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802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

AICAR Induces AMPK-Independent Cell Death in Adult T-Cell Leukemia/Lymphoma and Has Anti-Tumor Activity

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Introduction: Adult T-cell leukemia/lymphoma (ATL) is an aggressive T cell leukemia/lymphoma caused by human T-cell lymphotropic virus type I (HTLV-1) and has a poor outcome. Recently, we reported that AMPKα, the catalytic unit of AMP-activated protein kinase (AMPK), is highly expressed in cells from patients with ATL and that an AMPK inhibitor had anti-tumor activity in ATL mice [1]. On the other hand, acadesine or 5-aminoimidazole-4-carboxamide riboside (AICAR) is anAMPK activator, and was recently shown to have tumor suppressive effects on B cell chronic lymphocytic leukemia via the activation of AMPK. However, the effect of AICAR on the death of ATL-related cell lines is unknown. This study evaluated the effects of AICAR on death in ATL-related cell lines and its anti-tumor activity.
Results: We demonstrated that AICAR inhibited the proliferation of ATL-related cell lines (S1T, MT-1 and MT-2) but not non-HTLV-1-infected Jurkat cells and peripheral blood mononuclear cells from healthy individuals. However, AICAR did not increase the phosphorylation levels of AMPKα. We found that AICAR increased annexin V-positive cell numbers in the sub-G0/G1 phase, and decreased the mitochondrial membrane potential and caspase-3/8/9 activation, which are hallmarks of apoptosis. However, AICAR did not increase the phosphorylation levels of AMPKα. On the other hand, HTLV-1 Tax, an HTLV-1-encoded oncogenic factor, expression did not affect AICAR-induced cell death. Moreover, AICAR induced the expression of death receptors (DR) DR4 and DR5 *in vitro*. Furthermore, AICAR inhibited the growth and infiltration of S1T cells transplanted subcutaneously in NOD/SCID/gamma mice.
Conclusion: This is the first evidence to demonstrate the AMPK-independent effects of AICAR on death in ATL-related cell lines and its anti-tumor activity. Thus, AICAR might be a candidate for the treatment of ATL.
Disclosures : No relevant conflicts of interest to declare.
1. Aikawa A, Kozako T, Uchida Y, et al. Cell death induced by dorsomorphin in adult T-cell leukemia/lymphoma is AMPK-independent. *Febs j*. 2020;287(18):4005-4015.

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