

川芎嗪通过调控Wnt信号通路抑制肺癌细胞增殖、侵袭和迁移的机制研究

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Title: Mechanism of tetramethylpyrazine inhibiting proliferation, invasion and migration of lung cancer cells by regulating Wnt signaling pathway

作者: 李高兵¹; 蔡东平²; 毛张凡³

1.襄阳市中医医院肺病科,湖北 襄阳 441000;2.襄阳市职业病防治院职业病科,湖北 襄阳 441000;3.武汉大学人民医院胸外科,湖北 武汉 430000

Author(s): Li Gaobing¹; Cai Dongping²; Mao Zhangfan³

1.Pulmonary Disease Department,Xiangyang Hospital of Traditional Chinese Medicine,Hubei Xiangyang 441000,China;2.Occupational Disease Department,Xiangyang Occupational Disease Prevention and Cure Institute,Hubei Xiangyang 441000,China;3.Thoracic Surgery,Renmin Hospital of Wuhan University,Hubei Wuhan 430000,China.

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摘要: 目的:探讨川芎嗪通过调控Wnt信号通路影响人肺癌A549细胞增殖、侵袭和迁移的机制研究。方法:将培养的人肺癌细胞A549随机分为四组:对照组、川芎嗪组、抑制剂组、川芎嗪+抑制剂组,噻唑蓝(MTT)法检测各组A549细胞增殖能力,流式细胞术检测各组A549细胞生长周期,Transwell实验检测各组A549细胞侵袭能力,划痕实验检测各组A549细胞迁移能力,蛋白免疫印迹(Western blot)检测各组A549细胞中β-连环蛋白(β-catenin)、c-myc、增殖细胞核抗原(PCNA)和基质金属蛋白酶-9(MMP-9)蛋白水平。结果:与对照组相比,川芎嗪组和抑制剂组均能够抑制A549细胞增殖,阻滞细胞周期至G1期,阻碍细胞侵袭和迁移,下调细胞中β-catenin、c-myc、PCNA和MMP-9蛋白水平,差异具有统计学意义(P<0.05)。与川芎嗪组和抑制剂组相比,川芎嗪+抑制剂组A549细胞增殖能力显著降低,细胞周期阻滞于G1期,细胞侵袭和迁移能力受到抑制,细胞中β-catenin、c-myc、PCNA和MMP-9蛋白水平显著降低,差异具有统计学意义(P<0.05)。结论:川芎嗪能够抑制人肺癌细胞A549细胞的增殖、侵袭和迁移,其作用机制与抑制Wnt信号通路的激活有关。

Abstract: Objective:To investigate the mechanism of tetramethylpyrazine on the proliferation, invasion and migration of human lung cancer A549 cells by regulating Wnt signaling pathway. Methods: Human lung cancer cells A549 were randomly divided into four groups: control group, tetramethylpyrazine group, inhibitor group, tetramethylpyrazine+inhibitor group. MTT assay was used to detect the proliferation of A549 cells. The growth cycle of A549 cells was detected by Transwell assay. The invasion ability of A549 cells was detected by Transwell assay. The migration ability of A549 cells was detected by scratch test. The β-catenin (β-catenin) in A549 cells was detected by Western blot, c-myc, proliferating cell nuclear antigen (PCNA) and matrix metalloproteinase-9 (MMP-9) protein levels. Results: Compared with the control group, both the tetramethylpyrazine group and the inhibitor group could inhibit the proliferation of A549 cells, block the cell cycle to the G1 phase, hinder cell invasion and migration, and down-regulate β-catenin, c-myc, PCNA and MMP in cells, the difference was statistically significant (P < 0.05). Compared with the tetramethylpyrazine group and the inhibitor group, the proliferative ability of the tetramethylpyrazine+inhibitor group A549 cells was significantly decreased, the cell cycle was arrested in the G1 phase, and the cell invasion and migration ability was inhibited. The levels of PCNA and MMP-9 protein were significantly lower, and the difference was statistically significant (P < 0.05). Conclusion: Tetramethylpyrazine can inhibit the proliferation, invasion and

migration of human lung cancer cell line A549, and its mechanism is related to the inhibition of Wnt signaling pathway activation.

