世界华人消化杂志®
wcjd@wjgnet.com

世界华人消化杂志 2013年1月28日; 21(3): 205-210
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

述评 EDITORIAL

EMT在消化系肿瘤中的研究进展

丛宁宁, 张庆瑜

丛宁宁, 张庆瑜, 天津医科大学总医院消化科 天津市 300052
丛宁宁, 硕士, 主要从事消化系肿瘤的研究.
国家自然科学基金资助项目, No. 81172356
天津市重点基础科技项目基金资助项目, No. 10JCZDJC18500
作者贡献分布: 本文综述由丛宁宁完成; 张庆瑜审校.
通讯作者: 张庆瑜, 主任医师, 300052, 天津市和平区鞍山道154号, 天津医科大学总医院消化科. zhangqy@tijmu.edu.cn
电话: 022-60362207
收稿日期: 2012-11-04 修回日期: 2012-12-30
接受日期: 2013-01-05 在线出版日期: 2013-01-28

Role of EMT in gastrointestinal tract tumors

Ning-Ning Cong, Qing-Yu Zhang

Ning-Ning Cong, Qing-Yu Zhang, Department of Gastroenterology, General Hospital of Tianjin Medical University, Tianjin 300052, China
Supported by: the Natura1 Science Foundation of Tianjin, No. 81172356; and the Foundation of Tianjin Science and Technology Commission, No. 10JCZDJC18500
Correspondence to: Qing-Yu Zhang, Chief Physician, Department of Gas-troenterology, General Hospital of Tianjin Medical University, 154 Anshan Road, Heping District, Tianjin 300052, China. zhangqy@tijmu.edu.cn
Received: 2012-11-04 Revised: 2012-12-30
Accepted: 2013-01-05 Published online: 2013-01-28

Abstract
Epithelial-mesenchymal transition (EMT) refers to the process by which cells transit from epithelial phenotype to mesenchymal phenotype. EMT is important for embryonic development, wound healing, and invasion of carcinomas. The molecular mechanisms of EMT are a hot topic of research in invasion and migration of malignant tumors, especially digestive carcinomas. Since malignant epithelial tumors account for a large proportion of tumors and are associated with very poor outcome and prognosis, exploration of the process of epithelial cell migration and invasion is of great significance for the prevention and treatment of tumors. The investigation of EMT provides a basis for understanding the pathogenesis of tumors and their prognosis and resistance to antitumor drugs. This review focuses on the molecular mechanisms and role of EMT in gastrointestinal tract tumors.

Key Words: Epithelial-mesenchymal transition; Gastrointestinal tract tumors

Cong NN, Zhang QY. Role of EMT in gastrointestinal tract tumors. Shijie Huaren Xiaohua Zazhi 2013; 21(3): 205-210

摘要
上皮-间质转化(epithelial-mesenchymal transition, EMT)是上皮细胞通过特定的程序转化为间质细胞的生物学过程, EMT在胚胎发育、创伤愈合、肿瘤的侵袭迁移等过程中起重要作用, EMT在恶性肿瘤的侵袭迁移病理过程中的分子机制成为研究热点, 尤其是消化系肿瘤方面. 由于上皮性肿瘤在恶性肿瘤中所占比例较大及转归预后较差, 探究上皮细胞在获得迁移侵袭能力的过程, 即EMT过程, 为消化系肿瘤的预防和治疗提供方向. EMT的研究将为消化系肿瘤患者的预后和抗肿瘤药物的应用提供依据. 本文对EMT的机制和在消化系肿瘤方面的研究进展作一综述.

关键词: 上皮-间质转化; 消化系肿瘤

丛宁宁, 张庆瑜. EMT在消化系肿瘤中的研究进展. 世界华人消化杂志 2013; 21(3): 205-210
http://www.wjgnet.com/1009-3079/21/205.asp

0 引言
在胚胎发育过程中, 上皮-间质转化(epithelial-mesenchymal transition, EMT)能促进组织重塑, 还可以促进创伤的愈合. 他与肿瘤的侵袭、转移和凋亡有密切的关系[1-3]. EMT的具体过程是指维持细胞顶端和基底部极性的紧密连接溶解, 顶部和基底部膜蛋白融合, 细胞获得了侵袭和迁移到细胞外基质的能力[4,5]. 组织或器官发生EMT后, 细胞的表形由鹅卵石样转变成纺锤体类似于成纤维细胞的形态学变化, 这个过程包括上皮细胞标志物E-钙黏蛋白(E-cadherin)表达下调, 间质细胞相关标志物波形蛋白(vimen-

■背景资料
消化系肿瘤的发病率和死亡率高, 预后较差. 近年来发现, 上皮-间质转化(EMT)在消化系肿瘤的侵袭迁移过程中发挥重要作用. 因此, 探讨其发生的分子机制是最近研究的热点. 多种信号通路可以调控EMT过程, 因此寻找信号通路中相应的靶点可为消化系肿瘤的防治提供依据.

