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MEETING ABSTRACT Open Access

Coordination of the canonical and noncanonical IKK/NF-κB signaling pathways in HTLV-I Tax-mediated tumorigenesis

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Although the mechanisms by which the HTLV-I Tax oncoprotein activates the two NF-κB signaling pathways have been well studied, there is still no convincing evidence demonstrating a functional role for NF-κB in the Tax-mediated tumorigenesis or HTLV-I-mediated adult T-cell leukemia/lymphoma (ATL). Moreover, how Tax is negatively regulated by cellular factors has not yet been explored. Using various transgenic mice and cells deficient in different key IKK/NF-κB signaling components, we have defined the differential but cooperative roles of the canonical and noncanonical NF-κB pathways in Tax-mediated tumorigenesis. One function of non-canonical NF-κB activation is to repress expression of the wwox tumor suppressor gene, which in turn facilitates Tax-induced canonical NF-κB activation. Mechanistic studies indicate that WWOX blocks Tax-induced IKKalpha recruitment and subsequent RelA phosphorylation. Furthermore, we have identified PDLIM2, an essential terminator of canonical NF-κB activation, as a negative regulator of Tax. PDLIM2 directly binds to and shuttles Tax from its activation sites to the nuclear matrix for ubiquitination-mediated degradation, thereby suppressing the tumorigenicities of HTLV-I- or Tax-transduced cells. Interestingly, PDLIM2 expression is epigenetically downregulated in HTLV-I-transformed T cells and primary ATL cells. These studies suggest that the counterbalance between PDLIM2 and HTLV-I may determine the ATL leukemogenesis and provide the first line of genetic evidence demonstrating the functional significance of NF-κB in Tax-mediated tumorigenesis. These studies also define, for the first time, a delicate cooperation of the two pro-oncogenic NF-κB pathways in tumorigenesis and a functional role of the WWOX tumor suppressor in NF-κB regulation and viral tumorigenesis.

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