Development of novel antitumor active drug for leukemia cells with simplified natural products

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T-cell derived acute lymphoblastic leukemia (T-ALL) is an aggressive type of leukemia with poor prognosis. We have identified two fungi-derived active compounds, 44D-L008 and 31D-F005, using high throughput screening (HTS). T-ALL-derived CCRF-CEM, but not Burkitt lymphoma-derived Raji, were killed in the presence of low concentrations of these compounds. 44D-L008 and 31D-F005 share a common chemical structure.

In this study, we synthesized several 44D-L008 and 31D-F005-related compounds and evaluated their anti-tumor activities in CCRF-CEM and Raji. we succeeded in synthesizing a compound Ra#61 that shows higher growth inhibitory activity on CCRF-CEM cells than identified natural compounds by HTS [1]. IC_{50} value of Ra#61 for CCRF-CEM was 68 nM. In addition, we performed similar tumor cell viability tests on another leukemia cell lines. We found that Ra#61 had the similar level of antitumor activity in HL-60, THP-1, and TF-1 as CCRF-CEM. To investigate whether Ra#61 induces apoptosis via an endogenous pathway, phenotypic changes of Ra#61 treated CCRF-CEM cells were examined. We found that mitochondrial membrane potential of CCRF-CEM was rapidly lost by Ra#61 treatment. In *in vivo* tests using immune-deficient mice transplanted with CCRF-CEM, Ra#61 showed a tumor growth-suppressing effect. In conclusion, Ra#61 is a novel anti-leukemia compound that is potentially effective not only for T-ALL but also for another type of leukemia.

1) Japanese Patent Application 2019-218270, “Pharmaceutical composition for the treatment of acute T lymphoblastic leukemia or lymphoma or acute myeloid leukemia”

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