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

Huijun Zhi[1], Liangpeng Yang[1], Yu-Liang Kuo[1], Yik-Khuan Ho[1], Hsiu-Ming Shih[2], Chou-Zen Giam[1*]

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Activation of I-κB kinases (IKKs) and NF-κB by the human T lymphotrpic 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-κB hyper-activation. Senescence induction by Tax is attenuated by mutations in Tax that reduce IKK/NF-κB activation and prevented by blocking NF-κB using a degradation-resistant mutant of I-κBα 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-κB 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-κB hyperactivation and trigger senescence. HBZ, however, modulates Tax-mediated viral replication and NF-κB activation, thus allowing HTLV-1-infected cells to proliferate, persist, and evolve. Finally, inactivation of the senescence checkpoint can facilitate persistent NF-κB activation and leukemogenesis.

* Correspondence: cgiam@usuhs.mil
[1]Department of Microbiology and Immunology Uniformed Services, University of the Health Sciences, Bethesda, MD, 20814, USA
Full list of author information is available at the end of the article

Author details
[1]Department of Microbiology and Immunology Uniformed Services, University of the Health Sciences, Bethesda, MD, 20814, USA. [2]Institute of Biomedical Sciences, Academia Sinica, Taipei, 115, Taiwan.

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