



MEETING ABSTRACT

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NF- κ B hyper-activation by HTLV-1 Tax induces cellular senescence, but can be alleviated by the viral anti-sense protein HBZ

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Activation of I- κ B kinases (IKKs) and NF- κ B by the human T lymphotropic virus type 1

(HTLV-1) trans-activator/oncoprotein, Tax, is thought to promote cell proliferation and transformation. Paradoxically, expression of Tax in most cells leads to drastic up-regulation of cyclin-dependent kinase inhibitors, p21CIP1/WAF1 and p27KIP1, which cause p53-/pRb-independent cellular senescence. Here we demonstrate that p21CIP1/WAF1-/p27KIP1-mediated senescence constitutes a checkpoint against IKK/NF- κ B hyper-activation. Senescence induction by Tax is attenuated by mutations in Tax that reduce IKK/NF- κ B activation and prevented by blocking NF- κ B using a degradation-resistant mutant of I- κ B α despite constitutive IKK activation. Small hairpin RNA-mediated knockdown indicates that RelA induces this senescence program by acting upstream of the anaphase promoting complex and RelB to stabilize p27KIP1 protein and p21CIP1/WAF1 mRNA respectively. Finally, we show that downregulation of NF- κ B by the HTLV-1 anti-sense protein, HBZ, delay or prevent the onset of Tax-induced senescence. We propose that the balance between Tax and HBZ expression determines the outcome of HTLV-1 infection. Robust HTLV-1 replication and elevated Tax expression drive IKK/NF- κ B hyperactivation and trigger senescence. HBZ, however, modulates Tax-mediated viral replication and NF- κ B activation, thus allowing HTLV-1-infected cells to proliferate, persist, and evolve. Finally, inactivation of the senescence checkpoint can facilitate persistent NF- κ B activation and leukemogenesis.

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