mTOR通路抑制剂GDC-0349对CCRF-CEM细胞增殖和凋亡的影响

《现代肿瘤医学》[ISSN:1672-4992/CN:61-1415/R] 期数: 2019年16期 **页码:** 2803-2806 **栏目:** 论著（基础研究） **出版日期:** 2019-07-08

Title: **Effect of GDC-0349,the mTOR pathway inhibitor,on proliferation and apoptosis of CCRF-CEM cells**

作者: 李 川; 胡 荣; 刘卓刚
中国医科大学附属盛京医院第一血液科，辽宁 沈阳 110031

Author(s): Li Chuan; Hu Rong; Liu Zhuogang
Department of Hematology,Shengjing Hospital,China Medical University，Liaoning Shenyang 110031,China.

关键词: mTOR通路抑制剂; GDC-0349; 急性T淋巴细胞白血病; 细胞增殖; 凋亡

Keywords: mTOR pathway inhibitor; GDC-0349; acute T lymphocytic leukemia; cell proliferation; apoptosis

分类号: R733.71

DOI: 10.3969/j.issn.1672-4992.2019.16.001

文献标识码: A

摘要: 目的：探讨mTOR通路抑制剂GDC-0349对急性T淋巴细胞白血病细胞株CCRF-CEM细胞增殖和凋亡的影响。方法：不同浓度GDC-0349作用于CCRF-CEM细胞，采用CCK-8法检测细胞增殖；流式细胞术检测细胞凋亡率；Western blot检测凋亡相关蛋白及AKT/mTOR通路相关蛋白的表达。结果：GDC-0349作用于CCRF-CEM细胞后细胞增殖率减少且凋亡率增加（P＜0.05）；凋亡相关蛋白Caspase3和BCL2下调，Cleaved-Caspase3增加（P＜0.05）；通路相关蛋白AKT、p-AKT及p-mTOR下调（P＜0.05）。结论：GDC-0349能够抑制AKT/mTOR通路活化，从而促进CCRF-CEM细胞凋亡，抑制细胞增殖。

Abstract: Objective:To investigate the effect of GDC-0349,the mTOR pathway inhibitor,on proliferation and apoptosis of acute T lymphocytic leukemia cell line CCRF-CEM.Methods:Different concentrations of GDC-0349 were applied to CCRF-CEM cells.Cell proliferation was detected by CCK-8 method.Apoptosis rate was detected by flow cytometry.Expressions of apoptosis-related proteins and AKT/mTOR pathway proteins were detected by Western blot.Results:In CCRF-CEM cells with GDC-0349,the cell proliferation rate decreased and the apoptotic rate increased (P＜0.05).Caspase3 and BCL2 were down-regulated (P＜0.05) and Cleaved-Caspase3 was up-regulated (P＜0.05).The expressions of AKT/mTOR pathway-related proteins were down-regulated,such as AKT,p-AKT and p-mTOR (P＜0.05).Conclusion:GDC-0349 can inhibit the AKT/mTOR pathway,then promote cell apoptosis and inhibit cell proliferation in CCRF-CEM cells.

