Butein kills acute lymphoblastic leukemic cells in vitro and in vivo through FOXO3a and caspase-dependent apoptotic pathways

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Introduction

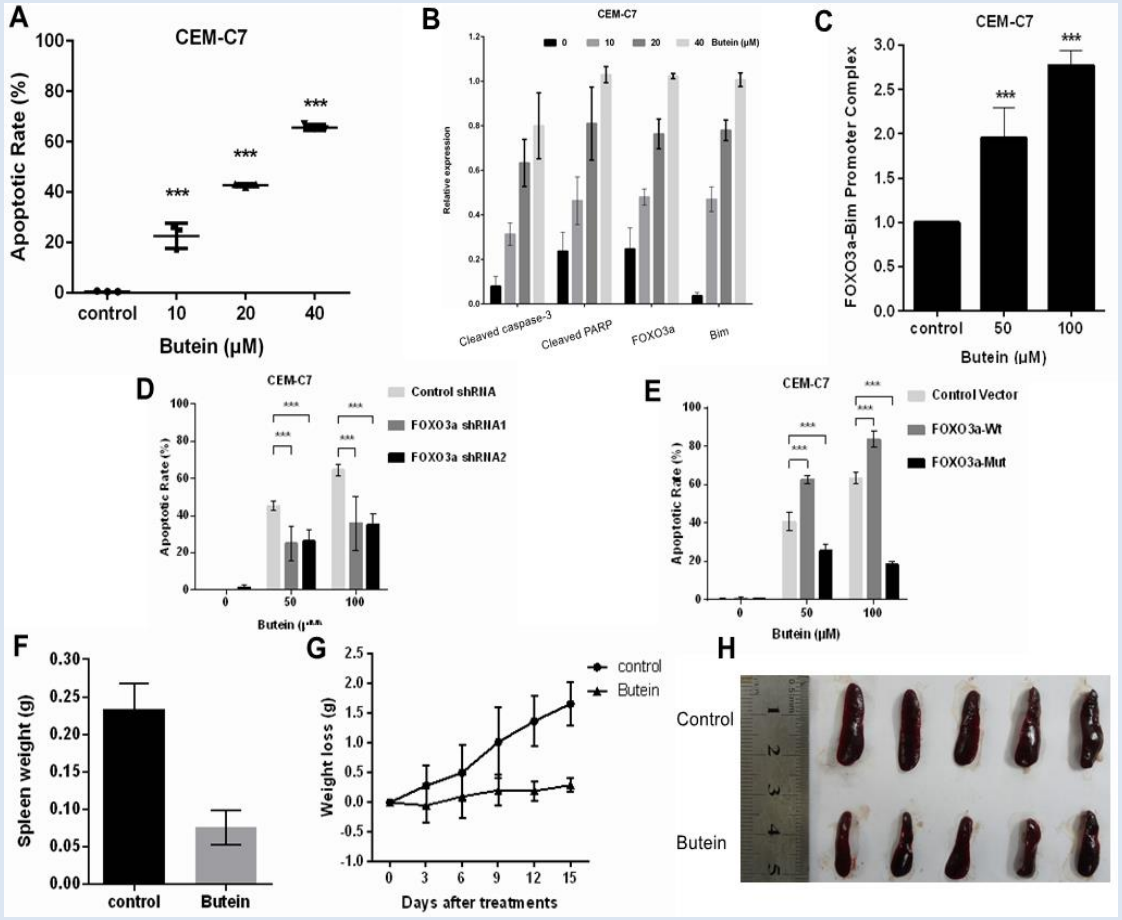
Acute lymphoblastic leukemia (ALL) is a common hematological malignancy in children[1-2]. Discovering and developing effective chemotherapeutic drugs are needed for ALL. In this study, the anti-leukemic effect and the potential molecular mechanisms of butein on ALL were investigated.

Materials and Methods

We examined the rate of apoptosis of ALL cell lines exposed to various concentrations of butein for 24 h using the flow cytometry. We tested the mRNA expression of the caspase-3, PARP, FOXO3a and Bim using qRT-PCR. The binding of FOXO3a on the Bim gene promoter was tested by CHIP. We established the xenograft mouse model to examine the anti-leukemic effect of butein in vivo.

Results

Butein was found to significantly induce the cellular apoptosis of ALL cell lines in a dose-dependent manner (Figure A). It also activated the cleavage of caspase-3 and PARP (Figure B). We also found that butein promoted FOXO3a localization, enhanced the binding of FOXO3a on the Bim gene promoter (Figure C). Moreover, we showed that FOXO3a knockdown significantly decreased the apoptosis by butein (Figure D), whereas overexpression of FOXO3a enhanced the butein-induced apoptosis. However, overexpression of FOXO3a mutation (C-terminally truncated FOXO3a DNA-binding domain) decreased the apoptosis by butein (Figure E). Furthermore, treatment with butein was highly efficacious in vivo with enhanced reduction of tumor burden in a xenograft model (Figure F-H).



Conclusions

Therefore, our results demonstrate the therapeutic potential of butein for ALL via FOXO3a and caspase-dependent apoptotic pathways.

References

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