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Dr. Xin-liang MAO received his PhD degree from Peking University and conducted his postdoctoral training in McMaster University of Canada and Stanford University of USA from 2000 to 2004. Dr. MAO then joined the Department of Hematology at Ontario Cancer Institute of University of Toronto for gene-targeted drug discovery against leukemia and multiple myeloma. In 2009, he took the professorship and serves as the Chair of the Department of Pharmacology in Soochow University, Suzhou, China. Dr. MAO has authored more than 60 papers in top peer-reviewed journals including *Blood*, *Leukemia*, *Cancer Research*, *Journal of Clinical Investigation*. Dr. MAO has filed more than 20 patents from China, US and Australia as a co-inventor. He also serves as a member of the editorial board in six academic journals including *Current Pharmaceutical Design*, *American Journal of Translational Research*, and *Scientific Reports*. Dr. MAO′s research interests focus on the identification of novel targets and novel agents against hematological malignancies. His research has been awarded from various agents, including Berlex Research Award, Progress Prize in Sciences and Technologies from Jiangsu Province and the Ministry of Education of China.

Saponins from Paris forrestii (Takht.) H. Li displays potent activity against acute myeloid leukemia by suppressing RNF6/AKT/mTOR signaling pathway

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Abstract: Acute myeloid leukemia (AML) is a heterogeneous disease characterized by the accumulation of immature myeloid progenitor cells in the bone marrow, compromising of normal hematopoiesis and ultimately resulting in bone marrow failure. Chemotherapy is the mainstay treatment for all AML patients, however, drug resistance and clinical relapse limits its efficacy. The 5-year survival rate of AML patients is only 26.6%. Survival rates are even lower among patients ages 65 to 74 years (5.3%) and 75 years or older (1.6%). Therefore, exploring novel therapeutic agents is urgent for improving the outcome of patients with AML. Saponins are amphipathic glycosides found in traditional Chinese medicines. In the present study, we isolated a panel of saponins from *Paris forrestii* (Takht.) H. Li, a unique plant found in Tibet and Yunnan provinces, China. By examining their activities in suppressing acute myeloid leukemia cell proliferation, total saponins from *Paris forrestii* (TSPf) displayed more potent activity than individual ones. TSPf induced more than 40% AML cell apoptosis within 24 h and decreased the viability of all leukemia cell lines. TSPf-induced apoptosis was confirmed by both Annexin V staining

and caspase-3 activation. TSPf downregulated pro-survival proteins Mcl-1, Bcl-xL and Bcl-2, but upregulated the expression of tumor suppressor proteins p53, p27, Bax and Beclin 1. The AKT/mTOR signaling pathway is frequently over activated in various AML cells, and TSPf was found to suppress the activation of both AKT and mTOR, but had no effects on their total protein expression. This was further confirmed by the inactivation of 4EBP-1 and p70S6K, two typical downstream signal molecules in the AKT/mTOR pathway. More specifically, TSPf-inactivated AKT/mTOR signaling was found to be associated with downregulated RNF6, a recently identified oncogene in AML. RNF6 activated AKT/mTOR, and consistently, knockdown of RNF6 led to inactivation of the AKT/mTOR pathway. Furthermore, TSPf suppressed the growth of AML xenografts in nude mice models. Oral administration of 100 mg·kg^{-1} body weight almost fully suppressed tumor growth within 14 d, without gross toxicity. This study thus demonstrated that TSPf displays potent anti-AML activity by suppressing the RNF6/AKT/mTOR pathway. Given its low toxicity, TSPf could be developed for the treatment of AML.

Key words: total saponins; ring finger protein 6; AKT/mTOR signaling pathway; acute myeloid leukemia
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YOUNG SCIENTISTS PRESENTATION

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MCL3 exhibited anti-tumor activity mediated by NF-κB/IL-6/State3 pathway in glioma

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Abstract: OBJECTIVE Evidience appears that parthenolide (PN) induces anti-tumor effects by NF-κB signal pathway. MCL3 the derivative of PN, is sesquiterpene lactone synthesized by the group of Professor Pan Xiandao. The study was to explore the anti-tumor activity and mechanism of MCL3 in glioma. **METHODS** The effect of MCL3 on the proliferation of glioma cell lines was examined by MTT assay. Apoptotic activity was investigated by flow cytometry. The Transwell cell invasion assay was used to determine the effect of MCL3 on the G422 cell invasive ability. The effect of MCL3 on the angiogenesis was analyzed by a capillary-like tube formation assay. The subcutaneously transplanted and orthotopic G422 cell xenograft models were used to detect the effect of MCL3 on tumor growth *in vivo*. The pathological changes were analyzed by H&E staining. Protein level related to the NF-κB signal pathway was dertimined by Western blotting. The effect of MCL3 on the NF-κB transcriptional activity was examined by a dual-luciferase reporter assay. **RESULTS** The anti-proliferative activity was observed following treatment with MCL3 for 96 h in G422, U-87 MG, U251 and Hs683 cell lines, and the IC_{50} was 8.94 μmol·L^{-1}, 6.44 μmol·L^{-1}, 14.8 μmol·L^{-1}, 18.9 μmol·L^{-1}, respectively. The percentage of apoptotic cells increased in MCL3-treated G422 cells, and the apoptosis rate was 26.4% (the apoptosis rate was 5.68% in control group) . MCL3 could inhibit the invasion in G422 cells, and the invasive inhibition rate was 43.63% (P<0.01) at 10.0 μmol·L^{-1}. MCL3 inhibited tube formation of EA.hy926 cells, and the inhibitory rate was 81.67% (P<0.01) at 10.0 μmol·kg^{-1}. At 40.00 mg·kg^{-1}, MCL3 supressed tumor growth by 79.03% (P<0.01) in tumor weight in subcutaneously transplanted G422 xenograft models, and by