

# SOX2/CDX2/HNF4 $\alpha$ 与胃癌相关性的研究进展

《现代肿瘤医学》[ISSN:1672-4992/CN:61-1415/R] 期数: 2019年24期 页码: 4475-4480 栏目: 综述 出版日期: 2019-11-08

**Title:** Advances in research on the relationship between SOX2/CDX2/HNF4 $\alpha$  and gastric cancer

**作者:** 孙妮娜<sup>1</sup>; 刘彩芳<sup>1</sup>; 石淼<sup>1</sup>; 张剑<sup>2</sup>; 韩川<sup>2</sup>; 3; 袁挺<sup>2</sup>; 4; 倪阵<sup>2</sup>; 5; 陆文全<sup>6</sup>; 陈升<sup>2</sup>; 7; 时永全<sup>1</sup>; 2

1.西安医学院,陕西 西安 710021; 2.空军军医大学西京消化病医院肿瘤生物学国家重点实验室,陕西 西安 710032; 3.火箭军峨眉疗养院消化内科,四川 峨眉 614200; 4.中国人民解放军150医院消化内科,河南 洛阳 471000; 5.中国人民解放军西部战区总医院消化内科,四川 成都 610083; 6.郑州大学第一附属医院消化内科,河南 郑州 450000; 7.中国人民解放军战略支援部队61068部队消化内科,陕西 西安 710100

**Author(s):** Sun Nina<sup>1</sup>; Liu Caifang<sup>1</sup>; Shi Miao<sup>1</sup>; Zhang Jian<sup>2</sup>; Han Chuan<sup>2</sup>; 3; Yuan Ting<sup>2</sup>; 4; Ni Zhen<sup>2</sup>; 5; Lu Wenquan<sup>6</sup>; Chen Sheng<sup>2</sup>; 7; Shi Yongquan<sup>1</sup>; 2

**关键词:** SOX2; CDX2; HNF4 $\alpha$ ; 肠化生; 胃肿瘤

**Keywords:** SOX2; CDX2; HNF4 $\alpha$ ; intestinal metaplasia; gastric cancer

**分类号:** R735.2

**DOI:** 10.3969/j.issn.1672-4992.2019.24.037

**文献标识码:** A

**摘要:** 胃癌的发生是由正常胃黏膜经历慢性萎缩性胃炎、肠化生、异型增生直至胃癌发生的多阶段渐进性过程。其中肠化生是胃癌尤其是肠型胃癌重要的癌前病变。有研究证实,在肠化生及胃癌的发生过程中,性别决定区Y框蛋白2(SRY related HMG box-2,SOX2)、尾侧型同源转录因子2(caudal related homeobox transcription factor-2,CDX2)和肝细胞核因子(hepatocyte nuclear factor,HNF)4 $\alpha$ 均有参与,而且3个分子间存在明显相关性。因此,本文对目前SOX2、CDX2和HNF4 $\alpha$ 与胃癌的相关研究进展作一综述。

**Abstract:** The occurrence of gastric cancer is a multi-stage progressive process in which normal gastric mucosa undergoes chronic atrophic gastritis,intestinal metaplasia,dysplasia,and gastric cancer.Among them,intestinal metaplasia is an important precancerous lesion of gastric cancer,especially intestinal type gastric cancer.Studies have confirmed that SOX2,CDX2 and HNF4 $\alpha$  are involved in the process of intestinal metaplasia and gastric cancer,and there is a significant correlation between the three molecules.Therefore,this article reviews the current research progress of SOX2,CDX2 and HNF4 $\alpha$  and gastric cancer.

