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THE FINE TUNING OF THE HEDGEHOG AND AUTOPHAGY PATHWAYS TO COMBAT ACUTE MYELOID LEUKEMIA

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GİRİŞ - AMAÇ

The Hedgehog (Hh) signaling pathway has been known to be an evolutionary conserved pathway, which is deregulated in several cancer types. Hh signaling pathway crosstalks with the other pathways among which is the PI3K/AKT/mTOR axes that has crucial role in the malignant cell proliferation, metabolism, differentiation, survival, motility and angiogenesis. In addition to these roles of PI3K/AKT/mTOR pathway, it is involved in the regulation of autophagy, which is an essential lysosomal degradation process for homeostasis. Depending on the cellular conditions and the tissue context, autophagy plays role in cancer whether preventing or triggering the tumor growth. These pathways have been shown to be deregulated in acute myeloid leukemia (AML), which is characterized by clonal expansion of immature progenitor cells and their infiltration into the bone marrow, peripheral blood and other tissues like spleen and liver. AML is an aggressive form of leukemia which has several molecular aberrations. Several studies indicated that autophagy has been used as survival and escape mechanism in AML. In this study, we aimed to study the crosstalk between Hh signaling pathway and the autophagy pathway and how affects the different AML cell lines.

METOD

For this purpose, we used CMK cell line as acute megakaryoblastic leukemia, MV4-11 and MOLM-13 as FLT3 mutant cell lines and NB4 as an acute promyelocytic leukemia and also, K562 as a control chronic myeloid leukemia. Initially, we checked the effects of the inhibition of Hh pathway on the survival and proliferation of AML cell lines using GANT61, Hh inhibitor, by performing MTT cell proliferation assay. Afterwards, we used different autophagy inhibitors to check how autophagy inhibition affects proliferation and survival of AML cells.

BULGULAR

After the treatment with autophagy inhibitors, which are NH4Cl, chloroquine, vinblastine and hydroxychloroquine and Hh inhibitor, GANT61, the proliferation of the different AML cell lines was shown to be decreased after 24, 48 and 72h incubation. All autophagy and Hh inhibitors decreased the proliferation of MOLM-13 cell line to 10%. Whereas GANT61 did not affect CMK and MV4-11 cells, autophagy inhibitors were observed to decrease proliferation of CMK cells compared to Hh inhibitor. We observed a 90-98 % decrease in the proliferation of NB4 cell line after autophagy inhibitors

treatment and 80% decrease of NB4 cell proliferation after Hh inhibitor treatment. K562 control cells were not affected by inhibitor treatment except for NH4Cl, compared to other cell lines. In the future, we are planning to study synergistic effects of autophagy and Hh inhibitors using IC50 and IC20 values, which will be determined through the proliferation test results.

SONUC

Although Hh signaling pathway has been known to be dispensable for regulation of normal adult hematopoiesis, it has been shown to be deregulated in some AML patients. According to this, targeting Hh signaling pathway alone might not sensitize AML cell lines to Hh inhibitors. Thus, we are planning to reveal how autophagy activation upon Hh inhibition controls this process. Using obtained data, we are going to study combination of Hh and autophagy inhibitors in order to observe synergistic effects of these inhibitors on AML.

ANAHTAR KELİMELER

Acute Myeloid Leukemia, Hedgehog, Autophagy, PI3K/AKT/mTOR, Combination therapy