世界华人消化杂志 2013年2月18日; 21(5): 373-380
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

述评 EDITORIAL

肿瘤干细胞相关信号通路与食管鳞癌的研究进展

沐 雨, 李苏宜

沐雨, 李苏宜, 东南大学附属中大医院肿瘤科 江苏省南京市 210009
李苏宜, 博士, 教授, 主任医师, 主要从事晚期食管癌内科临床及应用型基础研究工作.
南京市医学科技发展基金资助项目, No. YKK 11060
作者贡献分布: 本文由沐雨完成综述, 李苏宜审校.
通讯作者: 李苏宜, 教授, 210009, 江苏省南京市丁家桥87号, 东南大学附属中大医院肿瘤科. lkisuyi@csco.org.cn
电话: 025-83272338
收稿日期: 2012-12-12 修回日期: 2013-01-11
接受日期: 2013-01-30 在线出版日期: 2013-02-18

Advances in research of signaling pathways associated with cancer stem cells in esophageal squamous cell carcinoma

Yu Mu, Su-Yi Li

Yu Mu, Su-Yi Li, Department of Oncology, Zhongda Hospital, Southeast University, Nanjing 210009, Jiangsu Province, China
Supported by: the Medical Science and Technology Department Program of Nanjing, No. YKK 11060
Correspondence to: Su-Yi Li, Professor, Department of Oncology, Zhongda Hospital, Southeast University, 87 Dingjiaqiao, Nanjing 210009, Jiangsu Province, China. lkisuyi@csco.org.cn
Received: 2012-12-12 Revised: 2013-01-11
Accepted: 2013-01-30 Published online: 2013-02-18

Abstract
The discovery of cancer stem cells has led to a better understanding of mechanisms underlying the occurrence, development and metastasis of cancer. Three signaling pathways, Wnt, PIP3, and Hedgehog, play an important role in self-renewal and differentiation of stem cells. Once abnormalities occur in these signaling pathways, cancer stem cells will present aberrant differentiation and unlimited proliferation and eventually develop into tumors. Although there is still controversy over the existence of stem cells in esophageal squamous cell carcinoma (ESCC), more and more evidence suggests that the above three signaling pathways are important in promoting the differentiation of esophageal epithelial cells, accelerating the progression of ESCC and causing radiotherapy and chemotherapy resistance.

Key Words: Cancer stem cells; Esophageal squamous cell carcinoma; Signaling pathway

Mu Y, Li SY. Advances in research of signaling pathways associated with cancer stem cells in esophageal squamous cell carcinoma. Shijie Huaren Xiaohua Zazhi 2013; 21(5): 373-380 URL: http://www.wjgnet.com/1009-3079/21/373.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i5.373

摘要
由于肿瘤干细胞的发现, 人们对肿瘤发生、发展、转移机制有了进一步了解. Wnt/β-catenin、PIP3、Hedgehog等信号通路对肿瘤干细胞自我更新与分化起重要作用, 一旦信号通路发生异常, 即可促肿瘤干细胞异常分化和无限增殖. 虽不能完全确定食管鳞癌存在肿瘤干细胞, 但越来越多证据提示, 这3条肿瘤干细胞信号通路促食管上皮组织不良分化、食管癌发生发展进程甚至放化疗抵抗.

关键词: 肿瘤干细胞; 食管鳞癌; 信号转导

沐雨, 李苏宜. 肿瘤干细胞相关信号通路与食管鳞癌的研究进展. 世界华人消化杂志 2013; 21(5): 373-380 URL: http://www.wjgnet.com/1009-3079/21/373.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i5.373

0 引言
1959年, Makino等[1]首次提出肿瘤干细胞假说, 并指出肿瘤可能由肿瘤干细胞产生. 2001年, 肿瘤干细胞(cancer stem cells, CSCs)概念被正式提出. CSCs是存在于肿瘤组织中少量具有无限增殖和不定向分化潜能细胞群体, 是形成不同分化程度肿瘤细胞和肿瘤胞不断生长、转移的根源. 肿瘤组织具干细胞特性细胞不足5%, 但决定肿瘤发生、侵袭、转移、播散和对放化疗敏感性. 研究表明, 肿瘤干细胞受Wnt[2-6]、PIP3[7-12]、Hedgehog[13-16]等信号调节途径调控, 不同肿瘤发生发展过程均发挥重要作用. 越来越多证据提

■背景资料
食管癌是我国的高发肿瘤, 具有发病率高、死亡率高等特点. 我国食管癌病理类型以食管鳞状细胞癌(ESCC)为主. 越来越多的研究提示ESCC存在肿瘤干细胞, 并且受到肿瘤干细胞相关信号通路的调节, 与其不良生物学行为及药物耐受等密切相关.

■同行评议者
杜祥, 教授, 主任医师, 上海复旦大学附属肿瘤医院; 程英升, 教授, 同济大学附属第十人民医院影像临床医学中心

■研发前沿
西方人对于肿瘤干细胞相关信号通路Wnt、PIP3、Hedgehog等在食管腺癌及Barrett食管中发挥的重要调控作用进行了很多研究. 借鉴西方的研究经验, 许多中国学者结合中国国情认真严谨地开展了一系列肿瘤干细胞相关信号通路与ESCC关系的系统研究.

示, 这3条肿瘤干细胞信号通路促食管上皮组织不良分化、食管癌发生发展进程甚至放化疗抵抗. 现就这3条信号转导通路与食管癌干细胞及食管鳞状细胞癌(esophageal squamous cell carcinoma, ESCC)的关系进行综述.

1 食管上皮干细胞与食管鳞癌干细胞

由于肿瘤发生是正常细胞至少4-7次突变累积的过程, 只有干细胞有足够长寿命累积多次突变形成CSCs引发肿瘤, 倾向认为CSCs起源于成体组织干细胞[17]. 食管上皮干细胞主要分布区是基底层的乳头间基底层(the interpapillary basal layer, IBL), 这些细胞体内呈现增殖极不活跃以及分裂不对称、体外培养具较强克隆形成能力特点及最幼稚分化表型[18]. Okumura等[19]研究证明, 食管上皮干细胞呈低亲和性神经营养素受体p75NTR阳性, 具增殖、自我更新及多向分化能力. 而越来越多的研究提示p75NTR更是ESCC的CSCs表面标志, Okumura等[20]免疫组织化学法检测中高分化食管癌组织p75NTR阳性表达细胞分布在肿瘤侵袭性边缘1-2层, 低分化食管癌组织呈弥散分布. Huang等[21]将ESCC细胞于无血清培养液(SFM)中培养和标记p75NTR, 证实其能在SFM中悬浮生长并形成细胞球, $p75NTR^+$细胞在细胞球中比例较普通培养细胞系中高. 高全力等[22]同样以$p75NTR^+$为富集标志建立细胞系并证实了其成瘤作用. 目前, 研究用ESCC的CSCs常以从ESCC细胞系中予以侧群细胞分选、表面标志分选或无血清培养基培养等方法获得, 实验室多采用p75NTR作为分选ESCC干细胞的表面标志[21,22]. Podoplanin是一种跨膜糖蛋白[23], 主要表达于生长中和成熟的淋巴管内皮细胞表面, 袁世发等[24]发现Podoplanin在食管肿瘤内淋巴管细胞也有表达. 人类乙醛脱氢酶1(aldehyde dehydrogenase 1, ALDH1)基因表达存在于细胞质, 其基因克隆和定位在9q21染色体, ALDH1在干细胞中表达增高, 维持干细胞特性和干细胞分化, 国内学者采用基因芯片检测具有干细胞特性的食管癌细胞株ALDH1各亚型均表达上调[25].

