CD155通过Ras/Erk通路促进肺腺癌细胞增殖及抑制其凋亡的分子机制

《现代肿瘤医学》[ISSN:1672-4992/CN:61-1415/R] 期数: 2019年20期 页码: 3580-3586 栏目: 论著（基础研究） 出版日期: 2019-09-08

Title: CD155 promotes proliferation and inhibits apoptosis in lung adenocarcinoma cells via Ras/Erk pathway

作者: 白 桦[1]; 张 松[2]; 肖 鹏[1]; 栗 敏[1]
1.郑州人民医院肿瘤内科，河南 郑州 450000;2.郑州大学第一附属医院放疗科，河南 郑州 450000

Author(s): Bai Hua[1]; Zhang Song[2]; Xiao Peng[1]; Li Min[1]
1.Department of Oncology,People's Hospital of Zhengzhou,Henan Zhengzhou 450000,China;2.Department of Radiology,the First Affiliated Hospital of Zhengzhou University,Henan Zhengzhou 450000,China.

关键词: CD155; Ras/Erk通路; SPRY2; 增殖; 细胞活性

Keywords: CD155; Ras/Erk pathway; SPRY2; proliferation; cellular activity

分类号: R734.2

DOI: 10.3969/j.issn.1672-4992.2019.20.008

文献标识码: A

摘要: 目的：研究CD155通过调控Ras/Erk通路对肺腺癌细胞活性、增殖、凋亡的影响，并探讨其作用的分子机制。方法:通过慢病毒转染法构建过表达或敲低CD155的人肺腺癌H23和H522细胞株，qRT-PCR检测肺腺癌细胞中CD155 mRNA表达水平，CCK-8法检测细胞活力，免疫荧光法测定细胞增殖和凋亡水平；Western blot检测PCNA、caspase-3、Ras、Erk1蛋白的表达及活化水平；小分子药物FTI 277或FR 180204处理过表达CD155的H23和H522细胞抑制Ras及Erk通路，检测对细胞活性、增殖、凋亡的影响；采用慢病毒共转染的方法构建CD155与SPRY2共同过表达的H23细胞系，免疫共沉淀法检测细胞中SPRY2、CD155蛋白间的结合关系，以同样的方法检测对细胞活性、增殖、凋亡的影响。结果:慢病毒转染肺腺癌H23和H522细胞可上调或下调细胞中CD155的表达，差异具有统计学意义（P < 0.05）；CD155过表达可促进肺腺癌细胞活性、增殖及PCNA蛋白的表达，抑制细胞凋亡及caspase-3的活化，敲低CD155则表现出相反的作用，差异具有统计学意义（P < 0.05）；CD155过表达可激活Ras和Erk1，敲低CD155则抑制Ras和Erk1的激活，差异具有统计学意义（P < 0.05）；抑制Ras和Erk通路可抑制过表达CD155引起的细胞增殖及活性的促进作用，缓解过表达CD155诱导的细胞凋亡，差异具有统计学意义（P < 0.05）；SPRY2过表达逆转CD155过表达对H23细胞增殖及活性的促进作用，抑制对Ras/Erk通路激活的促进作用，差异具有统计学意义（P < 0.05）。结论:CD155可通过提高Ras/Erk通路的激活程度，促进肺腺癌细胞在体外的增殖及活性，其作用机制可能是部分由CD155与SPRY2蛋白发生相互作用，降低了SPRY2蛋白对Ras/Erk通路的抑制作用引起的。

