Multistep mechanism of adult-T cell leukemia (ATL) development from HTLV-1 infection

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ABSTRACT

Adult T-cell leukemia (ATL) is an intractable malignancy of CD4+ T cells that is etiologically associated with infection by human T-cell leukemia virus-type I (HTLV-1). ATLL is developed in a few percentages of HTLV-1 carriers extremely longer periods after HTLV-1 infection. Since several additional genetic or epigenetic factors should be involved in the development of ATLL, we performed integrative genomic analysis of acute-type ATLL to find several clusters of translocational breakpoints. Recently, we isolated TCF8/ZEB1 (chr. 10p11), NDRG2 (chr. 14q11), BCL11B (chr. 14q32) as candidate suppressors or oncogenes adjacent to the cluster region of the chromosomal breakpoints, and found an adhesion molecule, CADM1 (TSLC1, IgSF4) as a novel surface marker of ATLL by comprehensive gene expression profiles. ZEB1 downregulation in ATLL is related to the resistance to TGFβ signaling with Smad7 overexpression and downregulation of NDRG2 in ATL is related to constitutive active of PI3K/AKT and NF-κB signaling pathways. After HTLV-1 infection in CD4+ lymphocytes, the infected T cells were under inflammation reaction with activation of PI3K/Akt and NF-κB signaling pathways; however, the inflammation reaction may enhance DNA methylation in many regions to inactive important genes including NDRG2. Since the downregulated NDRG2 could not suppressed the excessive activation of PI3K/AKT and NF-κB signaling pathways, cell growth advantages may enhance genetic and epigenetic abnormalities after HTLV-1 infection. Moreover, since the target genes of Tax and/or HBZ might be became targets of their genomic abnormalities in ATLL cells again, suggesting that the initial HTLV-1 infection might be involved in genetic and epigenetic abnormalities of ATLL throughout the ATLL development.

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