2 Wnt信号通路

Wnt信号转导通路在进化上高度保守, 在胚胎发育、细胞繁殖及凋亡等生命过程中发挥重要作用, 其功能异常与肿瘤发生、发展有关. β-连环素(β-catenin)稳定是经典Wnt信号通路核心, 正常成熟细胞β-catenin水平低, Wnt信号通路处于关闭状态. 当肿瘤干细胞处于活化状态时β-catenin降解障碍, 胞质内游离β-catenin增多并与TCF/LEF-1结合进入细胞核, 激活下游靶基因c-myc、cyclin D1转录, 而促多种肿瘤发生及发展: β-catenin水平失控致结肠直肠癌等发生[2]; Wnt通路对乳腺干细胞转化和维持稳态起重要作用[3], 乳腺癌Wnt通路状态与$CD44^+/CD24^-/Lin^-$细胞转移密切关系[4]; Wnt通路持续异常激活是引发间皮瘤、鼻咽癌重要机制[5,6]. ESCC组织Wnt信号通路在2000年被人首次关注, de Castro等[26]等免疫组织化学检测39例ESCC组织, 发现β-连环蛋白表达与p53, E-钙黏蛋白, Bcl-2和Ki-67表达相关. 所有被检测到β-catenin的表达均定位于细胞膜, 常呈异构形态. 其中7例也表达于细胞质和细胞核中, 且这7个肿瘤分别定位在食管上部(3)或中部(4)三分之一. 所有标本都表达Bcl-2, 而其中仅1例表达p53. 本文认为表达β-catenin的组织可能是ESCC中一个特异性表现亚型.

食管上皮分化过程与Wnt通路有关[27,28], ESCC发生发展与Wnt信号通路异常是否有关? Brown等[29]检测食管癌细胞系中常见易位断点, 发现大量为Wnt信号通路作用点, 提示Wnt通路在食管癌中可能活化. Salahshor等[30]检测30例ESCC标本Wnt信号重要成员发现, 许多下游基因或蛋白异常表达和/或局部富集, 包括糖原合成酶激酶-α/β(34%), AXIN2(48%), α-连环素(31%), MYC(73%), cycline D1(46%), 并且有13%标本呈β-catenin胞核积聚, 60%标本表现E-cadherin胞核积聚. 彭辉等[31]应用组织芯片检测ESCC组织样本Wnt信号通路4种主要蛋白, APC和E-cadherin阳性率分别69.6%、19.6%, 均低于各自正常组(98.0%, 96.3%, $P<0.01$), β-catenin和cycline D1在ESCC的异常表达率分别为65.5%和70.9%, 均高于各自正常组(1.2%, 0.8%, $P<0.01$). 2009年, Huang等[32]检测具有肿瘤干细胞样作用ESCC侧群细胞发现, Wnt信号通路相关基因FZD10、PTGS2、KLF5上调. 以上证据提示, ESCC发生发展与Wnt信号通路异常有关, β-catenin胞核中积累可能是ESCC发生关键步骤[33].

体外研究结论较一致: Wnt信号通路异常活化促ESCC细胞株分化增值, 抑制该通路某些节点可有效阻止ESCC不良生物学行为. Taniguchi等[34]在mRNA水平与正常细胞系比较, 食管癌细胞系Wnt抑制因子-1(Wnt inhibitor-1, WIF-1)

有73.7%(14/19)表达下调. 以基因修饰手法改变ESCC细胞株TE1的WIF-1表达状态后, 可有效转变其集落形成、细胞增殖、非停泊性生长等多种生物学行为. Chai等[35]发现生长相关基因CCN1可通过整合素α11诱导ESCC细胞癌中β-catenin重分布, 而β-catenin核异位又可诱导CCN1进一步升高, 两者相互作用在诱导ESCC发生过程中起重要作用. Mizushima等[36]在可提供Wnt家族成员Wnt-1环境介质中培养ESCC细胞株, 检测到胞质内β-catenin集聚. Zhou等[37]发现, ESCC的Wnt/β-catenin通路活化带动下游垂体瘤转化基因(PTTG)过表达, 在肿瘤发生过程起重要作用. Wang等[38]使用硝普钠和siRNA抑制β-catenin, 不仅β-catenin被抑制, 其下游c-myc和cycline D1也被抑制, 诱导细胞周期阻滞或细胞凋亡.

Wnt信号调节因子以启动子甲基化为失活方式, 去甲基化干预措施可抑制ESCC细胞株生长. Huang等[39]在ESCC患者中检测到启动子甲基化(86%, 56/70)和调控Wnt信号通路的序列特异性单链DNA结合蛋白2(SSBP2)下调. 在原本不表达SSBP2的ESCC细胞系TE1中引入SSBP2, 则细胞株明显活力下降和生长抑制. Meng等[40]等在ESCC细胞系EC9706对另一Wnt信号通路调节因子卷曲蛋白1(SFRP1)研究取得相似结果: 甲基化事件在ESCC中较无瘤组织多, 且启动子甲基化和组蛋白乙酰化可能联合作用调节其表达. Li等[41]发现ESCC中对抗Wnt信号通路蛋白Wnt5A由CpG岛甲基化引发沉默. Chan等[42]在12/19 ESCC细胞系检测到WIF-1下调或沉默(甲基化), 27%(25/92)原发肿瘤灶检测到WIF-1甲基化状态, 体外以去甲基化药物地西他宾干预抑制Wnt信号通路观察到明显肿瘤抑制作用. 另一些可通过或者至少是部分通过Wnt信号通路在ESCC成瘤过程中起调节作用的节点蛋白还包括: SOX17[43]、PREM5[44]、DKK1[45,46]、Wnt2[47]、TP63 P2启动子[48]等.

