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High resolution profiling of DNA copy number and gene expression changes in AIDS-related lymphoma

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The incidence of B cell non-Hodgkin lymphoma (NHL) is increased substantially in the HIV-1-infected immunosuppressed population. Clinically, AIDS-related lymphoma (ARL) is more aggressive and has a worse prognosis than in non-immunocompromised patients, though there has been significant improvement in the post-HAART era. While HIV-induced immunosuppression, chronic antigenic stimulation, and cytokine overproduction may contribute to differences in disease progression and outcome, distinct genetic changes in ARL may also mediate these effects. Chromosomal DNA copy number alterations are known to play a major role in lymphomagenesis and have been studied in non immunocompromised patients for some NHLs.

To determine whether ARL has distinct molecular features and pathogenetic mechanisms, we assessed genome-wide copy number changes and gene expression profiles using 24 HIV+ cases with B cell NHL obtained from the AIDS and Cancer Specimen Resource (ACSR). High resolution aCGH was performed using the 250 K NspI SNP platform (Affymetrix). Selecting for frequent aberrations present in >20 percent of the cases, 43 chromosomal gains and 30 chromosomal losses were identified. Many of these regions replicated copy number changes previously reported for high-grade B cell NHL, including: gains of X, 12, 11q, 8q, 2p16.1, 9p11.2, 17q21, and 3p; and losses of 1p36, 4q23, 9p21.3, 13q34, and 17q23. The aberrant regions ranged in size from 12 kb to 6.5 Mb, providing concise boundaries for these intervals, which harbor a relatively small number of genes. Several novel recurrent regions were also identified, including a loss of 7q21.2–q22.1, and gains of 4p16.1, 15q11.2, and 19p13.2. To identify coordinate changes in gene expression associated with the chromosomal aberrations, gene expression profiles were generated using the Human Genome U133 Plus 2.0 Array (Affymetrix). This approach identified specific candidate genes for these intervals that may contribute to ARL pathogenesis. Gene expression profiles were also used to cluster the ARL cases. Gene signatures that reliably distinguish activated B-cell (ABC) like Diffuse Large B Cell Lymphoma (DLBCL), germinal center B-cell (GCB) like DLBCL and Burkitt lymphoma (BL), were applied to the ARL gene expression profiles.

The ARL samples showed no correlation with the BL gene signature. In contrast, the ABC and GCB gene signatures divided the ARL samples into two distinct groups with either a predominantly ABC- or GCB-type expression. Assigning ABC and GCB phenotypes to these groups of samples, Goeman's global test found a highly significant association (p = 0.00012) of the ABC and GCB phenotypes with the DLBCL ABC and GCB predictor gene set. The classification of AIDS-related DLBCLs into distinct ABC and GCB groups has significant implications given the differences in pathogenesis, biology, and survival for these two subtypes of DLBCL.