世界华人消化杂志®
wcjd@wjgnet.com

世界华人消化杂志 2013年12月8日; 21(34): 3813-3820
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

Barrett食管的分子机制

黄颖秋

黄颖秋, 中国医科大学第五临床学院, 本溪钢铁(集团)总医院消化内科 辽宁省本溪市 117000
黄颖秋, 教授, 主任医师, 研究生导师, 主要从事胃肠动力疾病、消化系肿瘤及肝硬化的基础与临床研究.
作者贡献分布: 本文由黄颖秋独立完成.
通讯作者: 黄颖秋, 教授, 主任医师, 研究生导师, 117000, 辽宁省本溪市平山区人民路29号, 中国医科大学第五临床学院, 本溪钢铁(集团)总医院消化内科. huangyingqiu_bx@126.com
电话: 0414-2215137
收稿日期: 2013-08-02 修回日期: 2013-10-27
接受日期: 2013-11-06 在线出版日期: 2013-12-08

Molecular mechanisms responsible for pathogenesis of Barrett's esophagus

Ying-Qiu Huang

Ying-Qiu Huang, Department of Gastroenterology, General Hospital of Benxi Steel & Iron (Group); the Fifth Clinical College of China Medical University, Benxi 117000, Liaoning Province, China
Correspondence to: Ying-Qiu Huang, Professor, Chief Physician, Department of Gastroenterology, General Hospital of Benxi Steel & Iron (Group); the Fifth Clinical College of China Medical University, 29 Renmin Road, Pingshan District, Benxi 117000, Liaoning Province, China. huangyingqiu_bx@126.com
Received: 2013-08-02 Revised: 2013-10-27
Accepted: 2013-11-06 Published online: 2013-12-08

Abstract

Barrett's esophagus (BE) is defined as the metaplastic conversion of the distal esophageal squamous epithelium to intestinalized columnar epithelium. It is a premalignant condition associated with esophageal adenocarcinoma (EAC) and is the major risk factor for EAC. Recent studies suggest that the molecular mechanisms responsible for the pathogenesis of BE are closely related to transcription factors, signaling proteins and microRNAs (miRNAs). MiRNAs are expected to be used as novel biomarkers for the diagnosis, prognosis assessment and targeted treatment of EAC. This article summarizes recent results involving stem cells, immune factors, transcription factors, DNA methylation, nitric oxide, signaling pathways, microRNAs in the development of BE. Understanding of the molecular mechanisms behind the pathogenesis of BE has important implications for improved management of BE and EAC.

Key Words: Barrett's esophagus; Metaplasia; Stem cells; Transcription factors; Signaling pathways; miRNA; Pathogenesis

Huang YQ. Molecular mechanisms responsible for pathogenesis of Barrett's esophagus. Shijie Huaren Xiaohua Zazhi 2013; 21(34): 3813-3820 URL: http://www.wjgnet.com/1009-3079/21/3813.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i34.3813

摘要

Barrett食管(Barrett's esophagus, BE)是指食管下段的复层鳞状上皮被柱状上皮替代的一种病理现象. BE为食管腺癌(esophageal adenocarcinoma, EAC)的癌前状态及主要风险因素. 最近研究表明, BE的分子机制与转录因子、信号蛋白及microRNAs(miRNAs)等密切相关. miRNAs有望成为新的生物标志物, 用于EAC的诊断、预后评估和靶向治疗. 本文详尽阐述了干细胞、免疫因素、转录因子、DNA甲基化、一氧化氮、信号通路及miRNAs等因素在BE机制中的作用, 为改善BE和EAC的治疗提供了新的思路.

关键词: Barrett食管; 化生; 干细胞; 转录因子; 信号通路; miRNA; 发病机制

核心提示: Barrett食管(Barrett's esophagus)为食管腺癌(esophageal adenocarcinoma, EAC)的癌前状态, 分子机制十分复杂, 涉及细胞起源、免疫因素、转录因子、DNA甲基化、一氧化氮、信号蛋白及miRNAs等因素. miRNAs有望成为新的生物标志物, 用于EAC的诊断、预后评估和靶向治疗.

