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Poster presentation

Modeling HTLV-lymphomagenesis: immune activation induces immortalization and leukemogenicity of HTLV-I LTR-Tax transgenic CD4+T-cells

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Background

Infection with the human T-cell leukemia virus-1 (HTLV-1) results in a variety of diseases including adult T-cell leukemia/lymphoma (ATL). The pathogenesis of these disorders is poorly understood, however involves complex interactions with the host immune system. Previous studies from our laboratory and others have suggested that immune activation of infected T-cells increases the expression of the oncogenic HTLV-1 Tax transactivator protein from integrated HTLV-1 proviruses [1]. Thus, we have hypothesized that immune activation of infected T-cells may play an important role in disease pathogenesis through Tax induction, leading to increased proliferation of infected cells. To study this hypothesis, we employed transgenic mice in which Tax is regulated by the HTLV-1 LTR. These mice were previously shown to develop neurofibromas, but do not express Tax in T cells and do not develop lymphomas [2].

Results

A single round of T-cell receptor-stimulation of transgenic mouse LTR-Tax CD4+T-cells induced Tax expression, hyperproliferation, and immortalization in culture. The transition to cellular immortalization was accompanied by markedly increased expression of the anti-apoptotic gene, *mcl-1*, previously implicated as important in T-cell survival. Immortalized cells exhibited a $CD4^+CD25^+CD3^-$ phenotype commonly observed in ATL. Engraftment of immune-activated LTR-Tax CD4+T-cells into NOD/Shi-scid/IL-2Rγ null mice resulted in a leukemia-like phenotype with expansion and tissue infiltration of Tax+, CD4+lymphocytes. Furthermore, immune activated Tax CD4+ T-cells express CD4+ cell subset characteristics of several different CD4+ T-cell subtypes, including Th1, Th2, and Th17 cells, suggesting that HTLV-1 Tax induces changes in the normal pattern of CD4+ subtype specification. On-going studies are also employing retroviral-mediated, insertional mutagenesis to identify cellular genes that may collaborate with Tax in the induction of T-cell lymphomas in the HTLV-1 LTR-Tax transgenic mice.

Conclusion

Immune activation of infected CD4+T-cells results in the induction of Tax expression in CD4+cells from LTR-Tax transgenic mice as well as in infected human CD4+T-cells. This may lead to T-cell proliferation, additional genetic alterations, cellular immortalization and pathogenesis of HTLV-1-asssociated diseases including ATL in infected individuals.

References

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