論 文 要 旨

RLTPR Q575E: A novel recurrent gain-of-function mutation in patients with adult T-cell leukemia/lymphoma

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Abstract

Objectives: Adult T-cell leukemia/lymphoma (ATL) is an intractable T-cell malignancy caused by long-term infection with human T-cell leukemia virus type-1 (HTLV-1). While ATL pathogenesis has been associated with HTLV-1-derived oncogenic proteins, including Tax and HBZ, the contribution of genomic aberrations remains poorly defined.

Methods: To elucidate the genomic basis of ATL, whole exome sequencing was performed on cells from 47 patients with aggressive ATL.

Results: We discovered the novel mutation *RLTPR* Q575E in four patients (8.5 %) with a median variant allele frequency of 0.52 (range 0.11–0.68). Despite being reported in cutaneous T-cell lymphoma, three ATL patients carrying *RLTPR* Q575E lacked skin involvement. Patients carrying *RLTPR* Q575E also harbored *CARD11* (75 %), *PLCG1* (25 %), *PRKCB* (25 %), or *IKBKB* (25 %) mutations related to TCR/NF-κB signaling. Jurkat cells transfected with *RLTPR* Q575E cDNA displayed increased NF-κB activity, and significantly increased IL-2 mRNA levels under stimulation. RLTPR Q575E increased the interaction between RLTPR and CARD11, while RLTPR directly interacted with Tax.

Conclusions: We identified, and functionally validated, a novel gain-of-function mutation in patients with aggressive ATL. During TCR activation by Tax or gain-of-function mutations, *RLTPR* Q575E selectively upregulates NF-κB signaling and may exert oncogenic effects on ATL pathogenesis.