研究还发现Wnt信号通路某些关键基因与ESCC预后及放化疗敏感性有关. Li等[49]免疫组织化学检测121例标本, Axin蛋白表达与食管癌浸润深度(P = 0.033)呈负相关. 单因素分析显示Axin蛋白表达降低、淋巴结转移和远处转移是显著预后不良因素. 多变量分析Axin降低是不良预后指标(P = 0.005). DKK1[50]、WISP-1[51]及WIF-1[52]等异常表达可能是根治性术后食管癌患者不良预后指标. 研究发现, 干扰素诱导跨膜蛋白-1(interferon induced transmembrane protein 1, IFITM1)[53]与食管癌细胞株顺铂敏感性有关, LEF1和β-catenin[54]是导致食管癌细胞放疗无效重要基因.

3 PIP3信号通路

PTEN基因是第10号染色体同源丢失性磷酸酶-张力蛋白基因, 由多功能磷酸酶编码抑癌基因, 具磷酸酯酶活性和调节细胞周期、诱导肿瘤细胞凋亡及抑制其生长、侵袭转移等功能, 主要由3条途径共同完成: FAK、MAPK和PIP3(PTEN/PI3K/Akt). 其中主要通过PTEN/PI3K/Akt信号通路: 生长因子与细胞表面相应受体结合后, 激活细胞内3-磷脂酰肌醇激酶(phosphatidylinositol 3-hydroxy kinase, PI3K), 后者与丝-苏氨酸激酶(serine-threoninekinase, Akt)或蛋白激酶B(protein kinase B, PKB)结合, 激活PKB, 使细胞从G_1期进入S期, 促细胞增生, 避免细胞凋亡发生. PTEN编码蛋白对抗PI3K, 阻止PI3K调控生长因子信号转导通路, 使细胞停滞于G_1期, 诱导肿瘤细胞凋亡.

PTEN基因失活与肿瘤发生关系密切, 方式有突变、缺失、甲基化等, 以突变为主, PTEN基因在肿瘤干细胞中的失活可促进肿瘤的发生, 在多种肿瘤如恶性神经胶质瘤[7]、前列腺癌[8]、子宫内膜癌[9]、卵巢癌[10]、胃癌[11]、恶性黑色素瘤[12]中均已证实存在. 2008年, Chang等[55]免疫组织化学检测64例原发ESCC及其癌旁正常上皮组织, 癌组织中PTEN蛋白表达阳性率和染色等级均显著低于正常组织(P<0.001). ESCC的PTEN表达与肿瘤分化程度(P = 0.001), 浸润深度(P = 0.015)和pTNM分期(P = 0.048)均有关, PTEN阳性患者5年生存率82%, 而PTEN阴性患者仅39%(P = 0.0019). Zhang等[56]对PTEN通路下游PI3K蛋白对比检测发现在ESCC中表达阳性率为86.8%, 显著高于正常食管黏膜组织(10.0%, P<0.001), 且与分化程度、浸润深度、临床分期呈正相关. Ge等[57]对中国河北省某高发病率地区基因测序发现, PTEN IVS4^{+}/$^{+}$纯合子可能在食管癌的发展起到一定保护作用. Ma等[58]PCR法测226例ESCC和226例无瘤病例, 发现具PTEN rs2735343变异基因型预示着食管癌风险显著增高, 既有PTEN rs2735343变异又有P53 Arg72Pro多态性或吸烟, 则患病风险出现指数级叠加.

Hou等[59]从人胎盘组织和ESCC细胞分别对野生型和突变型PTEN基因进行克隆, 体外研究

■相关报道

中国食管鳞癌样本量大为研究提供了便利条件. 从大样本的检测发现相关信号通路关键节点蛋白表达量的变化, 到完整的体外干预和体内诱导, 从基础实验室数据得出推论, 到临床上证实某些新的相关标志物可预测复发预后或放化疗抵抗. 对于食管鳞癌, 我们对食管鳞癌的了解正日趋深入.

■创新盘点
食管鳞癌中肿瘤干细胞的研究还有很大的空间，而肿瘤干细胞的相关信号通路在ESCC中经大量研究证实也可发挥重要作用. 本文近年来对这一领域发表的文章进行总结，有针对性地选取Wnt、PIP3、Hedgehog 3条通路简要阐述其在ESCC中对易发性、生物学行为等的影响.

示EC9706细胞增殖可被野生型PTEN基因明显抑制, 而不能被突变型PTEN基因抑制; 体内研究示野生型PTEN基因可抑制裸鼠体内移植瘤的生长, 诱导细胞凋亡, 并提高EC9706细胞对顺铂敏感性. Li等[60]从ESCC标本中富集SP细胞, 发现其更强化疗抗性和繁殖功能, 体内实验证实其更强致瘤性, 该群细胞具有干细胞功能, 后续研究表明PIP3通路对此侧群细胞发挥重要调控作用. 另有RhoE[61]、PKCι[62]、CRT[63]、Id-1[64]等多种蛋白被证实可在体内和分子水平通过PIP3途径增强ESCC细胞抗失巢凋亡.

针对PTEN基因及其相关蛋白干预性研究结果较为一致, 提示其可有效改变ESCC组织细胞的不良生物学行为. ESCC标本乳酸脱氢酶(LDHA)升高, LDHA沉默则可降低AKT活化[65], PIM-1[66]降低Akt磷酸化水平. TC21通过PIP3信号通路, 增强食管癌细胞耐药性, 降低对顺铂敏感性, siRNA介导TC21下调增加癌细胞对顺铂[67]和放疗[68]敏感性. 过表达PI3K-C2β的Eca109细胞耐受顺铂细胞毒作用, 抑制Eca109细胞PI3K-C2β表达则显著增强顺铂诱导的细胞凋亡[69]. 最新研究[70]表明, cycline B1过表达可依赖Bcl-2蛋白调控的内在凋亡途径, 并通过PIP3信号通路衰减顺铂或紫杉醇诱导的ESCC细胞凋亡.

以上研究提示, 在其他肿瘤干细胞中发挥重要作用的PIP3通路, 在ESCC的发生发展、转移播散和放化疗敏感性等方面也在发挥关键调控效能.

4 Hedgehog信号通路

Hedgehog(HH)基因于1980年由Nusslein-Vollhard和Wieschaus在研究果蝇基因突变时发现. 果蝇只有一种HH基因, 而脊椎动物至少发现3种同源基因: Sonic hedgehog(SHH)、Indian hedgehog(IHH)和Desert hedgehog(DHH), 分别编码3种相应蛋白: SHH、IHH和DHH. 由这3种HH同源基因及下游相关分子组成Hedgehog信号通路, 在哺乳动物胚胎发育和组织发生过程中, 影响着细胞间识别、增殖及命运等众多生理过程. Hedgehog信号通路主要由配体Hedgehog、跨膜蛋白受体patched(Ptch) 和smoothened(Smo)以及下游的转录因子Gli(Gli1、Gli2和Gli3)级联构成. HH信号通路与肿瘤干细胞的关系最早在髓母细胞瘤[13]中被证实, 现在发现, Hedgehog信号通路异常可调节肿瘤干细胞, 与脑病神经瘤[14]、基底细胞癌[15]、肺癌[16]等多种肿瘤形成有关.

