Virus genetic variability involvement in transmissibility of HIV-1 immune activation and disease progression.

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For decades, immunologists and virologists have worked somewhat independently trying to understand AIDS disease progression for the benefit of improved patient care. Their efforts have resulted in the development of antiretroviral therapy (ART) as well as contributed to our understanding of immunological factors associated with disease progression. Disease progression occurs when virus replication is not sufficiently controlled, which is observed when HIV evades selective pressure imposed by the host immune system and/or antiviral drugs. The high evolutionary rate of HIV allows for continuous adaptation of the virus to different intra-host pressures (e.g. ART and immune response). We are starting to understand how the selection processes could optimize virus fitness and how the resulting changes in the virus can be transmitted.

Throughout the asymptomatic phase of HIV-1 infection in ART-naïve patients, the viral load is kept at relatively stable levels over several years, known as the set point viral load (SPVL). This is a dynamic process, in which some viruses are continuously adapting and escaping the immune selective pressure. It is well documented that SPVL levels can differ substantially between patients, and that a high SPVL value is one of the most important predictors of fast disease progression [1]. Fraser et al. found that high SPVL can be transmitted to newly infected patients and suggested that SPVL values may result from determinants of the virus itself and/or host factors such as immune activation profile or specific host genetic variants. Thus, SPVL reflects a complex interplay between the immune responses in the newly infected host and the replication capacity of the virus [2]. One important unresolved issue is the identification of the genetic regions of the virus that may be key determinants of the SPVL transmissibility. Recently, HIV/AIDS researchers have started to combine knowledge of virus evolution and of disease progression, which has resulted in
increasing numbers of publications that improve our understanding of the causes of HIV-1 genetic variability, SPVL transmissibility and faster disease progression.

The observation that syncytium-inducing viruses are strongly linked to HIV-1-driven disease progression was one of the first discoveries on how HIV-1 genetic variability could affect the clinical prognosis of infected patients [3]. Further studies discovered that the capacity to induce syncytia was linked to genetic variability in the env region and to the capacity of the virus to bind the co-receptor CXCR4. Most HIV-1 infections initially use the CCR5 co-receptor for entry into host cells and switch to use the CXCR4 co-receptor only after several years. Interestingly, this switch has been previously associated with accelerated progression to AIDS. Thus, it is reasonable to speculate that the env genetic region of HIV-1 is one of the determining factors driving increased risk for accelerated disease progression in infected individuals.

Many protease polymorphisms are involved in improving viral fitness in the presence of treatment or resistance mutations. Theys et al. recently demonstrated that they are also contributing to a higher viral load and lower CD4 count in therapy naïve patients without resistance mutations [4,5]. This is in keeping with the fact that the same polymorphic positions also contribute to the replication capacity of the virus [4,5]. Thus, while increasing viral fitness during treatment, these polymorphisms also modulate viral fitness and virulence in absence of therapy or major resistance mutations, most probably by improving enzymatic efficiency. These observations introduced for the first time the possibility that treatment could contribute to an increase in disease progression at the population level, through transmission of such fitness related polymorphisms in protease. Moreover, such findings suggest that protease may be an important genetic region potentially determining SPVL.

