T-cell receptor excision circles (TREC) and maintenance of long-term non-progression status in HIV-1 infection

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T-cell receptor excision circles (TREC) in peripheral blood mononuclear cells (PBMC) were evaluated in the Genetic Resistance to Human Immunodeficiency Virus cohort of HIV-1-seropositive non-progressors (NP). After a short follow-up, NP were sub-grouped as stable (NP-S), or with signs of disease progression (NP-P). Initial TREC were higher in NP-S compared to NP-P (P = 0.002), even after adjusting for CD4 and CD8 T-cell counts and viral load (P = 0.048), but not p24 antigenemia (P = 0.076). Higher initial TREC were 100% predictive of the maintenance of non-progression status during follow-up.

The development of quantitative competitive polymerase chain reaction (QC-PCR) assays to detect epiposomes from T-cell receptor (TCR) gene rearrangement [1] was originally described as a means of quantitating recent thymic emigrants [2]. Reduced T-cell receptor excision circles (TREC) in HIV-1 infection and their rebound with highly active antiretroviral therapy [3], however, reflect a balance between the production, proliferation, redistribution and elimination of circulating T cells that have recently undergone TCR rearrangement or few cell divisions since TCR rearrangement [2]. The decrease in TREC in HIV-1-infected adults is now thought largely to reflect cellular proliferation and death caused by viral immune activation [3]. It is also possible that reduced thymic output and increased proliferation are not mutually exclusive causes of the TREC decline in HIV infection [4,5].

Despite debate concerning the mechanism underlying the decrease in TREC in HIV-1 infection, the potential utility of TREC as a surrogate marker for evaluating the risk of disease progression and AIDS in HIV-1-infected individuals has been suggested [6,7]. In the studies described here, we measured TREC by QC-PCR [2] in the Genetic Resistance to Human Immunodeficiency Virus (GRIV) cohort, comprised solely of serum and peripheral blood mononuclear cell (PBMC) DNA samples from HIV-1-seropositive long-term non-progressors (NP) naive to antiretroviral therapy, and fast progressors (FP) [8]. On the basis of information obtained during a brief follow-up period (median 20 months), NP were sub-grouped into those maintaining non-progression status and therefore stable (NP-S), and those showing signs of disease progression (NP-P). Initial TREC (prior to follow-up) were compared between the NP sub-groups and FP by analysis of variance (ANOVA) and by covariance (ANCOVA) with CD4 and CD8 T-cell counts, p24 antigenemia and viral load as covariates. P values are reported on an adjusted scale with significance set at α = 0.05 after Bonferroni's correction for multiple comparisons (SPSS 10.0; SPSS Inc., Chicago, IL, USA).

TREC were reduced in HIV-1-seropositive NP and FP compared to seronegative individuals (Fig. 1; P < 0.0005) as reported by others [2-4,9]. By ANOVA, initial TREC (before follow-up) were higher in NP-S (stable during subsequent follow-up) compared to both unstable NP-P (P = 0.02) and FP (P = 0.025), in agreement with a previous report correlating higher TREC with a decreased risk of progression [6]. TREC in PBMC have previously been demonstrated to correlate with CD4 and CD8 T-cell subsets, including naive subsets [10,11], and to correlate inversely with activation status [3,11]. To determine if the difference in TREC between NP-S and NP-P was secondary to differences in lymphocyte counts, TREC were compared after adjusting for CD4 and CD8 T-cell counts by ANCOVA. Adjusted TREC remained higher in NP-S relative to NP-P (P = 0.023); in contrast, TREC were no longer significantly different in FP. Presumably, reduced TREC in FP largely reflects lower CD4 T-cell counts, although this does not appear to be the main explanation for lower TREC in NP-P. Other confounding factors of TREC in FP include the effect of antiretroviral therapy [2] in some FP (but not NP), and the much shorter duration of infection compared with NP (< 3 versus > 8 years; NP median = 11 years) [8]. After including p24 antigenemia as a covariate in ANCOVA, the difference in TREC between NP-S and NP-P was no longer significant, although a trend was present (P = 0.076). However, the difference in TREC between NP-S and NP-P was significant using viral load as a covariate in ANCOVA (P = 0.048) instead of p24 antigenemia. The difference in TREC between NP-S and NP-P may be due to immune activation status [3], although other mechanisms may also contribute [4,5]. Several previously identified correlates of TREC were observed in NP-S, such as the duration of infection and CD4 T-cell counts [2,3]. TREC was inversely related to p24 antigenemia across the GRIV cohort as a whole. Median ages were similar for all groups.
Because higher TREC were associated with stable long-term non-progression in HIV-1 infection, the predictive value of initial TREC in the maintenance of non-progression status during subsequent follow-up was estimated. TREC above the lower 95% confidence limit for the mean of the NP group (634 mol/μg) were designated high, and those below were considered low (Fig. 1). High TREC in NP-S were treated as true positives; low TREC in NP-P were true negatives. The predictive value of higher TREC for the maintenance of long-term non-progression status during subsequent follow-up (median 20 months) was 100% (NP-S). The predictive value of lower TREC for progression was only 25.5%, comparable to CD4 T-cell count (26.4%), p24 antigenemia (22.7%) and viral load (21.7%).

Although lower TREC did not rule out continued non-progression in NP, at least during the short follow-up period, longer prospective studies may appear to support the prognostic value of lower TREC for the risk of disease progression. It is possible that more NP with lower TREC would be re-classified as unstable (NP-P) with a longer follow-up.

The GRIV cohort is a collection of serum and PBMC DNA samples established to identify immune responses and genetic polymorphisms associated with long-term non-progression in HIV-1 infection. Unfortunately, because of the nature of the GRIV cohort, it is not possible to evaluate TREC in T-cell subsets or to adjust for differences in immune activation or proliferation using markers such as HLA-DR/CD38 or Ki67, respectively. TREC in PBMC may not be as accurate a marker as TREC in T-cell subsets, as a result of the presence of varying percentages of non-T-cells. Similarly, TREC are substantially influenced by immune activation and proliferation [3]. We were able, however, to adjust for CD4 and CD8 T-cell counts, p24 antigenemia and viral load by ANCOVA. The difference in TREC between stable NP-S and unstable NP-P is not solely caused by differences in CD4 and CD8 T-cell counts, although it may primarily reflect differences in immune activation status and proliferation. Regardless of the mechanism(s) responsible for the decline of TREC in HIV-1 infection, TREC in PBMC may be a useful surrogate marker for...
predicting the likelihood of continued clinical stability.

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