Berman等[71]将来源于食管、胃、胆、胰腺和结肠癌的细胞系进行培养, 使用RT-PCR检测其SHH和IHH的mRNA水平, 97%细胞系同时表达两者mRNA. Ptch和Gli作为HH信号活性的指示, 同时在多数肿瘤细胞系表达. Mori等[72]采用免疫组织化学法检测发现, ESCC组织标本Gli-1蛋白表达与肿瘤浸润深度和阳性淋巴结转移密切相关; 体外研究, Gli-1在31种食管癌细胞系中存在高表达, Gli-1基因和蛋白表达水平是反映Hedgehog信号通路活性可靠指标. 为进一步验证Hedgehog通路ESCC扮演角色, Yang等[73]采用PCR和原位杂交互为印证的方法检测一系列Hedgehog下游作用靶基因, 证实其下游基因HIP、PDGFRα、SMO和SUFU基因在ESCC呈高表达. 2012年, Yang等[74]发现PTCH1表达是Hedgehog信号通路最可靠生物标志物, 通过检测PTCH1发现Hedgehog信号通路活化是食管癌发生发展早期分子事件, 食管腺癌和食管鳞癌均有一定发生率.

Hedgehog信号通路一些蛋白或下游信号, 如Gli-1阳性[75]、BMI1阳性[76]等与新辅助化放疗后食管鳞癌患者的早期复发及预后不良明显相关, 其平均DFS、平均OS等显示显著差异, 提示Hedgehog通路激活参与促恶性肿瘤CRT后再生和发展. Zhu等[77]对100例新辅助化放疗ESCC活检标本进行PTCH1和GLI-1检测, 发现分别76%和72%标本表达升高, PTCH1和GLI-1表达与肿瘤大小, 局部进展和对放化疗反应程度显著相关. 单因素分析显示, 高PTCH1和GLI-1表达与局部复发快, DFS和OS差有关, 而多变量分析显示PTCH1和GLI-1分别为独立预后因素.

5 其他信号通路及信号通路交叉作用

ESCC最常见遗传病变是*p53*基因突变和EGFR过表达, Notch信号通路与两者负调控均有关, 且与Wnt通路相互影响[78]. Isohata等[79]指出, 未分化食管上皮细胞和大多数ESCC细胞共表达Hedgehog和EMT信号基因, 首次提出Hedgehog信号和EMT具有交叉作用. PTK6[80]可降低Akt和GSK3β磷酸化, 而激活β-catenin. Wei等[81]发现HH靶基因高表达与Akt活化有关. 对GLI1或P-AKT的表达与食管癌标本的临床病理特征之间的关系的分析发现: GLI1的表达与淋巴管浸润(P = 0.016), 血管侵犯(P = 0.006)和预后差(P = 0.003)有关, 而P-AKT的表达与血管侵犯(P = 0.031)和预后差(P = 0.031)有关. TE-1和TE-10细

胞系体外研究, PIP3途径在表皮生长因子、Gβγ及N-Shh刺激下在HH信号通路中发挥重要作用, Shh通路可在PIP3和MAPK协同作用促食管癌细胞存活和增殖. He等[82]还发现HH通路可通过sFRP-1作用抑制Wnt信号通路.

6 结论

现有研究证据提示, 肿瘤干细胞信号通路传导信号Wnt/β-catenin、PIP3、Hedgehog有效调控了ESCC的发生发展过程以及放化疗敏感性等生物学行为. 根据肿瘤干细胞相关信号通路转导通路机制研究线索, 揭示ESCC发病及发展机制, 成功发掘ESCC分子标志物, 针对不同亚型ESCC基因表达、侵袭转移、药物敏感和预后差异, 为ESCC的临床分子分型诊断与针对性根治提供新的研究方向, 因此进一步深入研究ESCC肿瘤干细胞相关信号通路转导机制十分必要.

■应用要点

本文阐述了对肿瘤干细胞发挥重要调控作用的信号通路与食管鳞癌的密切关系, 为未来诊治食管鳞癌、选择综合治疗方案等提供了新的思路.

7 参考文献

1 Makino S. The role of tumor stem-cells in regrowth of the tumor following drastic applications. *Acta Unio Int Contra Cancrum* 1959; 15: 196-198 [PMID: 14420161]

2 Longo KA, Wright WS, Kang S, Gerin I, Chiang SH, Lucas PC, Opp MR, MacDougald OA. Wnt10b inhibits development of white and brown adipose tissues. *J Biol Chem* 2004; 279: 35503-35509 [PMID: 15190075 DOI: 10.1074/jbc.M402937200]

3 Boras-Granic K, Wysolmerski JJ. Wnt signaling in breast organogenesis. *Organogenesis* 2008; 4: 116-122 [PMID: 19279723 DOI: 10.4161/org.4.2.5858]

4 Curtin JC, Lorenzi MV. Drug discovery approaches to target Wnt signaling in cancer stem cells. *Oncotarget* 2010; 1: 563-577 [PMID: 21317452]

5 Batra S, Shi Y, Kuchenbecker KM, He B, Reguart N, Mikami I, You L, Xu Z, Lin YC, Clément G, Jablons DM. Wnt inhibitory factor-1, a Wnt antagonist, is silenced by promoter hypermethylation in malignant pleural mesothelioma. *Biochem Biophys Res Commun* 2006; 342: 1228-1232 [PMID: 16516163 DOI: 10.1016/j.bbrc.2006.02.084]

6 Lin YC, You L, Xu Z, He B, Mikami I, Thung E, Chou J, Kuchenbecker K, Kim J, Raz D, Yang CT, Chen JK, Jablons DM. Wnt signaling activation and WIF-1 silencing in nasopharyngeal cancer cell lines. *Biochem Biophys Res Commun* 2006; 341: 635-640 [PMID: 16427602 DOI: 10.1016/j.bbrc.2005.12.220]

7 Tian XX, Zhang YG, Du J, Fang WG, Ng HK, Zheng J. Effects of cotransfection of antisense-EGFR and wild-type PTEN cDNA on human glioblastoma cells. *Neuropathology* 2006; 26: 178-187 [PMID: 16771172 DOI: 10.1111/j.1440-1789.2006.00679.x]

8 Davies MA, Kim SJ, Parikh NU, Dong Z, Bucana CD, Gallick GE. Adenoviral-mediated expression of MMAC/PTEN inhibits proliferation and metastasis of human prostate cancer cells. *Clin Cancer Res* 2002; 8: 1904-1914 [PMID: 12060635]