黄颖秋. Barrett食管的分子机制. 世界华人消化杂志 2013; 21(34): 3813-3820 URL: http://www.wjgnet.com/1009-3079/21/3813.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i34.3813

■背景资料
Barrett食管(Barrett's esophagus, BE)是胃食管反流病(gastroesophageal reflux disease, GERD)的并发症, 为食管腺癌(esophageal adenocarcinoma, EAC)的癌前状态. BE的潜在风险是并发EAC. 近几十年来, 美国的EAC发病率呈显著上升趋势, 已达食管癌的50%以上. 因此, 备受重视. 随着分子生物学技术的迅猛发展, BE分子机制领域的研究已取得长足进步, 对于EAC的早期诊断、治疗及预后评估均有其重要意义.

■同行评议者
吕宾, 教授, 浙江中医药大学附属医院(浙江省中医院); 张国梁, 主任医师, 天津市第一中心医院消化内科

■研发前沿
miRNAs作为一类小分子核苷酸, 与人类肿瘤的发生、发展以及预后密切相关, miRNAs在BE-EAC进程中的异常表达, 即可作为分子治疗靶点, 也可作为评估预后的分子生物学标志.

0 引言

Barrett食管(Barrett's esophagus, BE)是胃食管反流病(gastroesophageal reflux disease, GERD)的并发症, 为食管腺癌(esophageal adenocarcinoma, EAC)的癌前状态, 是指食管下段的复层鳞状上皮被单层柱状上皮替代的一种病理现象[1], 其是否应包含杯状细胞尚存争议[2,3]. 因忽视杯状细胞可能会使许多患者被额外贴上BE标签[4], 美国消化病学会仍将杯状细胞视为诊断BE的必要条件, 并将胃食管连接部(gastroesophageal junction, GEJ)的内镜和组织学界定视为正确诊断BE的前提[5]. 大约4.1%的BE患者有特殊型肠化(specialized intestinal metaplasia, SIM), 且常与贲门黏膜型化生并存[6]. BE的潜在风险是并发EAC[7], 尤其是长段BE与EAC的发生更为密切[8]. 近年来, 美国食管鳞状细胞癌(esophageal squamous cell carcinoma, ESCC)的发病率呈下降趋势, 但EAC却呈显著上升趋势, 已引起高度重视[9]. 但我国情况似有不同, EAC仅占食管癌的1%-5%[10], 其特征也与GEJ癌迥异[11]. 随着分子生物学技术的发展, BE的基础研究已取得长足进步[12,13]. 应用基因芯片分析BE黏膜及其周围鳞状上皮的差异基因, 从RNA或蛋白质水平探讨BE的分子机制有望为BE的治疗提供新的分子靶点[14,15]. 本文就BE的分子机制概述如下.