参考文献/REFERENCES

- [1] Akhurst T. Staging of non-small-cell lung cancer [J]. *PET Clin*, 2018, 13(3):1-10.
- [2] Mei J, Xiao Z, Guo C, et al. Prognostic impact of tumor-associated macrophage infiltration in non-small cell lung cancer: A systemic review and meta-analysis [J]. *Oncotarget*, 2016, 7(23):34217-34228.
- [3] Jiang YM, Wang DQ. Advances in pharmacological studies of tetramethylpyrazine [J]. *Modern Chinese Medicine*, 2016, 18(10):1364-1370. [姜宇懋, 王丹巧. 川芎嗪药理作用研究进展 [J]. *中国现代中药*, 2016, 18(10):1364-1370.]
- [4] Yong A, Zhu B, Ren C, et al. Discovery of new monocarbonyl ligustrazine-curcumin hybrids for intervention of drug-sensitive and drug-resistant lung cancer [J]. *J Med Chem*, 2016, 59(5):1747-1760.
- [5] Sun X, Yin ZP, Yin HM. Effects of tetramethylpyrazine on invasion and migration of human hepatoma HepG-2 cells in vitro [J]. *Practical Hepatology*, 2018(1):118-120. [孙晓, 尹中普, 尹红梅. 川芎嗪对人肝癌HepG-2细胞体外侵袭和迁移的影响 [J]. *实用肝脏病杂志*, 2018(1):118-120.]
- [6] Bo YI, Liu D, Ming HE, et al. Role of the ROS/AMPK signaling pathway in tetramethylpyrazine-induced apoptosis in gastric cancer cells [J]. *Oncol Lett*, 2013, 6(2):583-589.
- [7] Tai D, Wells K, Arcaroli J, et al. Targeting the WNT signaling pathway in cancer therapeutics [J]. *Oncologist*, 2015, 20(10):1189-1198.
- [8] Xiao YF, Yong X, Tang B, et al. Notch and Wnt signaling pathway in cancer: Crucial role and potential therapeutic targets (Review) [J]. *Int J Oncol*, 2016, 48(2):437-449.
- [9] Ni ML, Xie L, Qin BB. Expression and significance of Wnt/ β -catenin signaling pathway in non-small cell lung cancer tissues [J]. *Guangdong Medical*, 2016, 37(15):2299-2301. [倪明立, 谢玲, 秦贝贝. Wnt/ β -catenin信号通路在非小细胞肺癌组织的表达及意义 [J]. *广东医学*, 2016, 37(15):2299-2301.]
- [10] Huo JT, Zhang XQ, Yan J, et al. Activation of Wnt signaling pathway by ligustrazine in improving brain tissue inflammation in rats with Alzheimer's disease [J]. *Zhejiang J Clin Med*, 2015, 8:1262-1264. [霍江涛, 张小乔, 严洁, 等. 川芎嗪激活Wnt信号通路改善阿尔茨海默病大鼠脑组织炎症性研究 [J]. *浙江临床医学*, 2015, 8:1262-1264.]
- [11] Wang S, Lei T, Man Z. The reversal effect and its mechanisms of Tetramethylpyrazine on multidrug resistance in human bladder cancer [J]. *Plos One*, 2016, 11(7):e0157759.
- [12] Zhou Y, Ji Z, Yan W, et al. Tetramethylpyrazine inhibits prostate cancer progression by downregulation of forkhead box M1 [J]. *Oncol Rep*, 2017, 38(2):837-842.
- [13] Wu N, Xu L, Yang Y, et al. Tetramethylpyrazine-mediated regulation of CXCR4 in retinoblastoma is sensitive to cell density [J]. *Mol Med Rep*, 2017, 15(5):2481-2488.
- [14] Bi L, Yan X, Chen W, et al. Antihepatocellular carcinoma potential of tetramethylpyrazine induces cell cycle modulation and mitochondrial-dependent apoptosis: Regulation of p53 signaling pathway in HepG2 cells in vitro [J]. *Integr Cancer Ther*, 2016, 15(2):226-236.
