiple polymorphisms across the genome, and within an individual a polymorphism at one site can coexist as a mixed population with the corresponding consensus at that site. Despite the complexity of the viral population in a donor, heterosexual transmission typically results in the outgrowth of a single transmitted/founder virus (2, 3). Thus, transmission reduces the genetic diversity seen in the donor to a single viral genome that is identical to the consensus sequence at some positions but carries polymorphisms at other positions.

Carlson et al. compared the predominant amino acid sequence in the proteins encoded by the HIV-1 genes gag, pol, and nef of the paired donors and recipients. The surprising outcome is that a donor genome that more closely matched the consensus was more likely to be transmitted than were donor genomes that on average encoded more amino acid polymorphisms. This outcome is most easily explained if there is a period at or immediately after transmission when the virus is replicating in the recipient under adverse conditions and the probability of spread is influenced by viral fitness.

There is a conceptual framework for describing the probability of virus spread, which is captured in the reproductive number \( R_e \). \( R_e \) is the average number of cells infected from a single host cell (4). When \( R_e \) is greater than 1, the infection will spread to other cells, and when \( R_e \) is less than 1, the infection will die out. During the first rounds of HIV-1 viral replication, \( R_e \) is low but rapidly increases after the initial seeding of a systemic infection. Thus, a viral genome sequence that slightly increases \( R_e \) increases the probability that the virus will spread to the point where exponential growth takes over and a systemic infection is assured.

After detecting mutations that alter fitness and affect replication during this early period of selection, Carlson et al. made further comparisons within subsets of the cohort. The reduction in population complexity during transmission clearly includes a stochastic bottleneck that limits transmission of all viruses (e.g., the mucosal barrier) but also includes a fitness bottleneck that selects for transmission of high-fitness variants. The fitness bottleneck was more severe in female-to-male transmission compared to male-to-female transmission, with infection of females allowing the transmission of genomes encoding more polymorphisms. Moreover, exposure to higher donor viral load or recent genital ulcer or inflammation (GU) in a male recipient could attenuate the fitness bottleneck in female-to-male transmission but not the reverse. Whereas Carlson et al. examined polymorphisms in virion proteins (Gag and Pol) and a viral protein expressed in the host cell (Nef),
an earlier study indicated that a bottleneck selecting for reduced glycosylation of the virion surface Env protein is also stronger in female-to-male transmission (5).

That the fitness bottleneck observed in female-to-male transmission is more severe, but can be reduced by viral load and/or GUI, suggests that barriers to infection of the first cell may reduce transmission in males compared to females. The exposed surface area of epithelium and/or the density of target cells in or just beneath the epithelium in the male versus the female genital tract may be sufficient to explain this difference, but the ability to spread after infection of the initial cell may also be selected (see the figure). The transmitted virus is well adapted to entering cells with a high density of its receptor CD4 (5–7), making CD4+ T cells the most likely target, although the virus can infect macrophages less efficiently (6, 8, 9). Examination of vaginal tissue in macaques after exposure to the related virus SIV showed that resting CD4+ T cells are the predominant infected cells, but infected activated CD4+ T cells are also observed (10). A paucity of CD4+ T cells in genital tract tissue could suffice to define the low probability of the first infected cell both being infected and then passing virus on to the next cell. It has been suggested that a local innate immune response generates type 1 interferon, a cytokine that can limit viral replication (11, 12). Whether the selection for fitness is due to low target cell density, a local innate immune response, or both is not known.

This new view of HIV-1 transmission suggests that there may be more initial infectious events than infections that become systemic (R0 ≪ 1). There are exposures of target cells to virus that fail to initiate an infection, and there is spread of virus from the initially infected cell(s) that fails to become a systemic infection, collectively adding a bias to the distribution of polymorphisms in the transmitted/founder virus population. Thus, there is a period during transmission of a low R1 that HIV-1 must navigate in the new host to initiate a successful infection. ■

REFERENCES

IMAGING TECHNIQUES

Low-energy electron diffraction at ultrafast speeds

Thermally induced structural changes in a thin polymer film could be resolved with picosecond time resolution

By Erik T. J. Nibbering

Low-energy electron diffraction (LEED) has been used to determine the surface structure of crystalline materials because the diffracted electrons only probe the top atomic layers. First reported by Davisson and Germer in 1927 (1), the LEED technique became widely used when ultrahigh vacuum techniques introduced in the 1960s allowed surfaces to remain relatively free from adsorbed background gases during a typical experiment. However, the information LEED provides about the relative ordering of atoms on a surface, whether at atomic resolution or on a larger mesoscopic scale, can only be understood in a time-averaged, quasi-stationary manner. Dynamical aspects, such as changes with temperature, have been only grasped indirectly with well-developed theoretical models to describe the averaged measured quantities. Time-resolved monitoring of LEED patterns would enable direct visualization of lattice motions or light-induced ultrafast phase transitions.

On page 200 of this issue, Gulde et al. (2) report an ultrafast implementation of LEED and have resolved the ultrafast melting of a poly(methylmethacrylate) (PMMA) layer adsorbed to a graphene substrate.

In LEED, electrons are generated at a cathode, accelerated, and focused by electrodes into an electron beam pointing to the sample of interest. The diffracted electrons are then usually detected in reflection using phosphorescent screens (see the figure, panel A).

Gulde et al. achieved time resolution in the picosecond regime with a pump-probe configuration in their transmission ultrafast LEED (T-ULEED) experiment. An ultrashort laser pump pulse heats up the PMMA layer, and the structural changes resulting from the melting process are monitored as a function of time delay by probing its diffraction patterns (distinct from those of graphene) with electron pulses lasting a few picoseconds (see the figure, panel B). The electron pulses are generated from a sharp tungsten tip (50-nm radius of curvature) by illumination with a second-harmonic pulse originating from the same laser output as the laser pump pulse. This method ensures accurate timing (time delay t) between the two pulses.

The PMMA layer on graphene consists of three domains of two-dimensional folded
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Science 345 (6193), 136-137.
DOI: 10.1126/science.1257425