■同行评议者
庄林, 主任医师, 昆明市第三人民医院肝病科

■研发前沿
EMT相关的信号通路阻断剂在消化系肿瘤治疗中的应用和研发受到国内外专家的广泛关注, 是肿瘤领域的研究热点.

tin)、N-钙黏蛋白(N-cadherin)等表达上调, 发生EMT后细胞的黏附力下降, 侵袭和转移能力增加[6].

1 促进EMT的转录因子

1.1 ZEB1/ZEB2 miR-200通过作用于锌指E-盒结合同源异形盒(zinc-finger E-box binding homeobox, ZEB)抑制E-cadherin的表达来改变细胞的表型, 内源性miR-200作用于ZEB1和ZEB2的3'非编码区, miR-200通过转录后机制调控蛋白的表达. ZEB1和ZEB2结合到E-cadherin启动子区域的E-box基序上, 抑制E-cadherin的转录, ZEB蛋白对人类恶性肿瘤的调控非常复杂, ZEB2在乳腺癌、胃癌、胰腺癌的前期表达上调. 研究表明ZEB2的表达受miR-200的调控, 而miR-200在肿瘤转移的早期表达下调的. 因此, 肿瘤转移的早期, miR-200的表达下调, ZEB2的表达上调, 使E-cadherin表达下降, 诱导了EMT的发生, 使肿瘤细胞的侵袭迁移能力增强[7,8].

从多种组织器官的miRNA表达情况的调查研究中发现miR-200和miR-205在维持上皮细胞的表型方面起着重要的作用, 二者均能调控ZEB1和ZEB2表达. 在癌症转移的早期阶段, miR-200和miR-205的表达下调[9,10].

1.2 Twist Twist是具有螺旋-环-螺旋结构的转录因子, 他能抑制E-cadherin的表达, 诱导EMT的发生. E-cadherin表达下调或缺失时, Twist的表达上调. 最近实验证明分别敲低β-连环蛋白(β-catenin)和Twist后, 细胞在侵袭迁移方面发生的变化相似, 因此在E-cadherin表达缺失或下调的情况下, Twist的诱导不依赖β-catenin. E-cadherin表达缺失时, β-catenin、Twist是调节细胞表型变化方面相互独立的两个因子. 在E-cadherin表达缺失后, Twist是下游重要的调节因子, 是E-cadherin缺陷细胞发生迁移所必须的[11]. Yang等[12]通过一系列体内外实验证明Twist能够特异的增强癌细胞向血管内转移的过程, 在细胞存活、增长率、外渗方面没有显著的影响. 对这些基因的研究有利于发现新的肿瘤标志物和分子靶点. 在胃癌中, Ru等[13]用多元统计学分析得出侵袭程度、远处转移和Twist的表达上调三者都是相互独立的预后指标. 因此, Twist的表达水平可以作为胃癌发展和预后的有力指标.

1.3 Snail Wang等[14]认为Snail是转录因子家族中的一种, 能够抑制E-cadherin的基因的表达, 在EMT中起着很重要的作用. 而且, 在癌症中Snail的异常表达也能诱发EMT. Galaktionov等[15]曾报道Snai介导EMT的过程中, 同时伴随着基质金属蛋白酶类(matrix metalloproteinase, MMP)合成的增加, MMP能降解胞外间质, 加速细胞的侵袭和迁移. Slug是Snail家族成员之一, Zhang等和Lin等[16,17]研究认为Slug能够促进细胞的侵袭迁移, 与MMP-9的表达上调紧密相关, 但与E-cadherin表达没有关系. 在研究中还发现MMP-9的上调和肿瘤的淋巴结转移有重要的相关关系, Slug的表达水平可以作为恶性肿瘤手术后的预后标志. Slug还可以介导细胞骨架蛋白的重塑, 研究表明Slug可以作为癌症治疗的靶点.

2 EMT相关的信号通路

2.1 EMT与Wnt/β-catenin信号通路的关系 最近研究表明, E-cadherin胞内区域、β-catenin与其他蛋白在胞膜上形成复合物, 当E-cadherin胞外区域被蛋白水解酶降解脱落后, β-catenin被释放, 由胞膜进入胞核, 抑制了E-cadherin的转录, 进而产生EMT[18-20]. Yee[21]发现Wnt抑制因子1(Wnt inhibitory factor 1, WIF1)在前列腺癌中因启动子区域甲基化而表达缺失, 在前列腺癌细胞中WIF表达受抑制从而启动Wnt通路, 使E-cadherin表达下调, N-cadherin、vimentin和fibronectin的表达上调, 促进EMT现象的发生. 当WIF表达恢复后, Wnt通路受抑制, 前列腺癌细胞MMP-2、MMP-9水平下降, 侵袭和能动性下降. 在表皮细胞癌A431细胞中, Snail诱导EMT的过程中激活Wnt5a-Ror2信号通路, 使MMP-2表达上调, 侵袭迁移能力增强[22].