9 Sakurada A, Hamada H, Fukushige S, Yokoyama T, Yoshinaga K, Furukawa T, Sato S, Yajima A, Sato M, Fujimura S, Horii A. Adenovirus-mediated delivery of the PTEN gene inhibits cell growth by induction of apoptosis in endometrial cancer. *Int J Oncol* 1999; 15: 1069-1074 [PMID: 10568810]

10 Minaguchi T, Mori T, Kanamori Y, Matsushima M, Yoshikawa H, Taketani Y, Nakamura Y. Growth suppression of human ovarian cancer cells by adenovirus-mediated transfer of the PTEN gene. *Cancer Res* 1999; 59: 6063-6067 [PMID: 10626791]

11 Hang Y, Zheng YC, Cao Y, Li QS, Sui YJ. Suppression of gastric cancer growth by adenovirus-mediated transfer of the PTEN gene. *World J Gastroenterol* 2005; 11: 2224-2229 [PMID: 15818730]

12 Stewart AL, Mhashilkar AM, Yang XH, Ekmekcioglu S, Saito Y, Sieger K, Schrock R, Onishi E, Swanson X, Mumm JB, Zumstein L, Watson GJ, Snary D, Roth JA, Grimm EA, Ramesh R, Chada S. PI3 kinase blockade by Ad-PTEN inhibits invasion and induces apoptosis in RGP and metastatic melanoma cells. *Mol Med* 2002; 8: 451-461 [PMID: 12435856]

13 Berman DM, Karhadkar SS, Hallahan AR, Pritchard JI, Eberhart CG, Watkins DN, Chen JK, Cooper MK, Taipale J, Olson JM, Beachy PA. Medulloblastoma growth inhibition by hedgehog pathway blockade. *Science* 2002; 297: 1559-1561 [PMID: 12202832 DOI: 10.1126/science.1073733]

14 Kenney AM, Cole MD, Rowitch DH. Nmyc upregulation by sonic hedgehog signaling promotes proliferation in developing cerebellar granule neuron precursors. *Development* 2003; 130: 15-28 [PMID: 12441288 DOI: 10.1242/dev.00182]

15 Roop D, Toftgård R. Hedgehog in Wnterland. *Nat Genet* 2008; 40: 1040-1041 [PMID: 19165916 DOI: 10.1038/ng0908-1040 DOI: 10.1038/ng0908-1040]

16 Watkins DN, Berman DM, Burkholder SG, Wang B, Beachy PA, Baylin SB. Hedgehog signalling within airway epithelial progenitors and in small-cell lung cancer. *Nature* 2003; 422: 313-317 [PMID: 12629553 DOI: 10.1038/nature01493]

17 Sell S. On the stem cell origin of cancer. *Am J Pathol* 2010; 176: 2584-2594 [PMID: 20431026 DOI: 10.2353/ajpath.2010.091064]

18 Seery JP. Stem cells of theoesophageal epithelium. *J Cell Sci* 2002; 115: 1783-1789 [PMID: 11956310]

19 Okumura T, Shimada Y, Imamura M, Yasumoto S. Neurotrophin receptor p75(NTR) characterizes human esophageal keratinocyte stem cells in vitro. *Oncogene* 2003; 22: 4017-4026 [PMID: 12821936 DOI: 10.1038/sj.onc.1206525]

20 Okumura T, Tsunoda S, Mori Y, Ito T, Kikuchi K, Wang TC, Yasumoto S, Shimada Y. The biological role of the low-affinity p75 neurotrophin receptor in esophageal squamous cell carcinoma. *Clin Cancer Res* 2006; 12: 5096-5103 [PMID: 16951226 DOI: 10.1158/1078-0432.CCR-05-2852]

21 Huang SD, Yuan Y, Liu XH, Gong DJ, Bai CG, Wang F, Luo JH, Xu ZY. Self-renewal and chemotherapy resistance of p75NTR positive cells in esophageal squamous cell carcinomas. *BMC Cancer* 2009; 9: 9 [PMID: 19134212 DOI: 10.1186/1471-2407-9-9]

22 高全立. 肿瘤干细胞的分离鉴定. 郑州大学, 2009

23 Breiteneder-Geleff S, Matsui K, Soleiman A, Meraner P, Poczewski H, Kalt R, Schaffner G, Kerjaschki D. Podoplanin, novel 43-kd membrane protein of glomerular epithelial cells, is down-regulated in pu-

■同行评价
本文内容新颖, 观点清晰, 条理分明, 对肿瘤干细胞相关信号通路与ESCC的研究进行很好的概括总结.