参考文献/REFERENCES

[1] Baghbani E,Khaze V,Sadreddini S,et al.PTPN22 silencing in human acute T-cell leukemia cell line (Jurkat cell) and its effect on the expression of miR-181a and miR-181b [J] .Advanced Pharmaceutical Bulletin,2018,8(2):277-282.
[2] Guo W,Schubbert S,Chen JY,et al.Suppression of leukemia development caused by PTEN loss [J] .Proceedings of the National Academy of Sciences of the United States of America,2011,108(4):1409-1414.
[3] Estrada AA,Shore DG,Blackwood E,et al.Pyrimidoaminotropanes as potent,selective,and efficacious small molecule kinase inhibitors of the mammalian target of rapamycin (mTOR) [J] .Journal of Medicinal Chemistry,2013,56(7):3090-3101.
[4] Zhou Y,Peng Y,Tang H,et al.Autophagy induction contributes to GDC-0349 resistance in head and neck squamous cell carcinoma (HNSCC) cells [J] .Biochemical and Biophysical Research Communications,2016,477(2):174-180.
[5] Silva A,Yunes JA,Cardoso BA,et al.PTEN posttranslational inactivation and hyperactivation of the PI3K/Akt pathway sustain primary T cell leukemia viability [J] .Journal of Clinical Investigation,2008,118(11):3762-3774.
[6] Ksionda O,Mues M,Wandler AM,et al.Comprehensive analysis of T cell leukemia signals reveals heterogeneity in the PI3 kinase-Akt pathway and limitations of PI3 kinase inhibitors as monotherapy [J] .PLoS One,2018,13(5):e0193849.
[7] Imbert V,Nebout M,Mary D,et al.Co-targeting intracellular pH and essential amino acid uptake cooperates to

induce cell death of T-ALL/LL cells [J] .Leukemia & Lymphoma,2018,59(2):460-468.
[8] Ma W,Zhu M,Yang L,et al.Synergistic effect of TPD7 and berberine against leukemia Jurkat cell growth through regulating ephrin-B2 signaling [J] .Phytotherapy Research:PTR,2017,31(9):1392-1399.
[9] Bertacchini J,Heidari N,Medianl L,et al.Targeting PI3K/AKT/mTOR network for treatment of leukemia [J] .Cellular and Molecular Life Sciences:CMLS,2015,72(12):2337-2347.
[10] Kawata T,Tada K,Kobayashi M,et al.Dual inhibition of the mTORC1 and mTORC2 signaling pathways is a promising therapeutic target for adult T-cell leukemia [J] .Cancer Science,2018,109(1):103-111.
[11] Nitulescu GM,Margina D,Juzenas P,et al.Akt inhibitors in cancer treatment:The long journey from drug discovery to clinical use (Review) [J] .International Journal of Oncology,2016,48(3):869-885.
[12] Zhao W,Qiu Y,Kong D.Class I phosphatidylinositol 3-kinase inhibitors for cancer therapy [J] .Acta Pharmaceutica Sinica B,2017,7(1):27-37.
[13] Markham A.Copanlisib:First global approval [J] .Drugs,2017,77(18):2057-2062.
[14] Gazi M,Moharram SA,Marhall A,et al.The dual specificity PI3K/mTOR inhibitor PKI-587 displays efficacy against T-cell acute lymphoblastic leukemia (T-ALL) [J] .Cancer Letters,2017(392):9-16.
[15] Cosentino K,Garcia-Saez AJ.Bax and bak pores:Are we closing the circle [J] ?Trends in Cell Biology,2017,27(4):266-275.
[16] Eleftheriadis T,Pissas G,Liakopoulos V,et al.Cytochrome c as a potentially clinical useful marker of mitochondrial and cellular damage [J] .Frontiers in Immunology,2016(7):279.
[17] Khanzadeh T,Hagh MF,Talebi M,et al.Investigation of BAX and BCL2 expression and apoptosis in a resveratrol- and prednisolone-treated human T-ALL cell line,CCRF-CEM [J] .Blood Research,2018,53(1):53-60.
[18] Zadi Heydarabad M,Vatanmakanian M,Abdolalizadeh J,et al.Apoptotic effect of resveratrol on human T-ALL cell line CCRF-CEM is unlikely exerted through alteration of BAX and BCL2 promoter methylation [J] .Journal of Cellular Biochemistry,2018,119(12):10033-10040.
[19] Kang S,Dong SM,Kim BR,et al.Thioridazine induces apoptosis by targeting the PI3K/Akt/mTOR pathway in cervical and endometrial cancer cells [J] .Apoptosis:An International Journal on Programmed Cell Death,2012,17(9):989-997.

备注/Memo: National Natural Science Foundation of China(No.81500135）；国家自然科学基金资助项目（编号：81500135）

更新日期/Last Update: 1900-01-01