2.2 EMT与TGF-β信号通路的关系 转化生长因子(transforming growth factor, TGF)信号通路分为依赖Smad和不依赖Smad的信号通路, 在肿瘤发展的早期过程中, TGF-β是主要的肿瘤抑制因子, 能抑制细胞周期的前进和肿瘤的生长. 很多晚期或转移性肿瘤TGF-β通常是高表达的, 抵抗TGF-β介导的生长抑制, 推测可能的机制是TGF-β信号通路中蛋白的突变[23]. Oft等[24]使用CT26(鼠类高迁移能力的结肠癌间质细胞)皮下注射裸鼠导致肿瘤快速生长, 在TGF-β RII-dn稳定表达的CT26中, 肿瘤生长缓慢或抑制. 肿瘤的生长, 侵袭和转移需要TGF-β信号通路的激活. CT26细胞显示为间质细胞的表型, E-cadherin和ZO-1(紧密连接蛋白-1)表达下调, TGF-β RII-dn表达的CKR细胞细胞黏附蛋白上调, 间质细胞

表型逆转, 有部分上皮细胞的表型, 因此认为在晚期癌细胞抑制TGF-β信号通路, 能诱导MET. 赖氨酰氧化酶(LOX)是TGF-β激活后合成和分泌的, Behar等[25]认为LOX的表达水平和TGF-β信号通路紧密相关, 能够调控E-cadherin的表达和定位, 进而影响EMT的发生. 在胃癌和息肉性结直肠中, TGF-β RII的等位基因易失活甚至突变, 导致侵袭能力受损. TGF-β是以自分泌的方式介导的侵袭和迁移. Sbin等[26]在实验中发现TGF-β能诱导EMT, 抑制人类胰腺导管的增殖和分化, 通过调节各种的基因的表达和AKT和JNK等相关的信号通路.

2.3 EMT与NF-κB信号通路的关系 NF-κB-Rel家族包括5个成员, 即RelA(p65)、RelB、c-Rel、p105-p50(NF-κB1)和p100-p52(NF-κB2), 他们的N-末端均包含一个约300个氨基酸的高度同源序列, 称为Rel同源结构域(RHD), 介导其与DNA结合及二聚化, C端的反式激活结构域(transactivation domain, TD), 介导转录活性. 在未受到刺激的正常细胞中, NF-κB亚基与I-κBα、β或γ结合, 以非活性形式被阻滞在胞浆中. 受到炎症刺激后激活了活I-κB激酶(IKK)复合物, 磷酸化I-κB家族成员, 使其泛素化并被蛋白酶体降解. 降解后释放的NF-κB可转移到核内, 进而调节其下游的基因表达[27,28]. Li等[29]的研究证明, HK-2细胞和单核细胞共培养后, E-cadherin表达下降, 纤连蛋白上调, 诱导EMT的发生. 在NF-κB信号通路中, 细胞间细胞黏附分子1(intercellular cell adhesion molecule-1, ICAM-1)是调节细胞间联系的重要分子与单核细胞共培养的HK-2细胞激活NF-κB信号通路, 使ICAM-1上调, 诱导EMT. 在肿瘤的发展过程中, NF-κB能够与Ras和TGF-β依赖的信号通路协作, 在肝上皮细胞TGF-β能够通过TGF-β1激活激酶1(TAK1)激活依赖Smad的TGF-β信号通路, 而且TAK1还能使IKK复合物磷酸化, 促进NF-κB通路的激活. NF-κB通路的研究为新的药物和治疗方法提供依据[30].

2.4 EMT和Src/FAK信号通路的关系 Src可以诱导E-cadherin的胞吞, 通过激活E3泛素连接酶HaKai或激活Arf家族的GTP酶Arf6, 细胞间解离, 促进EMT的发生[31]. FAK是钙黏蛋白(cadherin)和整联蛋白(integrins)介导的黏附通路的调节介质, FAK或桩蛋白(paxillin)下调, 能使周边部位的Rac1表达增加, N-cadherin介导的细胞间黏附发生异常曾报道过integrins引起FAK信号通路的激活后, 还可以通过复合物激活Rac1[32]. EMT与PI3K/AKT等很多信号通路有着紧密的联系, 因此EMT成为最近研究的热点, 引起很多人的关注.

3 消化系肿瘤与EMT相关的调控

3.1 胃癌 研究发现在EBV-相关胃癌中, miR-200低表达, E-cadherin表达降低, 诱导EMT的发生, 使胃癌细胞失去了上皮细胞的特征获得了间质细胞的特征, E-cadherin下调后细胞间的黏附力下降, 促进了EMT的发生[33,34]. CDH1(E-cadherin的基因)功能的丢失与胃癌的易感性紧密相关. CDH1的启动子区域的超甲基化是低分化、弥散性胃癌的常见机制. CDH1启动子区域的超甲基化, 转录因子的介导, 环境生理因素如饮食、癌变、溃疡、胃炎都能使CDH1转录下调. CDH1的转录下调导致等位基因受抑制或失活[35].

