

C/EBP同源蛋白在紫檀芪抗人肺鳞癌Calu-1细胞中作用机制的研究

《现代肿瘤医学》[ISSN:1672-4992/CN:61-1415/R] 期数: 2019年19期 页码: 3365-3369 栏目: 论著 (基础研究) 出版日期: 2019-08-29

Title: Pterostilbene inhibits lung squamous cell carcinoma Calu-1 cell via activation of C/EBP homologous protein

作者: 庞赛楠; 孙大为; 王俊峰; 任凤海; 卜建龙; 孔祥龙; 朱开彬; 徐世东
哈尔滨医科大学附属肿瘤医院胸外科, 黑龙江 哈尔滨 150081

Author(s): Pang Sainan; Sun Dawei; Wang Junfeng; Ren Fenghai; Bu Jianlong; Kong Xianglong; Zhu Kaibin; Xu Shidong

Department of Thoracic Surgery, Harbin Medical University Cancer Hospital, Heilongjiang Harbin 150081, China.

关键词: 紫檀芪; 肺鳞癌; C/EBP同源蛋白; 凋亡

Keywords: pterostilbene; lung squamous cell carcinoma; C/EBP homologous protein; apoptosis

分类号: R734.2

DOI: 10.3969/j.issn.1672-4992.2019.19.003

文献标识码: A

摘要: 目的: 探讨紫檀芪(PT)抗人肺鳞癌Calu-1细胞作用机制及内质网应激(ERS)相关蛋白C/EBP同源蛋白(CHOP)在其中的作用。方法: 实验分为对照组、PT组(15 、 30 、 $45\ \mu\text{mol/L}$)，分别检测各组Calu-1细胞活力值、凋亡率、ROS含量及Caspase-3活性，以及CHOP蛋白和凋亡相关蛋白(Bcl-2、Bax)含量的变化。CHOP小干扰RNA(siRNA)特异性抑制CHOP蛋白表达后，PT(0 、 $30\ \mu\text{mol/L}$)处理细胞 $24\ \text{h}$ ，重复上述检测。结果: PT有效抑制Calu-1细胞增殖，促进凋亡($P<0.05$)，显著增加ROS含量及Caspase-3活性($P<0.05$)，并呈浓度依赖效应；Western blot检测结果显示PT上调CHOP及Bax的表达($P<0.05$)，抑制Bcl-2的表达($P<0.05$)；CHOP siRNA转染显著抑制CHOP表达，同时抑制PT对Calu-1细胞的上调CHOP蛋白表达和促凋亡作用($P<0.05$)。结论: 紫檀芪可有效抑制肺鳞癌Calu-1细胞活力、促进细胞凋亡，此作用可能与激活内质网应激相关蛋白CHOP有关。

Abstract: Objective: To investigate the anticancer effect of pterostilbene (PT) on human lung squamous cell carcinoma Calu-1 cell line and explore the role of endoplasmic reticulum stress (ERS) signaling related protein, C/EBP homologous protein (CHOP), in this process. Methods: Calu-1 cells were divided into the Control group and PT groups (15 , 30 , $45\ \mu\text{mol/L}$). The cell viability rate, the apoptotic rate and the activity of Caspase-3 and ROS level of cells were respectively detected. Western blot was used to detect the expression of CHOP and apoptosis related proteins (Bax and Bcl-2) in Calu-1 cells. Moreover, small interfering RNA (siRNA) of CHOP transfection was used to block the CHOP expression in Calu-1 cells, then PT treatments (0 , $30\ \mu\text{mol/L}$) were implemented for further detection as mentioned in $24\ \text{hours}$. Results: PT treatments resulted in a significant reduction in cell viability and upregulation of cell apoptosis and production of Caspase-3 and ROS in a dose-dependent manner. Western blot analysis showed that PT treatment resulted in a significant increase of CHOP and Bax expression, and decrease of Bcl-2 expression. Moreover, inhibition of CHOP by siRNA decreased the anticancer role of PT on Calu-1 cells. Conclusion: PT treatment can effectively inhibit the proliferation and enhance the apoptosis of Calu-1 cells, which may be related to the activation of CHOP.

参考文献/REFERENCES

- [1] Freddie B, Jacques F, Isabelle S, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. CA: A Cancer Journal for Clinicians, 2018, 68(6): 394-424.
- [2] Jamal-Hanjani M, Wilson GA, McGranahan N, et al. Tracking the evolution of non-small cell lung cancer [J]. N Engl J Med, 2017, 376(22): 2109-2121.
- [3] Killok D. Lung cancer: Alternative rearrangements-targeting ROS1 in NSCLC [J]. Nat Rev Clin Oncol, 2014, 11(11): 624.

