SUMMARY OF Ph.D. DISSERTATION

School	Student Identification Number	SURNAME, First name MARIKO, Watanabe

Title

The application of NF-κB inhibitors to the treatment of lymphoid malignancies with constitutive NF-κB activity

Abstract

【Background】Conventional chemotherapies have contributed to the improved prognosis of the malignancies. However, the agents used in conventional chemotherapies inhibit the basic growth machinery of cells, such as DNA replication or the division of cells. Molecular targeted therapy is a new strategy to target molecules responsible for survival of malignant cells based on the understanding of their biological basis. Eventually, this process provides a treatment that is highly selective for malignant cells. We experienced successful precedence of this strategy in the treatment acute promyelocytic leukemia and chronic myelogenous leukemia. Thus, molecular targeted therapy strategies may give us a chance to overcome the resistance of aggressive malignancy against conventional chemotherapies.

【Purpose】DHMEQ is a novel NF-κB inhibitor, which was initially developed as a compound for rheumatoid arthritis. We examined the effects of DHMEQ on hematopoietic malignancies with strong constitutive NF-κB activation (multiple myeloma: MM, chronic lymphocytic leukemia; CLL, Hodgkin lymphoma: HL and adult T-cell leukemia/lymphoma: ATL) and discussed about the translation of NF-kB inhibition by DHMEQ into the treatment of malignancies.

【Results】 DHMEQ almost completely inhibited the constitutive NF-κB activity in MM, CLL, HL and ATL at 1 hour after DHMEQ treatment and reduced cell viability of these cells in a dose- and time-dependent manner. DHMEQ-mediated induction of apoptosis was accompanied with the activation of membranous and mitochondrial caspase pathway, which was triggered by reduced expression of Bcl-xL ans c-FLIP. We show that NF-κB is constitutively activated in the infected cells of HTLV-1 carriers and DHMEQ treatment reduced the virus load. DHMEQ enhanced the effect of topoisomerase inhibitors by blocking inducible NF-κB. DHMEQ did not show a significant toxic effect on PBMC and the mice.

【Conclusion】Constitutive NF-κB activity in MM, CLL, HL and ATL is a molecular target of DHMEQ. Apoptosis induction in these cells is accompanied with the activation of caspases. Enhanced cytotoxicity of topoisomerase inhibitors by DHMEQ indicates that inducible NF-κB is another molecular target of NF-κB inhibitors. The result may give us a possibility to develop more effective treatment and to overcome the resistance of malignant cells against conventional chemotherapy. Furthermore, purging of HTLV-1 infected cells from virus carriers by DHMEQ may provide a basis for the prevention ATL by intervention with a small molecular weight compound with a definite target molecule.