肿瘤细胞和间质的相互作用在肿瘤发生发展过程中起着重要的作用, 作为间质主要成分的Ⅰ型胶原能够影响胃癌细胞间的黏附能力, 他可以使β-catenin酪氨酸磷酸化, 破坏E-cadherin/β-catenin复合物, 使骨架蛋白重构, β-catenin发生核易位, 使胃癌细胞的侵袭迁移能力增强. β-catenin还可以通过Wnt/β-catenin信号通路促进细胞的增殖[36].

3.2 结肠癌 P53是常见的抑癌基因, 能够调控侵袭性肿瘤中与转移有关的基因, 而P21在结肠癌中能够调控细胞周期而对增殖没有作用. 在P21不存在的情况下能够促进P53从野生型向突变型转变, 抑制E-cadherin的表达, 促进EMT的发生. 突变型的P53对E-cadherin的抑制是通过作用于E-cadherin近端启动子区域的E-box[37]. 在结肠癌中激活了Hedgehog-GLI信号通路, GLI1、PTCH1和SHH等标志物水平上调, 同时侵袭、迁移和增殖能力增强[38]. mTOR钠巴霉素的哺乳动物靶子(mammalian target of rapamycin, mTOR)位于AKT/PI3K信号通路的下游, 在结肠癌中mTOR是上调的, mTOR诱导EMT的过程是通过激活RhoA/Rac1信号通路. 抑制mTORC1和mTORC2后, 转移侵袭能力下降, 促进MET的发生, 而且对奥沙利铂的化学敏感性增强. RhoA和Rac1属于GTP家族的成员, 能够调控丝状肌动蛋白(filamentous actin, F-actin)的重构. 因此, RhoA/Rac1通路抑制剂对结肠癌的治疗有突破性的进展[39].

3.3 胰腺癌 在胰腺癌中叉头盒蛋白(forkhead box

■相关报道
Martin使用CT26(鼠类高迁移能力的结肠癌间质细胞)皮下注射裸鼠导致肿瘤快速生长, 在TGF-βRII-dn稳定表达的CT26中, 肿瘤生长缓慢或被抑制. 肿瘤的生长, 侵袭和转移需要TGF-β信号通路的激活. CT26细胞显示为间质细胞的表型, E-cadherin和ZO-1(紧密连接蛋白)表达下调, TGF-β RII-dn表达的CKR细胞细胞黏附蛋白上调, 间质细胞表型逆转, 有部分上皮细胞的表型, 因此认为抑制晚期癌细胞中TGF-β信号通路, 能诱导MET.

■创新盘点

本文创新性的综述了与EMT相关的信号通路，并系统阐述了EMT在消化系肿瘤中的调控机制，明确了EMT过程在消化系肿瘤侵袭和迁移中起重要作用.

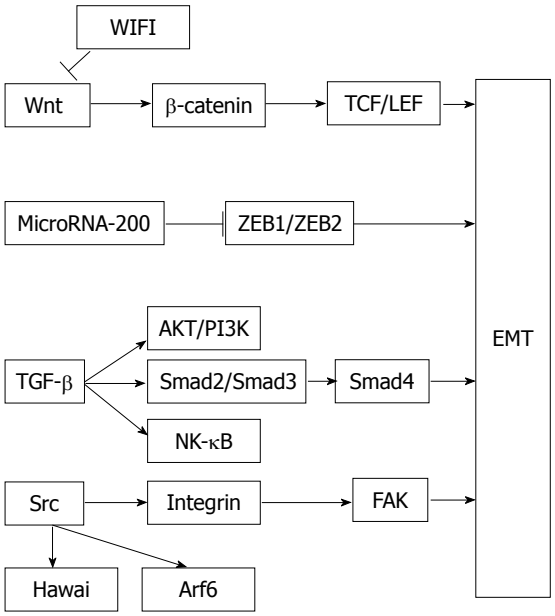

图 1 与EMT相关的信号通路.

protein M1, FoxM1)过表达, 能够促进上皮细胞表型的转变, 发生EMT[40]. 很多文献中报道FoxM1能够调控细胞周期和有丝分裂过程, 最近发现FoxM1能够增强肿瘤的侵袭能力和耐药性[41,42]. FoxM1过表达导致miR-200和let-7的表达下调, ZEB1、ZEB2等表达上调, 促进了EMT的发生, 而miR-200b的重新表达能够逆转EMT, 为胰腺癌的治疗提供依据[43].