romycin nephrosis. *Am J Pathol* 1997; 151: 1141-1152 [PMID: 9327748]
24 袁世发, 同李平, 丰帆, 张洪伟. 食管癌组织podoplanin的表达及其临床意义. 细胞与分子免疫学杂志 2011; 27: 435-437
25 苏华芳, 万秋燕, 邹燕, 张力, 李海英, 景钊, 吴式琇. 具干细胞特性食管癌耐放射细胞株基因表达分析. 肿瘤学杂志 2010; 16: 40-45
26 de Castro J, Gamallo C, Palacios J, Moreno-Bueno G, Rodríguez N, Feliu J, González-Barón M. beta-catenin expression pattern in primary oesophageal squamous cell carcinoma. Relationship with clinicopathologic features and clinical outcome. *Virchows Arch* 2000; 437: 599-604 [PMID: 11193470 DOI: 10.1007/s004280000266]
27 Woo J, Miletich I, Kim BM, Sharpe PT, Shivdasani RA. Barx1-mediated inhibition of Wnt signaling in the mouse thoracic foregut controls tracheo-esophageal septation and epithelial differentiation. *PLoS One* 2011; 6: e22493 [PMID: 21799872 DOI: 10.1371/journal.pone.0022493]
28 Chen H, Li J, Li H, Hu Y, Tevebaugh W, Yamamoto M, Que J, Chen X. Transcript profiling identifies dynamic gene expression patterns and an important role for Nrf2/Keap1 pathway in the developing mouse esophagus. *PLoS One* 2012; 7: e36504 [PMID: 22567161 DOI: 10.1371/journal.pone.0036504]
29 Brown J, Bothma H, Veale R, Willem P. Genomic imbalances in esophageal carcinoma cell lines involve Wnt pathway genes. *World J Gastroenterol* 2011; 17: 2909-2923 [PMID: 21734802 DOI: 10.3748/wjg.v17.i24.2909]
30 Salahshor S, Naidoo R, Serra S, Shih W, Tsao MS, Chetty R, Woodgett JR. Frequent accumulation of nuclear E-cadherin and alterations in the Wnt signaling pathway in esophageal squamous cell carcinomas. *Mod Pathol* 2008; 21: 271-281 [PMID: 18084253 DOI: 10.1038/modpathol.3800990]
31 彭辉, 钟雪云, 刘坤平, 李素梅. 应用组织芯片检测食管鳞状细胞癌中APC、β-catenin、E-cadherin和cycline D1的表达及其意义. 癌症 2009; 28: 38-41
32 Huang D, Gao Q, Guo L, Zhang C, Jiang W, Li H, Wang J, Han X, Shi Y, Lu SH. Isolation and identification of cancer stem-like cells in esophageal carcinoma cell lines. *Stem Cells Dev* 2009; 18: 465-473 [PMID: 18680391 DOI: 10.1089/scd.2008.0033]
33 Ren HZ, Wang JS, Pan GQ, Lv H, Wen JF, Luo GQ, Wang KS, Zhang PF. Comparative proteomic analysis of beta-catenin-mediated malignant progression of esophageal squamous cell carcinoma. *Dis Esophagus* 2010; 23: 175-184 [PMID: 19664078 DOI: 10.1111/j.1442-2050.2009.01001.x]
34 Taniguchi H, Yamamoto H, Hirata T, Miyamoto N, Oki M, Nosho K, Adachi Y, Endo T, Imai K, Shinomura Y. Frequent epigenetic inactivation of Wnt inhibitory factor-1 in human gastrointestinal cancers. *Oncogene* 2005; 24: 7946-7952 [PMID: 16007117 DOI: 10.1038/sj.onc.1208910]
35 Chai J, Modak C, Ouyang Y, Wu SY, Jamal MM. CCN1 Induces β-Catenin Translocation in Esophageal Squamous Cell Carcinoma through Integrin α11. *ISRN Gastroenterol* 2012; 2012: 207235 [PMID: 22701179 DOI: 10.5402/2012/207235]
36 Mizushima T, Nakagawa H, Kamberov YG, Wilder EL, Klein PS, Rustgi AK. Wnt-1 but not epidermal growth factor induces beta-catenin/T-cell factor-dependent transcription in esophageal cancer cells. *Cancer Res* 2002; 62: 277-282 [PMID: 11782388]
37 Zhou C, Liu S, Zhou X, Xue L, Quan L, Lu N, Zhang G, Bai J, Wang Y, Liu Z, Zhan Q, Zhu H, Xu N. Overexpression of human pituitary tumor transforming gene (hPTTG), is regulated by beta-catenin /TCF pathway in human esophageal squamous cell carcinoma. *Int J Cancer* 2005; 113: 891-898 [PMID: 15514942]
38 Wang W, Xue L, Liu H, Wang P, Xu P, Cai Y. Aberrant changes of Wnt2/beta-catenin signaling pathway induced by sodium nitroprusside in human esophageal squamous cell carcinoma cell lines. *Cancer Invest* 2010; 28: 230-241 [PMID: 19857041 DOI: 10.3109/07357900903095698]
39 Huang Y, Chang X, Lee J, Cho YG, Zhong X, Park IS, Liu JW, Califano JA, Ratovitski EA, Sidransky D, Kim MS. Cigarette smoke induces promoter methylation of single-stranded DNA-binding protein 2 in human esophageal squamous cell carcinoma. *Int J Cancer* 2011; 128: 2261-2273 [PMID: 20658532 DOI: 10.1002/ijc.25569]
40 Meng Y, Wang QG, Wang JX, Zhu ST, Jiao Y, Li P, Zhang ST. Epigenetic inactivation of the SFRP1 gene in esophageal squamous cell carcinoma. *Dig Dis Sci* 2011; 56: 3195-3203 [PMID: 21567192 DOI: 10.1007/s10620-011-1734-7]
41 Li J, Ying J, Fan Y, Wu L, Ying Y, Chan AT, Srivastava G, Tao Q. WNT5A antagonizes WNT/β-catenin signaling and is frequently silenced by promoter CpG methylation in esophageal squamous cell carcinoma. *Cancer Biol Ther* 2010; 10: 617-624 [PMID: 20603606]
42 Chan SL, Cui Y, van Hasselt A, Li H, Srivastava G, Jin H, Ng KM, Wang Y, Lee KY, Tsao GS, Zhong S, Robertson KD, Rha SY, Chan AT, Tao Q. The tumor suppressor Wnt inhibitory factor 1 is frequently methylated in nasopharyngeal and esophageal carcinomas. *Lab Invest* 2007; 87: 644-650 [PMID: 17384664]
43 Jia Y, Yang Y, Zhan Q, Brock MV, Zheng X, Yu Y, Herman JG, Guo M. Inhibition of SOX17 by microRNA 141 and methylation activates the WNT signaling pathway in esophageal cancer. *J Mol Diagn* 2012; 14: 577-585 [PMID: 22921431 DOI: 10.1016/j.jmoldx.2012.06.004]
44 Shu XS, Geng H, Li L, Ying J, Ma C, Wang Y, Poon FF, Wang X, Ying Y, Yeo W, Srivastava G, Tsao SW, Yu J, Sung JJ, Huang S, Chan AT, Tao Q. The epigenetic modifier PRDM5 functions as a tumor suppressor through modulating WNT/β-catenin signaling and is frequently silenced in multiple tumors. *PLoS One* 2011; 6: e27346 [PMID: 22087297 DOI: 10.1371/journal.pone.0027346]
45 Li S, Qin X, Liu B, Sun L, Zhang X, Li Z, Shan B, You J, Zhou Q. Dickkopf-1 is involved in invasive growth of esophageal cancer cells. *J Mol Histol* 2011; 42: 491-498 [PMID: 21909757 DOI: 10.1007/s10735-011-9347-1]
46 Sato N, Yamabuki T, Takano A, Koinuma J, Aragaki M, Masuda K, Ishikawa N, Kohno N, Ito H, Miyamoto M, Nakayama H, Miyagi Y, Tsuchiya E, Kondo S, Nakamura Y, Daigo Y. Wnt inhibitor Dickkopf-1 as a target for passive cancer immunotherapy. *Cancer Res* 2010; 70: 5326-5336 [PMID: 20551066 DOI: 10.1158/0008-5472.CAN-09-3879]
47 Fu L, Zhang C, Zhang LY, Dong SS, Lu LH, Chen J, Dai Y, Li Y, Kong KL, Kwong DL, Guan XY. Wnt2 secreted by tumour fibroblasts promotes tumour

progression in oesophageal cancer by activation of the Wnt/β-catenin signalling pathway. *Gut* 2011; 60: 1635-1643 [PMID: 21672941 DOI: 10.1136/gut.2011.241638]