## 参考文献/REFERENCES

- [1] Chen W,Zheng R,Baade PD,et al.Cancer statistics in China,2015 [J] .CA Cancer J Clin,2016,66(2):115-132.
- [2] Niu H,Jia Y,Li T,et al.SOX2 inhibition promotes promoter demethylation of CDX2 to facilitate gastric intestinal metaplasia [J] .Dig Dis Sci,2017,62(1):124-132.
- [3] Camilo V,Garrido M,Valente P,et al.Differentiation reprogramming in gastric intestinal metaplasia and dysplasia:Role of SOX2 and CDX2 [J] .Histopathology,2015,66(3):343-350.
- [4] Yuan T,Ni Z,Han C,et al.SOX2 interferes with the function of CDX2 in bile acid-induced gastric intestinal metaplasia [J] .Cancer Cell Int,2019 (19) :24.
- [5] Stegmann A,Hansen M,Wang Y,et al.Metabolome,transcriptome,and bioinformatic cis-element analyses point to HNF-4 as a central regulator of gene expression during enterocyte differentiation [J] .Physiological Genomics,2006,27(2):141-155.
- [6] Boyd M,Bressendorff S,Müller J,et al.Mapping of HNF4 $\alpha$  target genes in intestinal epithelial cells [J] .BMC Gastroenterol,2009 (9) :68.
- [7] Maier S,Wilbertz T,Braun M,et al.SOX2 amplification is a common event in squamous cell carcinomas of different organ sites [J] .Hum Pathol,2011,42(8):1078-1088.
- [8] Wang S,Tie J,Wang R,et al.SOX2,a predictor of survival in gastric cancer,inhibits cell proliferation and metastasis by regulating PTEN [J] .Cancer Lett,2015,358(2):210-219.
- [9] Sarkar A,Huebner AJ,Sulahian R,et al.Sox2 suppresses gastric tumorigenesis in mice [J] .Cell Rep,2016,16(7):1929-1941.