- [15] Shen J, Zeng L, Pan L, et al. Tetramethylpyrazine regulates breast cancer cell viability, migration, invasion and apoptosis by affecting the activity of Akt and caspase-3 [J]. *Oncol Lett*, 2018, 15(4):4557-4563.
- [16] Niu Y, Wang C, Zhang XY, et al. Effects and mechanism of ligustrazine on proliferation, migration and invasion of human lung adenocarcinoma A549 cells [J]. *Modern Oncology*, 2016, 24(10):1509-1512. [牛媛, 王成, 张晓燕, 等. 川芎嗪对人肺腺癌 A549细胞增殖、迁移和侵袭的作用与机制 [J]. *现代肿瘤医学*, 2016, 24(10):1509-1512.]
- [17] Zou Y, Zhao D, Yan C, et al. Novel ligustrazine-based analogs of piperlongumine potently suppress proliferation and metastasis of colorectal cancer cells in vitro and in vivo [J]. *J Med Chem*, 2018, 61(5):1821-1832.
- [18] Hua JY, He YZ, Jiang XH, et al. Mechanism of tetramethylpyrazine inhibiting proliferation and collagen synthesis of vascular smooth muscle cells [J]. *Chinese J Integrated Traditional and Western Medicine*, 2013, 33(9):1226-1231. [华军益, 何煜舟, 蒋旭宏, 等. 川芎嗪抑制血管平滑肌细胞增殖及胶原合成的作用机制研究 [J]. *中国中西医结合杂志*, 2013, 33(9):1226-1231.]
- [19] Zhang SP, Zhang X. Research progress of wnt signaling pathway in tumor regulation [J]. *Chinese Pharmacology Bulletin*, 2017, 33(1):14-18. [张世苹, 张旭. Wnt信号通路在肿瘤调控方面的研究进展 [J]. *中国药理学通报*, 2017, 33(1):14-18.]
- [20] Santiago L, Daniels G, Wang D, et al. Wnt signaling pathway protein LEF1 in cancer, as a biomarker for prognosis and a target for treatment [J]. *Am J Cancer Res*, 2017, 7(6):1389-1406.
- [21] Shi L, Wu YX, Yu JH, et al. Research of the relationship between β -catenin and c-myc-mediated Wnt pathway and laterally spreading tumors occurrence [J]. *Eur Rev Med Pharmacol Sci*, 2017, 21(2):252-257.
- [22] Kim Y, Jin D, Lee BB, et al. Overexpression of β -catenin and cyclin D1 is associated with poor overall survival in stage Ia-III squamous cell lung cancer irrespective of adjuvant chemotherapy [J]. *J Thorac Oncol*, 2016, 11(12):2193-2201.
- [23] Lim YD, Shin SH, Lee MH, et al. A natural small molecule, catechol, induces c-Myc degradation by directly targeting ERK2 in lung cancer [J]. *Oncotarget*, 2016, 7(23):35001-35014.
- [24] José ML, Einar H, Bodil B, et al. Synovial sarcoma. Evaluation of prognosis with emphasis on the study of DNA ploidy and proliferation (PCNA and Ki-67) markers [J]. *Anal Cell Pathol*, 2016, 16(1):45-62.

[25] Gil M, Yun KK, Kim KE, et al. Cellular prion protein regulates invasion and migration of breast cancer cells through MMP-9 activity [J]. *Biochem Biophys Res Commun*, 2016, 470(1):213-219.

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