3.4 肝癌 在肝癌Mahlavu细胞中, 生存素(Survivin)表达缺失, 导致细胞生长受抑制, 转移能力增强[44]. Tai等[45]发现Survivin使葡萄糖调节蛋白(GRP78)表达下调, 间质细胞的标志物vimentin表达增加, 使迁移能力增强. Survivin能够调节G_2/M的关卡, 通过抑制Capase-3的表达促进细胞的增殖. Survivin与Capase-3结合, 通过使P34激酶的磷酸化, 抑制Capase-3的表达[46,47]. Survivin等抗凋亡分子在肝癌中过表达, 肝癌细胞对凋亡诱导因子不敏感是肝癌没有有效治疗策略的原因之一, 通过化学的方法抑制Survivin, 如姜黄素等, 对肝癌的治疗有一定的指导意义[48]. TGF-β是促进肝细胞纤维化和癌变的重要调节因子, TGF-β在肝细胞的癌变过程中扮演对立的角色, TGF-β一方面能抑癌、抑制增殖、引起凋亡; 另一方面, 使肝细胞发生EMT, 促进肝细胞的癌变[49]. EMT的过程还包括肝细胞蛋白表达的下降, 成熟肝细胞转录因子HNF4a或HNF1a表达下调. 在肝癌发展的过程中, EMT的重要性逐渐被认识, EMT的分子机制的改变对研究抗肿瘤药物的有效性和敏感性至关重要, van Zijl等[50]建立EMT模型来监测抗癌药物的有效性, 发现上皮细胞对索拉菲尼和埃罗替尼敏感性高, 这种现象可能机制为上皮细胞的血管内皮生长因子受体(epidermal growth factor receptor, EGFR)的磷酸化水平上调, 而间质细胞对化疗药物如多柔比星、顺铂、表柔比星有较高的敏感性,可能与各种抗药蛋白的下调有关.

4 结论

EMT是非常复杂的网络系统(图1), 无论从通路, 转录因子, 还是microRNA等水平都做过很多研究, 但EMT的详细机制仍不清楚. 靶向治疗是当今比较热门且有效的治疗策略, 但目前尚未研制出完善的EMT的靶向药物, 目前抑制EGFR活性药物已投入临床应用, 但其效果尚未完成特异性评估. 因此, 我们仍需深入探索肿瘤中EMT的发生机制, 尤其在消化系肿瘤中的发生机制, 为消化系恶性肿瘤的治疗提供理论依据.

5 参考文献

1 Zhang Z, Liu ZB, Ren WM, Ye XG, Zhang YY. The miR-200 family regulates the epithelial-mesenchymal transition induced by EGF/EGFR in anaplastic thyroid cancer cells. *Int J Mol Med* 2012; 30: 856-862 [PMID: 22797360 DOI: 10.3892/ijmm.2012.1059.]

2 Wellner U, Schubert J, Burk UC, Schmalhofer O, Zhu F, Sonntag A, Waldvogel B, Vannier C, Darling D, zur Hausen A, Brunton VG, Morton J, Sansom O, Schüler J, Stemmler MP, Herzberger C, Hopt U, Keck T, Brabletz S, Brabletz T. The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs. *Nat Cell Biol* 2009; 11: 1487-1495 [PMID: 19935649 DOI: 10.1038/ncb1998.]

3 Yang J, Weinberg RA. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis. *Dev Cell* 2008; 14: 818-829 [PMID: 18539112 DOI: 10.1016/j.devcel.2008.05.009.]

4 Gibbons DL, Lin W, Creighton CJ, Rizvi ZH, Gregory PA, Goodall GJ, Thilaganathan N, Du L, Zhang Y, Pertsemlidis A, Kurie JM. Contextual extracellular cues promote tumor cell EMT and metastasis by regulating miR-200 family expression. *Genes Dev* 2009; 23: 2140-2151 [PMID: 19759262 DOI: 10.1101/gad.1820209.]

5 Adam L, Zhong M, Choi W, Qi W, Nicoloso M, Arora A, Calin G, Wang H, Siefker-Radtke A, McConkey D, Bar-Eli M, Dinney C. miR-200 expression regulates epithelial-to-mesenchymal transition in bladder cancer cells and reverses resistance to epidermal growth factor receptor therapy. *Clin Cancer Res* 2009; 15: 5060-5072 [PMID: 19671845 DOI: 10.1158/1078-0432.CCR-08-2245.]