- [10] Chen Y,Huang Y,Zhu L,et al.SOX2 inhibits metastasis in gastric cancer [J] .J Cancer Res Clin Oncol,2016,142(6):1221-1230.
- [11] Li YJ,Dong M,Kong FM,et al.MicroRNA-371-5p targets SOX2 in gastric cancer [J] .Oncotarget,2016,7(22):31993-2005.
- [12] KONG Qingyuan,HE De,HUANG Jianxian.Expression and clinical pathological characteristics of SOX2 in gastric cancer tissues [J] .J Clin Med,2015,16(1):4-6,108. [孔庆元,贺德,黄建贤.SOX2在胃癌组织中的表达及临床病理特征 [J] .实用临床医学,2015,16(1):4-6,108.]
- [13] XU Yi,DING Weiji,LI Wenpeng,et al.Expression and clinical significance of stem cell transcription factors SOX2 and OCT4 in gastric cancer tissues with different degrees of differentiation [J] .Chin J Cancer,2015,25(6):416-423. [徐毅,丁伟基,李文鹏,等.干细胞转录因子SOX2、OCT4在不同分化程度胃癌组织中的表达及其临床意义 [J] .中国癌症杂志,2015,25(6):416-423.]
- [14] LI Chunhui,PAN Lihui,LIU Haiwang,et al.Expression and relationship of SOX2,TGF- $\beta$ 1 and Smad3 in gastric cancer tissues [J] .J Pract Med,2015,31(5):750-753. [李春辉,潘理会,刘海旺,等.胃癌组织中SOX2与TGF- $\beta$ 1、Smad3的表达及相互关系 [J] .实用医学杂志,2015,31(5):750-753.]
- [15] CHEN Zhong,XIE Feng,ZHONG Fengyun,et al.Expression and clinical significance of stem cell marker Sox2 in gastric cancer tissues [J] .Tianjin Med J,2016,44(5):548-551. [陈忠,谢峰,钟丰云,等.胃癌组织中干细胞标志物 Sox2的表达及临床意义 [J] .天津医药,2016,44(5):548-551.]
- [16] XIE Zhengxing,DI Yanan,PENG Deyin,et al.Correlation between Helicobacter pylori infection and Sox2 protein in the pathogenesis of gastric cancer [J] .J Lab Med Clin Sci,2017,14(18):2711-2712,2715. [谢正兴,邸雅南,彭德银,等.幽门螺旋杆菌感染与Sox2蛋白在胃癌发病中的相关性研究 [J] .检验医学与临床,2017,14(18):2711-2712,2715.]
- [17] Chen XL,Chen XZ,Wang YG,et al.Clinical significance of putative markers of cancer stem cells in gastric cancer:A retrospective cohort study [J] .Oncotarget,2016,7(38):62049-62069.
- [18] Luo J,Yan R,He X,et al.SOX2 inhibits cell proliferation and metastasis,promotes apoptotic by downregulating CCND1 and PARP in gastric cancer [J] .Am J Transl Res,2018,10(2):639-647.
- [19] Tian Y,Jia X,Wang S,et al.SOX2 oncogenes amplified and operate to activate AKT signaling in gastric cancer and predict immunotherapy responsiveness [J] .J Cancer Res Clin Oncol,2014,140(7):1117-1124.
- [20] Matsuoka J,Yashiro M,Sakurai K,et al.Role of the stemness factors sox2,oct3/4,and nanog in gastric carcinoma [J] .J Surg Res,2012,174(1):130-135.
- [21] ZHANG Yanping,LI Ning,DENG Wenying,et al.Relationship between the expression of stem cell markers SOX-2 and  $\beta$ -catenin and recurrence and metastasis of gastric cancer [J] .Chin J Cancer,2014,24(09):684-689. [张燕平,李宁,邓文英,等.干细胞标志物SOX-2、 $\beta$ -catenin表达与胃癌术后复发转移关系 [J] .中国癌症杂志,2014,24(09):684-689.]
- [22] Zhang X,Hua R,Wang X,et al.Identification of stem-like cells and clinical significance of candidate stem cell markers in gastric cancer [J] .Oncotarget,2016,7(9):9815-9831.
- [23] Yang L,Xu JF,Kang Q,et al.Predictive value of stemness factor Sox2 in gastric cancer is associated with tumor location and stage [J] .PLoS One,2017,12(1):e0169124.
- [24] Hashimoto I,Nagata T,Sekine S,et al.Prognostic significance of KLF4 expression in gastric cancer [J] .Oncol Lett,2017,13(2):819-826.
- [25] Li N,Deng W,Ma J,et al.Prognostic evaluation of Nanog,Oct4,Sox2,PCNA,Ki67 and E-cadherin expression in gastric cancer [J] .Med Oncol,2015,32(1):433.
- [26] Saad RS,Ghorab Z,Khalifa MA,et al.CDX2 as a marker for intestinal differentiation:Its utility and limitations [J] .World J Gastrointest Surg,2011,3(11):159-166.
- [27] Liu YQ,Bai ZG,Ma XM,et al.CDX2 inhibits invasion and migration of gastric cancer cells by phosphatase and tensin homologue deleted from chromosome 10/Akt signaling pathway [J] .Chin Med J (Engl),2015,128(8):1065-1071.
- [28] Wei W,Li L,Wang X,et al.Overexpression of caudal type homeobox transcription factor 2 inhibits the growth of the MGC-803 human gastric cancer cell line in vivo [J] .Mol Med Rep,2015,12(1):905-912.
- [29] Kang JM,Lee BH,Kim N,et al.CDX1 and CDX2 expression in intestinal metaplasia,dysplasia and gastric cancer [J] .J Korean Med Sci,2011,26(5):647-653.
- [30] Zhang JF,Zhang JG,Kuai XL,et al.Reactivation of the homeotic tumor suppressor gene CDX2 by 5-aza-2'-deoxycytidine-induced demethylation inhibits cell proliferation and induces caspase-independent apoptosis in gastric cancer cells [J] .Exp Ther Med,2013,5(3):735-741.
- [31] ZHANG Qiujie.Expression of CDX2 in gastric cancer and its relationship with Ki67 [J] .Pract J Cancer,2016,31(7):1062-1064. [张秋杰.胃癌组织中CDX2表达及其与Ki67的关系分析 [J] .实用癌症杂志,2016,31(7):1062-1064.]
- [32] LIU Guisheng,ZHOU Zihan,GUO Xueyan,et al.Expression and significance of homeobox transcription factor CDX2 and hepatic intestinal cadherin CDH17 in intestinal metaplasia and gastric cancer tissues [J] .Shaanxi Med J,2017,46(3):290-293. [刘贵生,周子涵,郭雪艳,等.同源盒转录因子CDX2与肝肠钙粘连蛋白CDH17在肠上皮化生及胃癌组织中的表达及意义 [J] .陕西医学杂志,2017,46(3):290-293.]
- [33] ZHANG Peihua,SHEN Liwei,SONG Xiaohong,et al.Expression and clinical significance of CDX2 in gastric cancer tissues [J] .World Latest Medicine Information,2016,16(86):145-146. [张佩华,沈李伟,宋晓红,等.CDX2在胃癌组织中的表达及其临床意义 [J] .世界最新医学信息文摘,2016,16(86):145-146.]
- [34] LI Caiping.Expression and significance of CDX2 protein,P53 protein and Ki67 antigen in gastric cancer tissues [D] .Fuzhou:Fujian Medical University,2014:38. [李彩苹.CDX2蛋白、P53蛋白和Ki67抗原在胃癌组织中的

表达及意义 [D].福州:福建医科大学,2014:38.]