Abstract: Objective:To investigate the effects of CD155 on the activity,proliferation and apoptosis of lung adenocarcinoma cells by regulating Ras/Erk pathway,and to explore its molecular mechanism.Methods:Human lung adenocarcinoma H23 and H522 cell lines overexpressing or knocking down CD155 expression were constructed by lentiviral transfection.The expression of CD155 mRNA in lung adenocarcinoma cells was detected by qRT-PCR.Cell viability were detected by CCK-8 assay.Cell proliferation and apoptosis were measured by immunofluorescence.PCNA,caspase-3,Ras,Erk1 protein expression and activation levels were detected by Western blot.Small molecule drug FTI 277 or FR 180204 treated CD155-expressing H23 and H522 cells to inhibit Ras and Erk pathways.The effect of cell activity,proliferation and apoptosis was detected.The H23 cell line overexpressing CD155 and SPRY2 was constructed by co-transfection of lentivirus.The binding relationship between SPRY2 and CD155 protein was detected by immunoprecipitation.The same method detected the effects on cell activity,proliferation,and apoptosis.Results:Lentivirus-transfected lung adenocarcinoma H23 and H522 cells up-regulated or down-regulated the expression of CD155 in the cells,and the difference was statistically significant (P < 0.05).CD155 overexpression promoted the activity,proliferation and expression of PCNA protein in lung adenocarcinoma cells,inhibited apoptosis and activation of caspase-3.Knockdown of CD155 showed the opposite effect,and the difference was statistically significant (P <

0.05).CD155 overexpression activated Ras and Erk1.Knockdown of CD155 inhibited Ras and Erk1.The difference was statistically significant (P < 0.05).Inhibition of Ras and Erk pathways inhibited cell proliferation and activity induced by overexpression of CD155,and alleviated overexpression of CD155-induced apoptosis.The difference was statistically significant (P < 0.05).SPRY2 overexpression reversed the effect of CD155 overexpression on the proliferation and activity of H23 cells,and inhibited the activation of Ras/Erk pathway,the difference was statistically significant (P < 0.05).Conclusion:CD155 can promote the proliferation and activity of lung adenocarcinoma cells in vitro by increasing the activation of Ras/Erk pathway.The mechanism of action may be due to the interaction between CD155 and SPRY2 protein,which reduces the inhibition of the Ras/Erk pathway by SPRY2 protein.