6 Micalizzi DS, Farabaugh SM, Ford HL. Epithelial-mesenchymal transition in cancer: parallels between normal development and tumor progression. *J Mammary Gland Biol Neoplasia* 2010; 15: 117-134

[PMID: 20490631 DOI: 10.1007/s10911-010-9178-9.]
7 Bracken CP, Gregory PA, Kolesnikoff N, Bert AG, Wang J, Shannon MF, Goodall GJ. A double-negative feedback loop between ZEB1-SIP1 and the microRNA-200 family regulates epithelial-mesenchymal transition. *Cancer Res* 2008; 68: 7846-7854 [PMID: 18829540 DOI: 10.1158/0008-5472.CAN-08-1942.]
8 Burk U, Schubert J, Wellner U, Schmalhofer O, Vincan E, Spaderna S, Brabletz T. A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. *EMBO Rep* 2008; 9: 582-589 [PMID: 18483486 DOI: 10.1038/embor.2008.74.]
9 Burk U, Schubert J, Wellner U, Schmalhofer O, Vincan E, Spaderna S, Brabletz T. A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. *EMBO Rep* 2008; 9: 582-589 [PMID: 18483486]
10 Park SM, Gaur AB, Lengyel E, Peter ME. The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. *Genes Dev* 2008; 22: 894-907 [PMID: 18381893 DOI: 10.1101/gad.1640608.]
11 Onder TT, Gupta PB, Mani SA, Yang J, Lander ES, Weinberg RA. Loss of E-cadherin promotes metastasis via multiple downstream transcriptional pathways. *Cancer Res* 2008; 68: 3645-3654 [PMID: 18483246 DOI: 10.1158/0008-5472.]
12 Yang Z, Zhang X, Gang H, Li X, Li Z, Wang T, Han J, Luo T, Wen F, Wu X. Up-regulation of gastric cancer cell invasion by Twist is accompanied by N-cadherin and fibronectin expression. *Biochem Biophys Res Commun* 2007; 358: 925-930 [PMID: 17512904]
13 Ru GQ, Wang HJ, Xu WJ, Zhao ZS. Upregulation of Twist in gastric carcinoma associated with tumor invasion and poor prognosis. *Pathol Oncol Res* 2011; 17: 341-347 [PMID: 21104359 DOI: 10.1007/s12253-010-9332-0.]
14 Wang Y, Ngo VN, Marani M, Yang Y, Wright G, Staudt LM, Downward J. Critical role for transcriptional repressor Snail2 in transformation by oncogenic RAS in colorectal carcinoma cells. *Oncogene* 2010; 29: 4658-4670 [PMID: 20562906 DOI: 10.1038/onc.2010.218]
15 Galaktionov K, Lee AK, Eckstein J, Draetta G, Meckler J, Loda M, Beach D. CDC25 phosphatases as potential human oncogenes. *Science* 1995; 269: 1575-1577 [PMID: 7667636]
16 Zhang K, Chen D, Jiao X, Zhang S, Liu X, Cao J, Wu L, Wang D. Slug enhances invasion ability of pancreatic cancer cells through upregulation of matrix metalloproteinase-9 and actin cytoskeleton remodeling. *Lab Invest* 2011; 91: 426-438 [PMID: 21283078 DOI: 10.1038/labinvest.2010.201]
17 Lin CY, Tsai PH, Kandaswami CC, Lee PP, Huang CJ, Hwang JJ, Lee MT. Matrix metalloproteinase-9 cooperates with transcription factor Snail to induce epithelial-mesenchymal transition. *Cancer Sci* 2011; 102: 815-827 [PMID: 21219539 DOI: 10.1111/j.1349-7006.2011.01861.x.]
18 Fragiadaki M, Mason RM. Epithelial-mesenchymal transition in renal fibrosis - evidence for and against. *Int J Exp Pathol* 2011; 92: 143-150 [PMID: 21554437 DOI: 10.1111/j.1365-2613.2011.00775.x.]