1 BE的细胞起源

BE的细胞起源尚存争议, 可能与如下因素有关[16]: (1)来源于食管鳞状上皮的基底细胞; (2)来源于食管贲门腺体细胞; (3)来源于食管干细胞; (4)来源于骨髓干细胞. Goldman等[17]研究发现, 反复置于胆汁酸(bile acid, BA)中的食管鳞状细胞株HET-1A可抵抗酸化, 并可见柱状变异标志物表达, HET-1AR细胞还可激活STAT3、核因子κB(nuclear factor κB, NF-κB)、表皮生长因子受体(epidermal growth factor receptor, EGFR)、环氧合酶2(cyclooxygenase 2, COX2)、白介素-6(interleukin 6, IL-6)、磷酸化哺乳动物雷帕霉素靶蛋白(phosphorylate-mammalian target of rapamycin, p-mTOR)以及Mcl-1等信号通路, 提示鳞状细胞长期暴露于酸性BA可使之显示与BE标志物相同的特征. Quante等[18]采用转基因BE小鼠模型研究发现, 贲门腺体细胞通过促肿瘤因子IL-1β-IL-6信号级联放大(signaling cascade)及Dll1-依赖Notch信号通路分化形成BE细胞. 换言之, BE的潜在细胞起源为贲门腺体细胞[19]. 标记滞留细胞(label-retaining cells, LRCs)常被用于检测组织中的干细胞分布[20]. Pan等[20]发现, BE组织中的LRCs显著增加, 且具有无限增殖、自我更新和多向分化的干细胞特性, 提示BE上皮源于干细胞. Vega等[21]分别对正常食管黏膜(normal esophageal mucosa, NEM)、BE及EAC的DCAMKL-1、LGR5及Msi-1(干细胞标志物)表达情况研究发现, DCAMKL-1在NEM低表达, 但在BE及EAC高表达, EAC组织的基质DCAMKL-1染色较毗邻上皮显著增加, BE黏膜的DCAMKL-1、LGR5、Msi-1 mRNA表达均较NEM显著上调, 提示食管干细胞不仅为BE来源, 且在BE-EAC的进程中可能起重要作用[21,22]. 尽管骨髓来源细胞(bone marrow-derived cells, BMDCs)参与EAC上皮细胞和间质细胞的形成[23], 但骨髓干细胞是否为BE来源仍存争议, 其研究结果也大相径庭[24-26]. Upton等[24]和Barbera等[25]均证实BE源于骨髓干细胞, 但Aikou等[26]却得出截然相反的结论. 此外, Wang等[27]应用p63缺陷的BE小鼠模型研究发现, p63缺乏的胚胎细胞能迅速发展成基因表达类似于BE化生的小肠样化生, 此类胚胎细胞持续存在于成年小鼠和人食管黏膜鳞柱状上皮交界处, 并向毗邻的特异性鳞状细胞迁移, 提示BE的起源并非基因突变, 而是细胞谱系间的相互竞争所致. von Holzen等[28]对此研究[27]给予高度评价, 认为这是BE起源的一种神奇细胞, 是BE发病机制的一种全新概念, 对此类胚胎细胞的进一步研究有其重要意义.

2 BE与免疫细胞

BE进展至EAC可能存在树突状细胞(dendritic cells, DCs)分化成熟障碍导致的免疫逃逸(immune evasion). Somja等[29]将骨髓树突状细胞(myeloid dendritic cells, MDCs)与BE和EAC细胞株共同培养, 并与浆细胞样树突状细胞(plasmacytoid dendritic cells, PDCs)对比发现, MDCs有耐受表型, MDCs与EAC细胞株共同培养刺激调节性T细胞(regulatory T cell, Treg)从幼稚$CD4^+$ T细胞的变异, BE的化生或癌前组织中可见Treg浸润, 提示在BE-EAC进程中, 上皮细胞分泌的可溶性因子不仅影响DCs的分布并通过耐受逃逸促进EAC进展. Bobryshev等[30]发现, BE活检组织的贲门黏膜中含有大量DCs, 提示贲门黏膜的免疫炎症在修饰局部组织环境促进BE的SIM过程中起重要作用. Lind等[31]对BE化生组

织中免疫细胞的成分研究发现, BE组织的淋巴细胞归巢主要归因于肠归巢信号, 而非激活的炎症反应. Kavanagh等[32]认为, T淋巴细胞在引发GERD和BE的炎症反应中起重要作用, T细胞的免疫应答与其表型间的免疫平衡可能在BE-EAC的进程中至关重要. Trowbridge等[33]认为, $CD4^+$ T细胞、巨噬细胞、DCs等免疫细胞通过Wnt、Hedgehog、NF-κB、IL-6-JAK-STAT等信号通路参与GERD的发病机制, 而1,25-二羟维生素D(1,25-dihydroxyvitamin D)通过调节上述免疫细胞与信号通路之间的关系而参与BE及EAC的发病机制.