参考文献/REFERENCES

[1] Dubey AK,Gupta U,Jain S.Epidemiology of lung cancer and approaches for its prediction:a systematic review and analysis [J] .Chin J Cancer,2016,35(1):71-80.
[2] Gong Q,Liu C,Wang C,et al.Effect of silencing TEM8 gene on proliferation,apoptosis,migration and invasion of XWLC 05 lung cancer cells [J] .Mol Med Rep,2018,17(1):911-917.
[3] Iguchi-Manaka A,Okumura G,Kojima H,et al.Increased soluble CD155 in the serum of cancer patients [J] .Plos One,2016,11(4):e0152982.
[4] Nakai R,Maniwa Y,Tanaka Y,et al.Overexpression of Necl-5 correlates with unfavorable prognosis in patients with lung adenocarcinoma [J] .Cancer Sci,2010,101(5):1326-1330.
[5] Jian G,Zheng Q,Na X,et al.CD155,an onco-immunologic molecule in human tumors [J] .Cancer Sci,2017,108(10):1934-1938.
[6] Wang YJ,Chen C,Fang D,et al.NK cells play a significant role in immunosurveillance at the early stage of MLL-AF9 acute myeloid leukemia via CD226/CD155 interactions [J] .Sci China Life Sci,2015,58(12):1288-1298.
[7] Zheng Q,Wang B,Gao J,et al.CD155 knockdown promotes apoptosisviaAKT/Bcl-2/Bax in colon cancer cells [J] .J Cell Mol Med,2017,22(1):131-140.
[8] Li XY,Das I,Lepletier A,et al.CD155 loss enhances tumor suppression via combined host and tumor-intrinsic mechanisms [J] .J Clin Invest,2018,128(6):2613-2625.
[9] Sloan KE,Eustace BK,Stewart JK,et al.CD155/PVR plays a key role in cell motility during tumor cell invasion and migration [J] .Bmc Cancer,2004,4(1):73-93.
[10] Tane S,Maniwa Y,Hokka D,et al.The role of Necl-5 in the invasive activity of lung adenocarcinoma [J] .Exp Mol Pathol,2013,94(2):330-335.
[11] Enloe BM,Jay DG.Inhibition of Necl-5 (CD155/PVR) reduces glioblastoma dispersal and decreases MMP-2 expression and activity [J] .J Neurooncol,2011,102(2):225-235.
[12] PENG C,SUN ML,SU JJ,et al.Study on apoptosis of lung adenocarcinoma A549 cells induced by new gambogic acid via Ras/Raf/Erk signaling pathway [J] .Journal of New Drugs and Clinical Pharmacy,2016,27(2):189-193. [彭程,孙美灵,苏婧婧,等.新藤黄酸通过Ras/Raf/Erk信号通路诱导肺腺癌A549细胞凋亡的研究 [J] .中药新药与临床药理,2016,27(2):189-193.]
[13] Zheng G,Shen Z,Chen H,et al.Metapristone suppresses non-small cell lung cancer proliferation and metastasis via modulating RAS/RAF/MEK/MAPK signaling pathway [J] .Biomed Pharmacother,2017,90(3):437-445.
[14] Kono T,Imai Y,Yasuda S,et al.The CD155/poliovirus receptor enhances the proliferation of ras-mutated cells [J] .Int J Cancer,2008,122(2):317-324.
[15] Kajita M,Ikeda W,Tamaru Y,et al.Regulation of platelet-derived growth factor-induced Ras signaling by poliovirus receptor Necl-5 and negative growth regulator Sprouty2 [J] .Genes Cells,2007,12(3):345-357.
[16] WANG X,ZHANG PH.Research progress of Ras/Raf/MEK/ERK signaling pathway participating in autophagy regulation [J] .Journal of China Pharmaceutical University,2017,48(1):110-116. [王雪,张评浒.Ras/Raf/MEK/ERK信号通路参与自噬调控作用的研究进展 [J] .中国药科大学学报,2017,48(1):110-116.]
[17] Samatar AA,Poulikakos PI.Targeting RAS-ERK signalling in cancer:Promises and challenges [J] .Nat Rev Drug Discov,2014,13(12):928-942.
[18] Zhang M,Li Y,Dorfman RG.Sirt2 promotes the migration and invasion of gastric cancer through Ras/Erk/Jnk/Mmp-9 pathway by increasing Pepck1-related metabolism [J] .Neoplasia,2018,20(7):745-756.
[19] Chandramohan V,Bryant JD,Piao H,et al.Validation of an immunohistochemistry assay for detection of CD155,the poliovirus receptor,in malignant gliomas [J] .Arch Pathol Lab Med,2017,141(12):1697-1704.
[20] Lechuga CG,Simón-Carrasco L,Jacob HKC,et al.Genetic validation of cell proliferation via ras-independent activation of the Raf/Mek/Erk pathway [J] .Methods Mol Biol,2017(1487):269-276.
[21] DENG HP.Study on the mechanism of human soluble CD155 molecule production [D] .Xi'an:The Fourth Military Medical University,2007. [邓虎平.人可溶型CD155分子产生机制的研究 [D] .西安：第四军医大学,2007.]
[22] Huang DW,Huang M,Lin XS,et al.CD155 expression and its correlation with clinicopathologic characteristics,angiogenesis,and prognosis in human cholangiocarcinoma [J] .Onco Targets Ther,2017,31(10):3817-3825.
[23] Satoru A,Akihiko M,Hidemi T,et al.Prognostic significance of CD155 mRNA expression in soft tissue

sarcomas［J］.Oncol Lett,2013,5(6):1771-1776.
［24］ Nishiwada S,Sho M,Yasuda S,et al.Clinical significance of CD155 expression in human pancreatic cancer［J］.Anticancer Res,2015,35(4):2287-2297.
［25］ Hirota T,Irie K,Okamoto R,et al.Transcriptional activation of the mouse Necl-5/Tage4/PVR/CD155 gene by fibroblast growth factor or oncogenic Ras through the Raf-MEK-ERK-AP-1 pathway［J］.Oncogene,2005,24(13):2229-2235.

备注/Memo: -

更新日期/Last Update: 1900-01-01