19 Su J, Zhang A, Shi Z, Ma F, Pu P, Wang T, Zhang J, Kang C, Zhang Q. MicroRNA-200a suppresses the Wnt/β-catenin signaling pathway by interacting with β-catenin. *Int J Oncol* 2012; 40: 1162-1170 [PMID: 22211245 DOI: 10.3892/ijo.2011.1322.]
20 Mongroo PS, Rustgi AK. The role of the miR-200 family in epithelial-mesenchymal transition. *Cancer Biol Ther* 2010; 10: 219-222 [PMID: 20592490]
21 Yee DS, Tang Y, Li X, Liu Z, Guo Y, Ghaffar S, McQueen P, Atreya D, Xie J, Simoneau AR, Hoang BH, Zi X. The Wnt inhibitory factor 1 restoration in prostate cancer cells was associated with reduced tumor growth, decreased capacity of cell migration and invasion and a reversal of epithelial to mesenchymal transition. *Mol Cancer* 2010; 9: 162 [PMID: 20573255 DOI: 10.1186/1476-4598-9-162.]
22 Ren D, Minami Y, Nishita M. Critical role of Wnt5a-Ror2 signaling in motility and invasiveness of carcinoma cells following Snail-mediated epithelial-mesenchymal transition. *Genes Cells* 2011; 16: 304-315 [PMID: 21342370 DOI: 10.1111/j.1365-2443.2011.01487.x.]
23 Das S, Becker BN, Hoffmann FM, Mertz JE. Reversal of transforming growth factor-β induced epithelial-to-mesenchymal transition and the ZEB proteins. *Fibrogenesis Tissue Repair* 2012; 5 Suppl 1: S28 [PMID: 23259633]
24 Oft M, Heider KH, Beug H. TGFbeta signaling is necessary for carcinoma cell invasiveness and metastasis. *Curr Biol* 1998; 8: 1243-1252 [PMID: 9822576]
25 Behar S, Reicher-Reiss H, Abinader E, Agmon J, Barzilai J, Friedman Y, Kaplinsky E, Kauli N, Kishon Y, Palant A. Long-term prognosis after acute myocardial infarction in patients with left ventricular hypertrophy on the electrocardiogram. SPRINT Study Group. *Am J Cardiol* 1992; 69: 985-990 [PMID: 1532881]
26 Shin JA, Hong OK, Lee HJ, Jeon SY, Kim JW, Lee SH, Cho JH, Lee JM, Choi YH, Chang SA, Son HY, Kim JH, Yoon KH. Transforming growth factor-β induces epithelial to mesenchymal transition and suppresses the proliferation and transdifferentiation of cultured human pancreatic duct cells. *J Cell Biochem* 2011; 112: 179-188 [PMID: 21069735 DOI: 10.1002/jcb.22929]
27 Karin M, Cao Y, Greten FR, Li ZW. NF-kappaB in cancer: from innocent bystander to major culprit. *Nat Rev Cancer* 2002; 2: 301-310 [PMID: 12001991]
28 Kiefel H, Bondong S, Pfeifer M, Schirmer U, Erbe-Hoffmann N, Schäfer H, Sebens S, Altevogt P. EMT-associated up-regulation of L1CAM provides insights into L1CAM-mediated integrin signalling and NF-κB activation. *Carcinogenesis* 2012; 33: 1919-1929 [PMID: 22764136 DOI: 10.1093/carcin/bgs220]
29 Li Q, Liu BC, Lv LL, Ma KL, Zhang XL, Phillips AO. Monocytes induce proximal tubular epithelial-mesenchymal transition through NF-kappa B dependent upregulation of ICAM-1. *J Cell Biochem* 2011; 112: 1585-1592 [PMID: 21344487 DOI: 10.1002/jcb.23074.]
30 Huber MA, Azoitei N, Baumann B, Grünert S, Sommer A, Pehamberger H, Kraut N, Beug H, Wirth T. NF-kappaB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. *J Clin Invest* 2004; 114: 569-581 [PMID: 15314694]
31 Avizienyte E, Frame MC. Src and FAK signalling controls adhesion fate and the epithelial-to-mes-