3 BE与转录因子

BE的肠化生与转录因子(transcription factors)激活或失活密切相关[34-37]. DiMaio等[34]研究发现, 促进鳞状上皮发育的转录因子Sox2、p63在ESCC的表达显著高于EAC, 而腺癌相关基因(adenocarcinoma-associated gene)前梯度同源物2(anterior gradient homolog 2, AGR2)则在EAC高度表达. Sox2通过激活促进细胞增殖的AKT/mTORC1信号通路, 从而促进ESCC的肿瘤生长[35]. p63转录因子的缺乏或失活使残留的胚胎细胞迁移至炎症或GERD损伤的正常食管黏膜组织, 似乎可解释BE的肠上皮化生[36]. Zhao等[37]认为, 尾型相关同源盒转录因子(caudal-related homeodomain transcription factors, CDXs)CDX1和CDX2通常表达于小肠和大肠, 并在肠上皮的细胞增殖和变异中发挥重要作用, 顶端钠依赖性胆汁酸运输因子(apical sodium-dependent bile acid transporter, ASBT)主要表达于末端回肠, 在此作为胆盐重吸收的关键因素. 酸和胆汁反流诱发*CDXs*基因表达可能导致BE形成, CDXs介导启动子激活可能引起ASBT异常表达[37]. BE中除CDX1和CDX2表达上调外, ASBT也表达上调, 但CDX1/CDX2及ASBT在高度异型增生(high-grade dysplasia, HGD)的BE中则表达下调, 提示CDXs和ASBT是EAC进展的抑制因子(inhibitory factors)[37]. NF-κB在酸或胆汁酸环境下通过启动子脱甲基促进食管上皮CDX2表达致使BE肠化生[38], 并通过抑制DNA修复酶表达、促进CDX2表达而参与EAC的致癌机制[39]. 骨形态发生蛋白4(bone morphogenetic protein 4, BMP4)属于转化生长因子-β(transforming growth factor β, TGF-β)家族成员, 其下游靶序列(P-Smad1/5/8)在BE化生组织中显著表达, 而在正常鳞状上皮无表达[40]. 人的GERD模型常被用于研究非特殊型柱状上皮化生(non-specialized columnar type of metaplasia, NSCM)及BMP4和CDX2在BE形成中的作用[40]. Castillo等[40]采用免疫组织化学、实时定量PCR、Western blot及原位杂交技术对18例食管切除术患者残余食管标本中的BMP通路活性(BMP4/P-Smad 1/5/8)及CDX2、CDX1的表达情况研究发现, BMP4 mRNA、CDX2 mRNA在NSCM组织中的水平显著高于鳞状上皮组织, 提示BMP4通路在NSCM中被激活, CDX2的早期表达与BE的柱状上皮化生显著相关[40]. 转录因子Sox9和BMP4为Shh信号(sonic hedgehog signaling, Shh)通路的下游介质, Sox9主要表达于肠上皮细胞, 特别是干细胞和潘氏细胞, BMP4可诱发CDX2表达致使含有杯状细胞的肠上皮化生, Shh信号可能为诱发食管柱状上皮化生的初始因素[41]. Shh靶基因在BE和EAC的表达显著高于ESCC[42]. Clemons等[41]采用一种新的体内组织重构模型研究发现, Sox9足以驱动鳞状上皮的BE样柱状化生, 提示Shh介导的Sox9表达可能是BE发生的重要早期事件. 因此, Shh信号通路抑制剂有望于不久的将来被用于治疗BE和/或EAC[42]. 上皮细胞间充质转化(epithelial mesenchymal transition, EMT)使癌细胞从原始组织迁移并侵袭基质成分, 在肿瘤的演进中发挥关键作用, E-钙黏蛋白(E-cadherin)为细胞间黏附连接的主要分子, 转录因子Snail、Slug、Twist常抑制E-钙黏蛋白启动子而引发EMT, 促使肿瘤的侵袭和转移[43]. CD133是一种熟知的肿瘤始动细胞标志物[43]. Tomizawa等[43]采用免疫组织化学方法对源于BE的早期EAC标本中E-钙黏蛋白相关转录因子以及肿瘤干细胞标志物的特征研究发现, 肿瘤侵袭边缘可见大量的Snail、Slug、Twist和CD133表达, 提示早期癌症主要由转移潜能细胞组成, 此证据进一步表明对早期EAC有必要完全切除.