48 Ruptier C, De Gaspéris A, Ansieau S, Granjon A, Tanière P, Lafosse I, Shi H, Petitjean A, Taranchon-Clermont E, Tribollet V, Voeltzel T, Scoazec JY, Maguer-Satta V, Puisieux A, Hainaut P, Cavard C, Caron de Fromentel C. TP63 P2 promoter functional analysis identifies β-catenin as a key regulator of ΔNp63 expression. *Oncogene* 2011; 30: 4656-4665 [PMID: 21643019 DOI: 10.1038/onc.2011.171]

49 Li AF, Hsu PK, Tzao C, Wang YC, Hung IC, Huang MH, Hsu HS. Reduced axin protein expression is associated with a poor prognosis in patients with squamous cell carcinoma of esophagus. *Ann Surg Oncol* 2009; 16: 2486-2493 [PMID: 19582507 DOI: 10.1245/s10434-009-0593-3]

50 Makino T, Yamasaki M, Takemasa I, Takeno A, Nakamura Y, Miyata H, Takiguchi S, Fujiwara Y, Matsuura N, Mori M, Doki Y. Dickkopf-1 expression as a marker for predicting clinical outcome in esophageal squamous cell carcinoma. *Ann Surg Oncol* 2009; 16: 2058-2064 [PMID: 19408050 DOI: 10.1245/s10434-009-0476-7]

51 Nagai Y, Watanabe M, Ishikawa S, Karashima R, Kurashige J, Iwagami S, Iwatsuki M, Baba Y, Imamura Y, Hayashi N, Baba H. Clinical significance of Wnt-induced secreted protein-1 (WISP-1/CCN4) in esophageal squamous cell carcinoma. *Anticancer Res* 2011; 31: 991-997 [PMID: 21498727]

52 Liu JB, Qiang FL, Dong J, Cai J, Zhou SH, Shi MX, Chen KP, Hu ZB. Plasma DNA methylation of Wnt antagonists predicts recurrence of esophageal squamous cell carcinoma. *World J Gastroenterol* 2011; 17: 4917-4921 [PMID: 22171134 DOI: 10.3748/wjg.v17.i44.4917]

53 Fumoto S, Shimokuni T, Tanimoto K, Hiyama K, Otani K, Ohtaki M, Hihara J, Yoshida K, Hiyama E, Noguchi T, Nishiyama M. Selection of a novel drug-response predictor in esophageal cancer: a novel screening method using microarray and identification of IFITM1 as a potent marker gene of CDDP response. *Int J Oncol* 2008; 32: 413-423 [PMID: 18202764]

54 Li HZ, Gao XS, Xiong W, Zhao J, Zhang H, Zhou DM. Identification of differentially expressed genes related to radioresistance of human esophageal cancer cells. *Chin J Cancer* 2010; 29: 882-888 [PMID: 20868558]

55 Chang D, Wang TY, Li HC, Wei JC, Song JX. Prognostic significance of PTEN expression in esophageal squamous cell carcinoma from Linzhou City, a high incidence area of northern China. *Dis Esophagus* 2007; 20: 491-496 [PMID: 17958724]

56 Zhang Y, Liu YP, Du K, Wang H, Wang XL. [Expression and clinical significance of PI3K in esophageal squamous cell carcinoma]. *Zhonghua Zhongliu Zazhi* 2011; 33: 594-598 [PMID: 22325219]

57 Ge H, Cao YY, Chen LQ, Wang YM, Chen ZF, Wen DG, Zhang XF, Guo W, Wang N, Li Y, Zhang JH. PTEN polymorphisms and the risk of esophageal carcinoma and gastric cardiac carcinoma in a high incidence region of China. *Dis Esophagus* 2008; 21: 409-415 [PMID: 19125794 DOI: 10.1111/j.1442-2050.2007.00786.x]

58 Ma J, Zhang J, Ning T, Chen Z, Xu C. Association of genetic polymorphisms in MDM2, PTEN and P53 with risk of esophageal squamous cell carcinoma. *J Hum Genet* 2012; 57: 261-264 [PMID: 22336889 DOI: 10.1038/jhg.2012.15]

59 Hou G, Lu Z, Liu M, Liu H, Xue L. Mutational analysis of the PTEN gene and its effects in esophageal squamous cell carcinoma. *Dig Dis Sci* 2011; 56: 1315-1322 [PMID: 21116717 DOI: 10.1007/s10620-010-1474-0]

60 Li H, Gao Q, Guo L, Lu SH. The PTEN/PI3K/Akt pathway regulates stem-like cells in primary esophageal carcinoma cells. *Cancer Biol Ther* 2011; 11: 950-958 [PMID: 21467840]

61 Zhao H, Yang J, Fan T, Li S, Ren X. RhoE functions as a tumor suppressor in esophageal squamous cell carcinoma and modulates the PTEN/PI3K/Akt signaling pathway. *Tumour Biol* 2012; 33: 1363-1374 [PMID: 22477709 DOI: 10.1007/s13277-012-0384-5]

62 Liu SG, Wang BS, Jiang YY, Zhang TT, Shi ZZ, Yang Y, Yang YL, Wang XC, Lin DC, Zhang Y, Yang H, Cai Y, Zhan QM, Wang MR. Atypical protein kinase Cι (PKCι) promotes metastasis of esophageal squamous cell carcinoma by enhancing resistance to Anoikis via PKCι-SKP2-AKT pathway. *Mol Cancer Res* 2011; 9: 390-402 [PMID: 21310827 DOI: 10.1158/1541-7786.MCR-10-0359]

63 Du XL, Yang H, Liu SG, Luo ML, Hao JJ, Zhang Y, Lin DC, Xu X, Cai Y, Zhan QM, Wang MR. Calreticulin promotes cell motility and enhances resistance to anoikis through STAT3-CTTN-Akt pathway in esophageal squamous cell carcinoma. *Oncogene* 2009; 28: 3714-3722 [PMID: 19684620 DOI: 10.1038/onc.2009.237]

64 Li B, Tsao SW, Li YY, Wang X, Ling MT, Wong YC, He QY, Cheung AL. Id-1 promotes tumorigenicity and metastasis of human esophageal cancer cells through activation of PI3K/AKT signaling pathway. *Int J Cancer* 2009; 125: 2576-2585 [PMID: 19551863 DOI: 10.1002/ijc.24675]

65 Yao F, Zhao T, Zhong C, Zhu J, Zhao H. LDHA is necessary for the tumorigenicity of esophageal squamous cell carcinoma. *Tumour Biol* 2013; 34: 25-31 [PMID: 22961700]

66 Li S, Xi Y, Zhang H, Wang Y, Wang X, Liu H, Chen K. A pivotal role for Pim-1 kinase in esophageal squamous cell carcinoma involving cell apoptosis induced by reducing Akt phosphorylation. *Oncol Rep* 2010; 24: 997-1004 [PMID: 20811681]

