Transcriptomic Approach Predicts Tempo of Disease Progression in HIV-1 Infections

Yi-Wei Tang1,2*

Clinical laboratories perform various tests to determine the HIV-1 infection status of patients, to evaluate the progression of disease, and to monitor the effectiveness of antiretroviral therapy. The pathogenesis of HIV-1–infected patients includes a rapid-progression subset that represents 10%–15% of the HIV-1–positive population (1). Identifying biomarkers that distinguish these rapid progressors (RPs)3 from chronic progressors (CPs) is critical for early clinical intervention (2). A number of biomarkers, including levels of CD4+ T cells, have been used to predict HIV-1 disease progression (2, 3). Moreover, certain host genetic and immunologic markers that have been revealed by the human genome programs are now being used beyond monitoring viral pathogens to help manage HIV-1 infections (3, 4). There is ample evidence that allele frequencies and relative hazard values of the Δ32 polymorphism of C-C chemokine receptor 5 (CCR5), the CCR5 promoter polymorphism P1, the 64I polymorphism of C-C chemokine receptor 2 (CCR2), T-cell receptor excision circles, Toll-like receptors 4 and 9, interleukin-1 receptor α, and HLA homozygosity produce divergent patterns of progression to AIDS after infection (3–6).

In addition to these viral, genetic, and immunologic biomarkers, host transcriptomic biomarkers, including mRNAs and microRNAs (miRNAs), in patients with early HIV-1 infections appear to be useful for distinguishing RPs from CPs, according to a report in this issue of Clinical Chemistry (7). Zhang et al. from China Medical University and Duke University Medical Center used microarray techniques to analyze host miRNA-production profiles in peripheral blood mononuclear cells of RPs and CPs and noted decreased production of a series of miRNA molecules that affect proapoptotic pathways. Decreased production of a panel of 5 host miRNAs (miR-31, miR-200C, miR-99a, miR-503, and miR-526) was associated with rapid disease progression with a 94% predictive value (7).

The first miRNA to be described, lin-4, was inadvertently discovered in 1993 (8); however, the identification in 2000 of the miRNA let-7 and its ability to regulate lin-14 established this new class of regulatory nucleic acids and its potential value for disease diagnosis (9, 10). Recently, miRNAs were noted to play a crucial role in the host’s cellular response to viral infections (9, 11, 12). In HIV-1 infections, most host miRNAs with altered production are downregulated. In addition, host miRNA profiles have been shown to contribute to distinct clinical outcomes (7). These unique characteristics of circulating host miRNAs may provide alternative biomarkers for supplemental use in the diagnosis and prognosis of HIV-1 infections.

As pursued by the authors in their study, microarray-based techniques have proved useful for profiling miRNA production (7, 9, 13). Moreover, quantitative real-time PCR (qPCR) methods have demonstrated high sensitivity and specificity with their ability to accurately detect and quantify miRNAs in a given sample (11). This method has a considerably larger dynamic range than microarray analysis. qPCR has been adapted for increased throughput via the development of miRNA PCR arrays that can detect hundreds of miRNAs at once in a single reaction tube (11, 14). The precision of miRNA analyses will be greatly improved with the added resolution of the RNA-Seq approach, using next-generation sequencing technologies for transcriptome profiling (15).

Findings from this study have identified a distinct transcriptomic signature in peripheral blood mononuclear cells of RPs that should provide novel insights into the pathogenesis of HIV-1 infections. More importantly to the readers of Clinical Chemistry, the 5-miRNA panel discovered in this study opens up a new approach to the diagnosis of HIV-1 infections in clinical laboratories and evaluating the prognosis for HIV-1 infection. Although the results are promising, it is worth mentioning that the current study investigated only a relatively small number of highly selected HIV-1–infected patients, with CD4+ cell counts at approximately 120 days after infection being the main effector. A large, multicenter cohort study with a longer follow-up that focuses on clinical outcomes will be needed to address these variables. Technically, the
HIV-1 specificity remains uncertain when host miRNA molecules alone are used as biomarkers, because miRNAs are constantly regulated in various diseases and milieus. The best choice is likely to be a panel of miRNA molecules used in combination with other viral, genetic, and immunologic biomarkers. An integrated approach involving various techniques and disciplines would potentially be the most useful for rapid and accurate assessment of HIV-1 disease progression and prognosis.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

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