4 BE与DNA甲基化

Agarwal等[12]认为, DNA甲基化变异在BE上皮化生-异型增生-EAC的多级转化过程中非常普遍, 已证实BE进程中存在抑癌基因启动子、黏附分子、DNA修复基因的甲基化变异. 这些表观遗传变异可被用作EAC危险分级和早期检测的分子标志物[12]. 研究发现, 蛋白编码基因(protein-coding genes)甲基化变异与BE和EAC相关[44]. Wu等[44]应用高分辨率甲基化图谱分析显示, BE

■相关报道
Saad等采用基因芯片及qRT-PCR技术确认了一种与EAC相关的独特miRNA信号, 并以此作为与其他上消化道肿瘤鉴别的分子标志.

■创新盘点
本文详尽阐述了近5年BE分子机制领域的最新研究进展, 涉及BE的细胞起源、免疫逃逸、转录因子、DNA甲基化、一氧化氮、信号蛋白以及microRNAs等诸多因素.

和EAC包括非编码区域的甲基化减少, BE和EAC的长度非编码RNA AFAP1-AS1甲基化减少, 以此抑制EAC细胞的癌相关生物学功能. Alvi等[45]发现, 约70%已知印迹基因的DNA甲基化变异存在于有致癌倾向的BE组织中. 抑癌基因的DNA甲基化变异常见于BE和EAC, 这可能影响BE-EAC的启动和进展[46]. 构成细胞桥粒复合体(desmosome complex)的*PKP1*是一种新的EAC甲基化基因[46]. Kaz等[46]发现, *PKP1*的甲基化罕见于NEM鳞状上皮(5/55; 9.1%)和BE(5/39; 12.8%), 但常见于高度异型增生(high-grade dysplasia, HGD)的BE或EAC(20/60; 33.3%, $P<0.05$). 此外, BE和HGD/EAC的PKP1水平较NEM鳞状上皮者下降, BE细胞系CP-A和CP-D(二者通常表达PKP1)中的*PKP1*基因敲减导致细胞运动增加. Kaz等[46]认为, 继发于启动子甲基化以及其他机制的PKP1下降, 通过减少细胞桥粒装配和增加细胞活性可促进BE-EAC的进展. 此外, Kaz等[47]在另一项研究中应用甲基化基因芯片技术对NEM鳞状上皮、BE、BE/HGD及EAC的总基因甲基化状态检测发现, BE和EAC的甲基化状态存在高、低甲基化表型, 准确区分BE、BE/HGD及EAC的CpG位点可能有助于发现具有临床潜能的生物学标志物, 以此用于BE和EAC的诊断和预后评估.

