

1: [Leukemia](#). 2007 Aug;21(8):1669-78. Epub 2007 Jun 7.

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Impairment of Na(+),K(+)-ATPase in CD95(APO-1)-induced human T-cell leukemia cell apoptosis mediated by glutathione depletion and generation of hydrogen peroxide.

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Human T-cell leukemia is a malignant disease that needs various regimens of cytotoxic chemotherapy to overcome drug resistance. Recently, Na(+),K(+)-ATPase has emerged as a potential target for cancer therapy. However, its exact signaling pathway in human T-cell leukemia cell death has not been well defined. In the current study, we found CD95(APO-1) was able to trigger the internalization of plasma membrane Na(+),K(+)-ATPase in Jurkat cells or primary T cells as a mechanism to suppress its activity. **This internalization was closely relevant to intracellular glutathione (GSH) depletion in Jurkat cells downstream of Fas-associated death domain protein (FADD) and caspase 8. GSH depletion in Fas L-treated Jurkat cells induced the generation of hydrogen peroxide (H(2)O(2)), which subsequently increased the serine phosphorylation of Na(+),K(+)-ATPase alpha1 subunit.** Exogenous H(2)O(2) even mimicked the effect of Fas L to upregulate the serine phosphorylation of Na(+),K(+)-ATPase alpha1 subunit and suppress Na(+),K(+)-ATPase activity. Overall, our results indicate that CD95(APO-1) induces the FADD- and caspase 8-dependent internalization of Na(+),K(+)-ATPase through intracellular GSH loss, and the subsequent generation of H(2)O(2)-mediated serine phosphorylation of Na(+),K(+)-ATPase alpha1 subunit. Taken together, this study presents a novel regulatory mechanism of Na(+),K(+)-ATPase in CD95(APO-1)-mediated human T-leukemia cell apoptosis.

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