- [4] Ullah O, Li Z, Ali I, et al. Pterostilbene exerts a protective effect via regulating tunicamycin-induced endoplasmic reticulum stress in mouse preimplantation embryos in vitro cell [J/OL]. *Dev Biol-Animal*, 2018. <https://doi.org/10.1007/s11626-018-0308-9>.
- [5] Yang Y, Xiaolong Y, Weixun D, et al. Pterostilbene exerts antitumor activity via the Notch1 signaling pathway in human lung adenocarcinoma cells [J]. *PLoS One*, 2013, 8(5): e62652.
- [6] Feng Y, Yang Y, Fan C, et al. Pterostilbene inhibits the growth of human esophageal cancer cells by regulating endoplasmic reticulum stress [J]. *Cellular Physiology and Biochemistry*, 2016, 38(3): 1226-1244.
- [7] Luo B, Lee AS. The critical roles of endoplasmic reticulum chaperones and unfolded protein response in tumorigenesis and anticancer therapies [J]. *Oncogene*, 2013, 32(7): 805-818.
- [8] Papandreou I, Verras M, Mcneil B, et al. Plant stilbenes induce endoplasmic reticulum stress and their anti-cancer activity can be enhanced by inhibitors of autophagy [J]. *Experimental Cell Research*, 2015, 339(1): 147-153.
- [9] Zhao J, Zheng SY, Gu ZL, et al. Caspase-3 inhibitor reduces myocyte cell apoptosis induced by hypoxia in vitro [J]. *Chin J Exp Surg*, 2004, 21(9): 1037-1039.
- [10] Huang WC, Chan ML, Chen MJ, et al. Modulation of macrophage polarization and lung cancer cell stemness by MUC1 and development of a related small-molecule inhibitor pterostilbene [J]. *Oncotarget*, 2016, 7(26): 39363-39375.
- [11] María Benlloch, Obrador E, Valles SL. Pterostilbene decreases the antioxidant defenses of aggressive cancer cells in vivo a physiological glucocorticoids- and NRF2-dependent mechanism [J]. *Antioxidants & Redox Signaling*, 2016, 24(17): 974-990.
- [12] Dong J, Guo H, Chen Y. Pterostilbene induces apoptosis through caspase activation in ovarian cancer cells [J]. *European Journal of Gynaecological Oncology*, 2016, 37(3): 342.
- [13] Hsieh MJ, Lin CW, Yang SF, et al. A combination of pterostilbene with autophagy inhibitors exerts efficient apoptotic characteristics in both chemosensitive and chemoresistant lung cancer cells [J]. *Toxicological Sciences An Official Journal of the Society of Toxicology*, 2014, 137(1): 65.
- [14] Ko CP, Lin CW, Chen MK, et al. Pterostilbene induce autophagy on human oral cancer cells through modulation of Akt and mitogen-activated protein kinase pathway [J]. *Oral Oncology*, 2015, 51(6): 593-601.
- [15] Kosuru R, Rai U, Prakash S, et al. Promising therapeutic potential of pterostilbene and its mechanistic insight based on preclinical evidence [J]. *European Journal of Pharmacology*, 2016, 15(789): 229-243.
- [16] Pan MH, Chiou YS, Chen WJ, et al. Pterostilbene inhibited tumor invasion via suppressing multiple signal transduction pathways in human hepatocellular carcinoma cells [J]. *Carcinogenesis*, 2009, 30(7): 1234.
- [17] Tolba MF, Abdel-Rahman SZ. Pterostilbene, an active component of blueberries, sensitizes colon cancer cells to 5-fluorouracil cytotoxicity [J]. *Scientific Reports*, 2015(5): 15239.
- [18] Clarke H, Chambers J, Liniker E, et al. Endoplasmic reticulum stress in malignancy [J]. *Cancer Cell*, 2014, 25(5): 563-573.
- [19] Ron D, Walter P. Signal integration in the endoplasmic reticulum unfolded protein response [J]. *Nat Rev Mol Cell Biol*, 2007, 8(7): 519.
- [20] Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma(ENDEAVOR): An interim overall survival analysis of an open-label, randomised, phase 3 trial [J]. *Lancet Oncol*, 2017, 18(10): 1327-1337.

备注/Memo: 黑龙江省卫生计生委科研课题(编号: 2016-099)

更新日期/Last Update: 2019-08-29