It is a great opportunity to study viral genes involved in transmissibility of disease progression when epidemics with more than one HIV-1 subtype overlap within a population, leading to an increased prevalence of recombinants of two distinct virus subtypes (A-K). This is because there are differences in capacity to accelerate disease progression among subtypes. For example, individuals infected with the subtype D, on an average, progress faster to AIDS than subtype A infected patients [6]. Many of these newly recombined strains do not survive for long. However, recombination between subtypes may give rise to more pathogenic strains if genomic fragments from these different subtypes join together in a virus achieving a higher SPVL. Furthermore, in such epidemiologic scenarios, it is reasonable to expect that only recombinant viruses with the best evolutionary fitness would tend to survive in the affected population, and become Circulating Recombinant Forms (CRFs). This would support the idea that recombination may be an attractive way by which HIV-1 increases overall fitness in a population of infected individuals. This fact does not necessarily imply that virus recombination affects disease progression in consecutive transmissions at a population level. However, more aggressive forms of HIV-1 have been reported in some CRFs, such as the recently examined CRF19_cpx [7], CRF02/A3 [8] and CRF14_BG [9]. Additional studies on CRFs in different populations could clarify whether single or combined genes are the key drivers of accelerated disease progression in a newly infected individual.
A recent report on an aggressive CRF sheds light on the understanding of the HIV-1 genetic region, which may be responsible for transmissibility of accelerated disease progression. Kouri et al [7] examined the aggressive CRF19_cpx, which is found in epidemic proportions only in Cuba. The investigators described how this virus replicates to achieve very high viral loads, leading to progression to AIDS within three years after initial infection. This dramatically accelerated disease progression indicates that CRF19_cpx may be the most aggressive CRF detected so far. CRF19_cpx is a recombinant form of the HIV-1 subtypes A, D and G. Interestingly, CRF19_cpx is subtype D, with regards to its protease, the subtype associated to faster disease progression [6]. Using in silico estimations, Kouri et al. described that this protease has a very high fitness. CRF19_cpx is subtype A with regards to the envelope, the subtype associated to slower disease progression [6], questioning the role of env in the transmissibility of disease progression. CRF19_cpx uses the CXCR4 co-receptor early on for its entry mechanism into the patient’s cells which is consistent with accelerated disease progression [7], whereas subtype A is known to mainly use CCR5. Higher levels of chemokine RANTES were found in CRF19_cpx infected patients and this was correlated with higher viral load [10]. Chemokines RANTES, CCL3 and CCL4 are the natural ligands of CCR5 and block virus entry through the CCR5 co-receptor. These chemokines have been shown to protect against CCR5 co-receptor using HIV-1 variants, but not against CXCR4 using variants [11]. Bayesian network analysis allowed investigation of the relationship between the variables and together with other information Kouri et al hypothesized that efficient HIV CRF19_cpx replication, potentially driven by an evolutionary fit protease, is putting a heavy burden on the immune system making the host prone to co-infection and high RANTES host defense response. This in turn blocks HIV entry through the CCR5 co-receptor, forcing viral escape by using the CXCR4 co-receptor for cell entry, and subsequent accelerated disease progression. The results from this study would thus support the argument that protease may be a contributing gene to the transmissibility of disease progression.

In another publication this year, the relationship between HIV-1 replicative capacity, gag sequence, immune activation and disease progression was investigated [12]. The authors demonstrated that patients infected with HIV-1 variants with gag sequences that contributed to a higher replicative capacity exhibited a significantly higher immune activation and a faster drop of CD4 levels than patients infected with HIV-1 variants with a lower replicative capacity. While the focus of this report was on Gag [12], it would be interesting to also verify the fitness of protease in these patients, since it is known that gag and protease are co-evolving genes [13].

High HIV-1 replication itself is known to exhaust the host immune response [14]. Co-infections exacerbate this phenomenon by promoting a vicious cycle of increasing the stress on the immune system, increasing HIV-1 replication, inducing immune response exhaustion, resulting in further co-infections and faster disease progression. In the study by Kouri et al [7] oral candidiasis co-infection was identified as a risk factor for fast progression associated only with CRF19_cpx infection. This vicious cycle mechanism of co-infection and virus replication has been confirmed recently in
a study of 717 untreated participants led by the SWISS Cohort [15]. The authors demonstrated that sCD14 (a marker of LPS bioactivity) is significantly associated with both I-FABP (a marker of gastrointestinal disruption) and viral load, reinforcing the role of microbial translocation in the pathogenesis of untreated HIV-1 infection.

HIV-1 is considered a major public health problem. While antiretroviral therapy contributes significantly to keeping infected individuals in a healthy state, a considerable percentage of patients still progress to AIDS. The high viral replicative capacity associated with sustained and uncontrolled immune activation makes aggressive HIV-1 variants a real threat to the control of the global epidemic of HIV-1. The rapid deterioration in health status of patients infected with aggressive HIV strains can put individuals at risk of death even before they are aware of their HIV infection. Here we summarized the potential role of various HIV-1 genes (gag, pol and env) in disease progression and its transmissibility, strengthening the need of future viral whole-genome studies associated with a systems immunology approach of the host. Only the understanding of the fine-tuning between virus replicative mechanisms and immune activation might put a damper on disease progression, which does occur albeit slowly even in HAART responders.

Disclosure

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