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SCIENCE DIRECT
Infection, Genetics and Evolution 5 (2005) 327–334
Infection, Genetics and Evolution
www.elsevier.com/locate/meegid

Review

Adaptation, co-evolution, and human susceptibility to HIV-1 infection

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Received 19 August 2004; received in revised form 29 October 2004; accepted 4 November 2004
Available online 22 December 2004

Abstract

Infection with HIV-1, a retrovirus of animal origin, has reached pandemic proportions. For this the virus, characterized by rapid mutation rate, has adapted to the host immunity and to the human cellular environment. Humans are also exerting considerable pressure on HIV-1 through the use of antiretroviral agents. On the other hand, long term exposure of humans to other retroviruses and retroelements may have already shaped the human genome. Thus, despite a recent entry of HIV-1 in humans, this pathogen might be already exerting evolutionary pressure on humans, by selecting a repertoire of restriction genes and susceptibility loci.

Keywords: Restriction genes; Comparative genomics; Viral fitness; Immune escape

Contents

1. Introduction

"*The closer you look at life, the more rapid and intense the rate of evolutionary change*"

Jonathan Weiner, *The Beak of the Finch*

Darwin believed evolution occurred over very long periods of time and generally moved in a set direction toward fitness, in the same direction the environment was heading. HIV-1, by means of its inherent capacity to mutate, and thus evade and adapt, might serve to assess co-evolution with humans over the short period that elapsed since its estimated entry into the human population during the first half of the last century (Korber et al., 2000). In this paper, I review the selective pressures exerted by humans on the virus and potential evolutionary influences exerted by the virus on the human population under the weight of the current pandemic. I will pay special attention to the growing knowledge on the elaborate innate defense mechanisms

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doi:10.1016/j.meegid.2004.11.001

against retroviruses, and on the potential role of human genetic variants of antiviral genes and of host proteins needed for the viral life cycle in modulating human susceptibility to HIV-1 infection.

2. Adaptation of HIV-1 to the human population

Humans exert powerful selective pressures on HIV-1. Some are exogenous in nature, such as the pressure exerted by antiretroviral drugs leading to the selection of drug resistance, while others are of endogenous nature, such as the pressure generated by the adaptive immune system leading to the selection of immune escape mutants. These two processes shape the virus in a fashion that may lead to population-specific HIV-1 variants. In these processes, evolution may be characterized by steps of diminished viral fitness. In population biology, fitness is defined by the relative reproductive capacity of an individual based on its contribution to the next generation. In virological terms, fitness is best described by the relative replication rates of viruses in competition kinetics (Bleiber et al., 2001). This is reflected, in vitro, by growth competition between two different virus variants mixed in a single culture, and in vivo, by observing the patterns of re-growth of the wild type virus when specific pressures have been removed (discontinuation of antiretroviral pressure, or transmission to a new host). In addition, fitness may be described through analysis of its determinants: the catalytic activity of viral enzymes, viral infectivity, maturation, burst size, or replication capacity of the viral isolate or recombinant clone (Bleiber and Telenti, 2001).

2.1. Adaptation to drug pressure

Although the fitness of resistant HIV-1 strains overlaps that of susceptible clinical isolates, resistant strains are overall less infectious and replication competent (Telenti et al., 1999; Kaufmann et al., 2000; Bleiber et al., 2001). Mutations selected by reverse transcriptase (RT) and protease (PR) inhibitors frequently involve changes of enzyme active site residues. Reduction in primer extension activity by mutant RT has been demonstrated in vitro (Back et al., 1996; Back and Berkhout, 1997). Mutant PR enzymes exhibit diminished catalytic efficiency in the processing of viral Gag and Gag–Pol polyproteins (Schock et al., 1996; Zhang et al., 1997; Rayner et al., 1997; Croteau et al., 1997; Carrillo et al., 1998). These modifications in enzyme processivity may translate into the accumulation of immature viral particles. Kinetic analysis of consecutive proteolytic cleavages of the Gag–Pol polyprotein suggests that HIV-1 would cease being viable when the efficiency of a mutant protease is less than 61% of the wild type activity for each step of cleavage (Rasnick, 1997). Mutation in both PR and RT can contribute to diminished viral fitness, and either enzyme may display a profound impairment (Bleiber et al., 2001). Resistance to HIV-1 fusion inhibitors is also associated with impaired fitness, while resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) modifies viral physiology only minimally (Schmit et al., 1996; Rayner et al., 1997). This has been attributed to drug binding being remote from the RT active site (Esnouf et al., 1995), and explains the occasional identification of NNRTI resistance mutations as natural polymorphisms (Havlir et al., 1996).

Given the remarkable plasticity of the HIV-1 genome, selection of compensatory mutations leading to improved enzyme function takes place. This process involves structurally relevant amino acid substitutions in target enzymes (e.g., in the hinge or flap regions of the viral protease) (Schock et al., 1996; Borman and Clavel, 1996), changes that improve processing of enzyme substrate (e.g., Gag cleavage sites) (Doyon et al., 1996; Zhang et al., 1997; Carrillo et al., 1998; Bally et al., 2000). Alternatively, compensatory mutations may occur at distance (Nijhuis et al., 1999; Peters et al., 2001). However, these pathways of compensation may not provide an immediate or full remediation of viral fitness deficits (Mammano et al., 1998) as there could be evolutionary and adaptive limits of HIV-1 (Yuste et al., 1999; Nijhuis et al., 1999). Diminished fitness underlies the lower pathogenicity of multidrug-resistant strains (Kaufmann et al., 1998). Fitness cost can also be translated into transmissibility cost. Resistant strains, and in particular multidrug resistant viruses, are less transmissible in a population (Yerly et al., 2004), a phenomenon that can be ascribed to adaptive attenuation.

2.2. Adaptation to immune pressure

Viruses adapt to the host they infect through a process of HLA-associated selection (Moore et al., 2002). Immune selective pressure forces the emergence of viruses with escape mutations that results in infected cells not being recognized by cytotoxic T lymphocytes (CTL) (Lieberman, 2002). Escape mutations tend to be maintained after transmission into a new host who shares the restricting HLA molecule (Leslie et al., 2004). The extent to which escape mutations revert to wild-type sequence will depend on the fitness cost of the escape mutation (Altman and Feinberg, 2004; Friedrich et al., 2004). Some escape mutants may have no or very little fitness cost (Leslie et al., 2004), and thus they may be maintained after transmission, and contribute to drive evolution of the virus at population level. MHC-restricted immune responses will shape the viral genetic diversity over time, providing a selective pressure that is a function of the frequency of various alleles as the virus is passed from one host to the next. In this scenario, it may be predicted that the population consensus sequence is likely to represent the genotype best adapted to the most frequently encountered disease-modifying MHC alleles (or haplotypes) (Moore et al., 2002). Trachtenberg