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Genetically restricted HIV-1 sub populations are associated with and migrate within metastatic sites of AIDS-related lymphoma

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Background

AIDS-Related Lymphoma (ARL) is a disease mediated in part by HIV-infected macrophages and persists despite current HIV therapy protocols. The primary difference between lymphoma seen in non HIV-infected individuals and ARL is that ARL is uniformly high grade and widely metastatic. This fact, coupled with finding almost 50 percent of tumors have HIV expressing macrophages, has created interest in studying a potential viral component to lymphoma evolution. The expansion of HIV quasispecies *in vivo*, which can be evaluated using a variety of computational algorithms, allows precise assignment of viral evolutionary relationships when applied to sequences obtained from multiple sites of infection. In this study, we used an advanced HIV phylodynamic approach to track the evolution of ARL metastasis in a multisite autopsy study and identified a significant relationship between HIV dynamics and lymphoma progression.

Methods

Multi-site frozen autopsy specimens were obtained through the AIDS and Cancer Specimen Resource (ACSR) from patients who died with ARL. A variety of lymphoid and non-lymphoid tissues were classified as abnormal or normal by histology examination and stained with antibodies to CD68, MAC 387 and HIV p24. Quantitative HIV genetic studies qualified diseased and non diseased tissues to having > 1 copy of HIV/2000 genomic equivalents for further genetic analyses. We extracted 406 HIV-1 genomes, spanning the 3' *env-LTR* segment of HIV that were sequenced from multiple sites from two multi-site autopsies. Viral dynamic analyses included phylogeny, migration assessment, population growth and selection studies using advanced bioinformatics methodologies.

Results

Detailed phylogenetic analysis clearly showed distinct subpopulations of tumor and non-tumor viruses with lymph node viruses moving between both groups. Gene flow analysis showed that viruses from normal tissues rarely migrated to lymphoma tissues ($p < 0.0001$). This evidence strongly indicates a relationship between specific HIV genetic variants and the development of tumors. Additionally, a 10-fold faster evolution of viruses was found within lymphoma tissues as compared to normal tissues (median effective viral population in lymphoma tissue = 60,000 compared to 6,000 in normal tissue) and up to a four-fold increase in purifying selection in lymphoma viruses indicated that the lymphoma virus was both fast replicating and genetically stable (non-tumor dN/dS = 1.23 compared to tumor dN/dS = 0.26).

Conclusion

The results strongly support the existence of a fast replicating lymphoma-related virus, distinct from other circulating viruses in two patients who died with metastatic ARL. The positive selection of viral sequences in one of the cases suggests a non-random association of a lymphoma

specific viral element within viruses associated with tumor metastasis. Earlier studies that localized HIV to tumor associated macrophages suggests that this viral evolution is relatively specific for a macrophage pool of viruses and hence might be relatively resistant to current HAART therapies dedicated at blocking primary infection rather than eradicating macrophage associated infection. These data suggest the addition of drugs that target infected macrophages may influence the evolution of ARL. Sequences that cluster with ARL versus non tumor sites within these two individuals are currently being evaluated to test whether a true lymphoma virus might evolve in the context of ARL lymphomagenesis.