■应用要点
研究与EMT相关的信号通路, 阻断信号通路中相应靶点的抗肿瘤药物在消化系肿瘤的治疗和预防中有重要应用价值.

■同行评价
本文内容丰富，新颖，具有一定的指导意义.

enchymal transition. *Curr Opin Cell Biol* 2005; 17: 542-547 [PMID: 16099634]
32 Yano H, Mazaki Y, Kurokawa K, Hanks SK, Matsuda M, Sabe H. Roles played by a subset of integrin signaling molecules in cadherin-based cell-cell adhesion. *J Cell Biol* 2004; 166: 283-295 [PMID: 15263022]
33 Shinozaki A, Sakatani T, Ushiku T, Hino R, Isogai M, Ishikawa S, Uozaki H, Takada K, Fukayama M. Downregulation of microRNA-200 in EBV-associated gastric carcinoma. *Cancer Res* 2010; 70: 4719-4727 [PMID: 20484038 DOI: 10.1158/0008-5472.CAN-09-4620.]
34 Lin Z, Wang X, Fewell C, Cameron J, Yin Q, Flemington EK. Differential expression of the miR-200 family microRNAs in epithelial and B cells and regulation of Epstein-Barr virus reactivation by the miR-200 family member miR-429. *J Virol* 2010; 84: 7892-7897 [PMID: 20484493 DOI: 10.1128/JVI.00379-10]
35 Graziano F, Humar B, Guilford P. The role of the E-cadherin gene (CDH1) in diffuse gastric cancer susceptibility: from the laboratory to clinical practice. *Ann Oncol* 2003; 14: 1705-1713 [PMID: 14630673]
36 Li A, Zhou T, Guo L, Si J. Collagen type I regulates beta-catenin tyrosine phosphorylation and nuclear translocation to promote migration and proliferation of gastric carcinoma cells. *Oncol Rep* 2010; 23: 1247-1255 [PMID: 20372837]
37 Roger L, Jullien L, Gire V, Roux P. Gain of oncogenic function of p53 mutants regulates E-cadherin expression uncoupled from cell invasion in colon cancer cells. *J Cell Sci* 2010; 123: 1295-1305 [PMID: 20332115 DOI: 10.1242/jcs.061002]
38 Varnat F, Duquet A, Malerba M, Zbinden M, Mas C, Gervaz P, Ruiz i Altaba A. Human colon cancer epithelial cells harbour active HEDGEHOG-GLI signalling that is essential for tumour growth, recurrence, metastasis and stem cell survival and expansion. *EMBO Mol Med* 2009; 1: 338-351 [PMID: 20049737 DOI: 10.1002/emmm.200900039]
39 Gulhati P, Bowen KA, Liu J, Stevens PD, Rychahou PG, Chen M, Lee EY, Weiss HL, O'Connor KL, Gao T, Evers BM. mTORC1 and mTORC2 regulate EMT, motility, and metastasis of colorectal cancer via RhoA and Rac1 signaling pathways. *Cancer Res* 2011; 71: 3246-3256 [PMID: 21430067 DOI: 10.1158/0008-5472.CAN-10-4058.]
40 Li J, Wang Y, Luo J, Fu Z, Ying J, Yu Y, Yu W. miR-134 inhibits epithelial to mesenchymal transition by targeting FOXM1 in non-small cell lung cancer cells. *FEBS Lett* 2012; 586: 3761-3765 [PMID: 23010597 DOI: 10.1016/j.febslet.2012.09.016]
41 Laoukili J, Stahl M, Medema RH. FoxM1: at the crossroads of ageing and cancer. *Biochim Biophys Acta* 2007; 1775: 92-102 [PMID: 17014965]
42 Kalin TV, Wang IC, Ackerson TJ, Major ML, Detrisac CJ, Kalinichenko VV, Lyubimov A, Costa RH. Increased levels of the FoxM1 transcription factor accelerate development and progression of prostate carcinomas in both TRAMP and LADY transgenic mice. *Cancer Res* 2006; 66: 1712-1720 [PMID: 16452231]
43 Bao B, Wang Z, Ali S, Kong D, Banerjee S, Ahmad A, Li Y, Azmi AS, Miele L, Sarkar FH. Over-expression of FoxM1 leads to epithelial-mesenchymal transition and cancer stem cell phenotype in pancreatic cancer cells. *J Cell Biochem* 2011; 112: 2296-2306 [PMID: 21503965 DOI: 10.1002/jcb.23150.]
44 Guha M, Altieri DC. Survivin as a global target of intrinsic tumor suppression networks. *Cell Cycle* 2009; 8: 2708-2710 [PMID: 19717980]
45 Tai CJ, Chin-Sheng H, Kuo LJ, Wei PL, Lu HH, Chen HA, Liu TZ, Liu JJ, Liu DZ, Ho YS, Wu CH, Chang YJ. Survivin-mediated cancer cell migration through GRP78 and epithelial-mesenchymal transition (EMT) marker expression in Mahlavu cells. *Ann Surg Oncol* 2012; 19: 336-343 [PMID: 21516372 DOI: 10.1245/s10434-011-1692-5]
46 Altieri DC. Survivin, cancer networks and pathway-directed drug discovery. *Nat Rev Cancer* 2008; 8: 61-70 [PMID: 18075512]
47 Lin CC, Calvo E, Papadopoulos KP, Patnaik A, Sarantopoulos J, Mita AC, Preston GG, Mita MM, Rodon J, Mays T, Yeh IT, O'Rourke P, Takimoto CH, Dancey JE, Chen H, Tolcher AW. Phase I study of cetuximab, erlotinib, and bevacizumab in patients with advanced solid tumors. *Cancer Chemother Pharmacol* 2009; 63: 1065-1071 [PMID: 18795291 DOI: 10.1007/s00280-008-0811-x.]
48 Caja L, Bertran E, Campbell J, Fausto N, Fabregat I. The transforming growth factor-beta (TGF-β) mediates acquisition of a mesenchymal stem cell-like phenotype in human liver cells. *J Cell Physiol* 2011; 226: 1214-1223 [PMID: 20945437 DOI: 10.1002/jcp.22439]
49 Franco DL, Mainez J, Vega S, Sancho P, Murillo MM, de Frutos CA, Del Castillo G, López-Blau C, Fabregat I, Nieto MA. Snail1 suppresses TGF-beta-induced apoptosis and is sufficient to trigger EMT in hepatocytes. *J Cell Sci* 2010; 123: 3467-3477 [PMID: 20930141 DOI: 10.1242/jcs.068692.]
50 van Zijl F, Mall S, Machat G, Pirker C, Zeillinger R, Weinhaeusel A, Bilban M, Berger W, Mikulits W. A human model of epithelial to mesenchymal transition to monitor drug efficacy in hepatocellular carcinoma progression. *Mol Cancer Ther* 2011; 10: 850-860 [PMID: 21364009 DOI: 10.1158/1535-7163.MCT-10-0917.]

编辑 田滢 电编 鲁亚静