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Oral presentation

Post-translational modifications of the Tax oncoprotein of human T-cell leukemia virus control cytoplasmic and nuclear steps in Tax-mediated activation of the NF-κB pathway

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Background

The transcription factor NF-κB is critical for induction of cancer, including adult T-cell leukemia, which is linked to infection by human T-cell leukemia virus type 1 (HTLV-1) and expression of its regulatory protein Tax. HTLV-1-mediated immortalization of T lymphocytes, a basic event for subsequent cell transformation, results mainly from the ability of Tax to trigger T-cell proliferation through various mechanisms including activation of specific cellular genes via the NF-κB pathway, promotion of cell cycle progression and deregulation of apoptosis.

Methods

A series of Tax mutants with substitutions of serine or lysine residues were analyzed by two dimensional gel electrophoresis for the identification of the various modified forms of Tax. The intracellular localization of each mutant and its colocalization with cellular factors such as the RelA subunit of NF-κB and the p300 transcriptional coactivator were analyzed by laser scanning confocal microscopy. The ability of these mutants to activate gene expression via the NF-κB pathway was also analyzed by dual luciferase reporter assay.

Results

We observed that Tax was modified by ubiquitination, sumoylation and acetylation in a phosphorylation-dependent manner and that these post-translational modifications were instrumental to Tax-mediated activation of the NF-κB pathway. In the cytoplasm, ubiquitinated Tax molecules activated the IκB kinase complexes leading to the translocation of the RelA subunit of NF-κB into the nucleus. Phosphorylation-dependent translocation of Tax into the nucleus lead to Tax sumoylation, a modification critical for the assembly of Tax-containing nuclear bodies and for the recruitment of the RelA subunit of NF-κB and the transcriptional coactivator p300 in these nuclear structures. These nuclear bodies also included a form of Tax, which was acetylated by p300 on a lysine located in its carboxy-terminal domain. Our results indicate that the four modifications act in concert to implement sequential steps of the Tax-mediated NF-κB activation cascade.

Conclusion

We conclude that a hierarchical sequence of post-translational modifications create populations of Tax molecules having different intracellular localizations and interacting partners and exhibiting different functions in the transcriptional properties of this viral oncoprotein.