67 Hasan R, Chauhan SS, Sharma R, Ralhan R. siRNA-mediated downregulation of TC21 sensitizes esophageal cancer cells to cisplatin. *World J Gastroenterol* 2012; 18: 4127-4135 [PMID: 22919244 DOI: 10.3748/wjg.v18.i31.4127]

68 Huang S, Li XQ, Chen X, Che SM, Chen W, Zhang XZ. Inhibition of microRNA-21 increases radiosensitivity of esophageal cancer cells through phosphatase and tensin homolog deleted on chromosome 10 activation. *Dis Esophagus* 2012 Sep 7. *[Epub ahead of print]* [PMID: 22958183 DOI: 10.1111/j.1442-2050.2012.01389.x]

69 Liu Z, Sun C, Zhang Y, Ji Z, Yang G. Phosphatidylinositol 3-kinase-C2β inhibits cisplatin-mediated apoptosis via the Akt pathway in oesophageal squamous cell carcinoma. *J Int Med Res* 2011; 39: 1319-1332 [PMID: 21986133]

70 Ou Y, Ma L, Ma L, Huang Z, Zhou W, Zhao C, Zhang B, Song Y, Yu C, Zhan Q. Overexpression of cyclin B1 antagonizes chemotherapeutic-induced

apoptosis through PTEN/Akt pathway in human esophageal squamous cell carcinoma cells. *Cancer Biol Ther* 2013; 14: 45-55 [PMID: 23114644 DOI: 10.4161/cbt.22627]
71 Berman DM, Karhadkar SS, Maitra A, Montes De Oca R, Gerstenblith MR, Briggs K, Parker AR, Shimada Y, Eshleman JR, Watkins DN, Beachy PA. Widespread requirement for Hedgehog ligand stimulation in growth of digestive tract tumours. *Nature* 2003; 425: 846-851 [PMID: 14520411]
72 Mori Y, Okumura T, Tsunoda S, Sakai Y, Shimada Y. Gli-1 expression is associated with lymph node metastasis and tumor progression in esophageal squamous cell carcinoma. *Oncology* 2006; 70: 378-389 [PMID: 17179732]
73 Yang L, Bian Y, Huang S, Ma X, Zhang C, Su X, Chen ZJ, Xie J, Zhang H. Identification of signature genes for detecting hedgehog pathway activation in esophageal cancer. *Pathol Oncol Res* 2011; 17: 387-391 [PMID: 21210262 DOI: 10.1007/s12253-010-9337-8]
74 Yang L, Wang LS, Chen XL, Gatalica Z, Qiu S, Liu Z, Stoner G, Zhang H, Weiss H, Xie J. Hedgehog signaling activation in the development of squamous cell carcinoma and adenocarcinoma of esophagus. *Int J Biochem Mol Biol* 2012; 3: 46-57 [PMID: 22509480]
75 Yoshikawa R, Nakano Y, Tao L, Koishi K, Matsumoto T, Sasako M, Tsujimura T, Hashimoto-Tamaoki T, Fujiwara Y. Hedgehog signal activation in oesophageal cancer patients undergoing neoadjuvant chemoradiotherapy. *Br J Cancer* 2008; 98: 1670-1674 [PMID: 18475300 DOI: 10.1038/sj.bjc.6604361]
76 Yoshikawa R, Tsujimura T, Tao L, Kamikonya N, Fujiwara Y. The oncoprotein and stem cell renewal factor BMI1 associates with poor clinical outcome in oesophageal cancer patients undergoing preoperative chemoradiotherapy. *BMC Cancer* 2012; 12: 461 [PMID: 23046527 DOI: 10.1186/1471-2407-12-461]
77 Zhu W, You Z, Li T, Yu C, Tao G, Hu M, Chen X. Correlation of hedgehog signal activation with chemoradiotherapy sensitivity and survival in esophageal squamous cell carcinomas. *Jpn J Clin Oncol* 2011; 41: 386-393 [PMID: 21127038 DOI: 10.1093/jjco/hyq217]
78 Naganuma S, Whelan KA, Natsuizaka M, Kagawa S, Kinugasa H, Chang S, Subramanian H, Rhoades B, Ohashi S, Itoh H, Herlyn M, Diehl JA, Gimotty PA, Klein-Szanto AJ, Nakagawa H. Notch receptor inhibition reveals the importance of cyclin D1 and Wnt signaling in invasive esophageal squamous cell carcinoma. *Am J Cancer Res* 2012; 2: 459-475 [PMID: 22860235]
79 Isohata N, Aoyagi K, Mabuchi T, Daiko H, Fukaya M, Ohta H, Ogawa K, Yoshida T, Sasaki H. Hedgehog and epithelial-mesenchymal transition signaling in normal and malignant epithelial cells of the esophagus. *Int J Cancer* 2009; 125: 1212-1221 [PMID: 19431210 DOI: 10.1002/ijc.24400]
80 Ma S, Bao JY, Kwan PS, Chan YP, Tong CM, Fu L, Zhang N, Tong AH, Qin YR, Tsao SW, Chan KW, Lok S, Guan XY. Identification of PTK6, via RNA sequencing analysis, as a suppressor of esophageal squamous cell carcinoma. *Gastroenterology* 2012; 143: 675-686. e1-e12 [PMID: 22705009 DOI: 10.1053]
81 Wei L, Xu Z. Cross-signaling among phosphinositide-3 kinase, mitogen-activated protein kinase and sonic hedgehog pathways exists in esophageal cancer. *Int J Cancer* 2011; 129: 275-284 [PMID: 20839260 DOI: 10.1002/ijc.25673]
82 He J, Sheng T, Stelter AA, Li C, Zhang X, Sinha M, Luxon BA, Xie J. Suppressing Wnt signaling by the hedgehog pathway through sFRP-1. *J Biol Chem* 2006; 281: 35598-35602 [PMID: 17035233]

编辑 李军亮 电编 鲁亚静

ISSN 1009-3079 (print) ISSN 2219-2859 (online) DOI: 10.11569

• 消息 •

《世界华人消化杂志》于 2012-12-26 获得 RCCSE 中国权威学术期刊 (A+) 称号

本刊讯 《世界华人消化杂志》在第三届中国学术期刊评价中被武汉大学中国科学评价研究中心(RCCSE)评为“RCCSE中国权威学术期刊(A+)”. 本次共有6 448种中文学术期刊参与评价, 计算出各刊的最终得分, 并将期刊最终得分按照从高到低依次排列, 按照期刊在学科领域中的得分划分到A+、A、A-、B+、B、C级6个排名等级范围. 其中A+(权威期刊)取前5%; A(核心期刊)取前5%-20%; A-(扩展核心期刊)取前20%-30%; B+(准核心期刊)取前30%-50%; B(一般期刊)取前50%-80%; C(较差期刊)为80%-100%. (《世界华人消化杂志》编辑部)

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Room 1701, 17/F, Henan Building,
No. 90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

