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HTLV-I infection of Humanized SCID mice recapitulates Adult T-cell Leukemia/Lymphoma (ATLL) development

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Human T-lymphotropic virus type-1 (HTLV-1) is the etiologic agent of Adult T-cell leukemia/lymphoma (ATLL), an aggressive $CD4^+/CD25^+$T cell malignancy. The early molecular events induced by HTLV-1 infection as well as the role of various viral genes in the induction of leukemia remain unclear, predominantly due to the lack of an animal model that recapitulates ATLL development. We have previously demonstrated that HTLV-1 is capable of infecting human hematopoietic progenitor and stem cells ($CD34^+$HP/HSCs) and that infection of $CD34^+$HPCs has dramatically different biological effects in comparison to infection of mature T lymphocytes. To determine if HTLV-1 infection of $CD34^+$HP/HSCs recapitulates leukemogenesis *in vivo*, human hematopoiesis was reconstituted in NOD/SCID mice by injection of human $CD34^+$HPCs infected *ex vivo* with HTLV-1. Humanized NOD/SCID (HU-SCID) mice infected with HTLV-1 (HTLV-1-HU-SCID) consistently developed $CD4^+CD25^+$T cell lymphomas with clinical characteristics associated with ATLL at ~10 weeks post-reconstitution and show significantly elevated levels of HTLV-1 infected human $CD4^+$T cells in the thymus, mesenteric lymph node, spleen and peripheral blood. Lymphoma cells successfully engrafted in naïve NOD/SCID mice when injected into the peritoneal cavity and maintain the expression of viral proteins, $gp46^{env}$ and $p19^{gag}$. Moreover these infected mice showed hyperproliferation of infected human stem cells ($CD34^+CD38^-$) in the bone marrow suggesting that HP/HSCs represents viral reservoir target cells which maintain HTLV-1 infection for extended periods of time *in vivo*. We speculate that HTLV-1 infection of hematopoietic stem cells establishes a virally-infected "cancer stem cell" which subsequently gives rise ATL in patients. Notably, $CD34^+$HPCs isolated from HTLV-1 infected patient PBL demonstrate proviral integrations, suggesting that these cells harbor infection in humans. $CD34^+$HPCs transduced with a lentivirus vector expressing the HTLV-1 Tax gene (Tax1) also results in $CD4^+/CD25^+$T cell leukemia/lymphoma in HU-SCID mice, suggesting that Tax1 expression is sufficient for lymphomagenesis. HTLV-1 infection of humanized NOD/SCID mice represents a novel *in vivo* model which recapitulates viral lymphomagenesis and provides a compelling system to investigate and characterize molecular events in human stem cells in the initiation and progression to ATLL.