[35] ZHAI Meijuan,FU Qiong,CAI Lubing.Expression and clinical significance of CDX-2 and COX-2 in gastric cancer [J].Chin J Integr Med,2013,19(2):133-136. [翟梅娟,付琼,蔡路兵.CDX-2和COX-2在胃癌中的表达及临床意义 [J].中国中西医结合外科杂志,2013,19(2):133-136.]

[36] SU Shuai,CHEN Xin,JIANG Kui,et al.Expression and significance of CDX2 COX-2 and NF- $\kappa$ B in gastric cancer and precancerous lesions [J].Chin J Clin Oncol,2013,40(22):1387-1390. [苏帅,陈鑫,姜葵,等.CDX2 COX-2和NF- $\kappa$ B在胃癌和癌前病变中的表达和意义 [J].中国肿瘤临床,2013,40(22):1387-1390.]

[37] Ikarashi S,Nishikura K,Ajioka Y,et al.Re-evaluation of phenotypic expression in undifferentiated-type early gastric adenocarcinomas using mucin core protein and CDX2 [J].Gastric Cancer,2013,16(2):208-219.

[38] Zhang Y,Wang H,Bi C,et al.Expression of CDX2 in gastric cardia adenocarcinoma and its correlation with H.pylori and cell proliferation [J].Oncotarget,2016,7(34):54973-54982.

[39] Masood MA,Loya A,Yusuf MA.CDX2 as a prognostic marker in gastric cancer [J].Acta Gastroenterol Belg,2016,79(2):197-200.

[40] Tanaka T,Jiang S,Hotta H,et al.Dysregulated expression of P1 and P2 promoter-driven hepatocyte nuclear factor-4alpha in the pathogenesis of human cancer [J].J Pathol,2006,208(5):662-672.

[41] Chang HR,Nam S,Kook MC,et al.HNF4alpha is a therapeutic target that links AMPK to WNT signalling in early-stage gastric cancer [J].Gut,2016,65(1):19-32.

[42] Moore BD,Khurana SS,Huh WJ,et al.Hepatocyte nuclear factor 4alpha is required for cell differentiation and homeostasis in the adult mouse gastric epithelium [J].Am J Physiol Gastrointest Liver Physiol,2016,311(2):G267-G275.

[43] Kojima K,Kishimoto T,Nagai Y,et al.The expression of hepatocyte nuclear factor-4 $\alpha$ ,a developmental regulator of visceral endoderm,correlates with the intestinal phenotype of gastric adenocarcinomas [J].Pathology,2006,38(6):548-554.

[44] Ma Y,Wei X,Wu Z.HNF-4alpha promotes multidrug resistance of gastric cancer cells through the modulation of cell apoptosis [J].Oncol Lett,2017,14(6):6477-6484.

[45] Ma L,Zeng J,Guo Q,et al.Mutual amplification of HNF4 $\alpha$  and IL-1R1 composes an inflammatory circuit in Helicobacter pylori associated gastric carcinogenesis [J].Oncotarget,2016,7(10):11349-11363.

[46] Uozaki H,Barua RR,Minhua S,et al.Transcriptional factor typing with SOX2,HNF4aP1,and CDX2 closely relates to tumor invasion and Epstein-Barr virus status in gastric cancer [J].Int J Clin Exp Pathol,2011,4(3):230-240.

[47] Takano K,Hasegawa G,Jiang S,et al.Immunohistochemical staining for P1 and P2 promoter-driven hepatocyte nuclear factor-4 $\alpha$  may complement mucin phenotype of differentiated-type early gastric carcinoma [J].Path Int,2009,59(7):462-470.

---

**备注/Memo:** National Natural Science Foundation of China(No.81470805, 81873554) ; 国家自然科学基金项目(编号: 81470805, 81873554)

---

更新日期/Last Update: 1900-01-01