5 BE与一氧化氮

一氧化氮(nitric oxide, NO)由诱生型一氧化氮合酶(inducible nitric oxide synthase, iNOS)介导产生, 不仅在食管神经肌肉调控[48]和GERD发病机制[49]中至关重要, 在BE-EAC的进程中可能也起重要作用[50,51]. 此外, NO还涉及组织和细胞中的DNA损伤诱导和细胞信号转导异常[50]. McAdam等[50]应用实时PCR、Western blot及NO敏感荧光探针技术对NO及iNOS在体外食管细胞DNA损伤诱导和NF-κB信号传导中的作用研究显示, 类似于胃酸和胆汁酸样的反流成分(脱氧胆酸, DCA)能诱导食管细胞的iNOS基因和蛋白质表达, 从而促进NO生成, iNOS的表达上调不依赖于NF-κB活性; 通过微核试验(micronucleus assay)判断, DCA诱导DNA损伤不依赖于NF-κB, 仅部分依赖于iNOS和NO; 通过转录因子酶联免疫吸附试验以及*NF-κB*连锁基因(如*IL-8*)的基因表达研究显示, 这些相同的反流成分也激活了致癌的转录因子NF-κB. 值得一提的是, NF-κB活性的基础水平(可能由DCA诱导的NF-κB)有赖于iNOS/NO, 这可能导致一个正反馈循环, 以此被诱导的iNOS成为NF-κB上游, 延长并潜在地放大此信号, 并通过NO激活NF-κB[50]. 此外, EAC的iNOS蛋白质水平显著增加, 提示NO与EAC的进展有关[50]. Kusaka等[51]研究发现, BE组织中表皮生长因子受体(epidermal growth factor receptor, EGFR)、CDX2及硝基络氨酸的表达显著高于食管鳞状上皮, 提示NO可能通过EGFR磷酸化直接诱导CDX2表达, NO在GEJ周围的鳞状上皮至BE的进程中起重要作用. Goldman等[52]研究显示, 反流物中的胆汁酸能立即激活NOS的全部3个亚型, 致使NO增加和钠-氢交换(sodium-hydrogen exchanger, NHE)抑制, 进而引起细胞内酸化增加和DNA损伤, 这可能导致基因突变和肿瘤进展[52]. 此研究揭示了胆汁酸诱发DNA损伤的新机制. 因此, 除胃酸反流外, 胆汁反流在BE患者也应被控制[52]. 已证实, NO可致BE的双链DNA断裂以及在肿瘤侵入中发挥作用[53]. Clemons等[53]应用实时逆转录PCR技术对BE/HGD和EAC的细胞株研究发现, NO诱导细胞株中的基质金属蛋白酶(matrix metalloproteinase, MMP)-1、-3、-7、-9、-10以及金属蛋白酶组织抑制剂(tissue inhibitor of metalloproteinase, TIMP)-1、-2、-3表达. 此外, 以NO诱导MMP-1和TIMP-1表达增加对BE活检标本的间接体内治疗提示, NO通过下调上皮细胞的MMP和TIMP表达而增加侵袭[53]. 对活检标本的微阵列分析和免疫组织化学研究显示, 在非异型增生BE至EAC的进程中, 尽管不能直接归因于NO的作用, 但MMP-1、-3、-7、-10和TIMP-1的表达增加[53]. 因此, NO通过下调MMP和TIMP表达以提高侵袭潜力而在BE致癌机制中发挥作用.

6 BE与信号通路

BE-EAC的进程可能受WNT、Notch、BMP、Sonic HH、TGF-β等与小肠增殖分化相关的信号通路调控[54,55]. Mendelson等[56]分别对正常食管黏膜、BE、EAC及其细胞株中的TGF-β和Notch信号组分评估显示, 与β2SP/TGF-β信号缺失伴随的Notch信号持续激活对EAC有潜在靶向治疗价值. Chen等[57]检测了41对食管活检标本中WNT和Notch信号关键调节因子(Tcf4、Cdx2、Hes1和Math1)的表达情况, 并分别用酸、胆汁酸及二者混合物对正常食管细胞处理后观察各组的食管细胞形态学变化. 结果显示, Tcf4、Cdx2、Hes1和Math1的表达水平在SIM

组和HGD组均显著增加[57]. 用400 μmoL胆汁酸处理后第7天, 可见明显的超微结构变化以及关键调节因子的过表达[57]. 此研究表明, WNT和Notch信号关键调节因子的异常表达在BE组织以及经酸、胆汁酸和二者混合物处理的正常食管细胞均可被观察到[57]. 但Moyes等[58]研究发现, WNT信号异常激活可能只在BE化生启动中起次要作用, 而在异型增生的进程中发挥更关键作用. Dvorak等[59]和Gibson等[60]认为, IL-6/STAT3信号通路在BE-EAC的进程中也起重要作用. 此外, 血管内皮生长因子(vascular endothelial growth factor, VEGF)可激活VEGF受体(VEGF receptor, VEGFR)以自分泌方式促进肿瘤细胞增殖[61]. Zhang等[61]发现, 自分泌VEGFR信号通过磷脂酶C(phospholipase C, PLC)依赖途径促进BE上皮的肿瘤细胞增殖. 因此, 减少自分泌VEGFR信号的靶向治疗策略(如: 应用舒尼替尼)有望被用于预防或治疗BE癌变[61].

7 BE与microRNAs

microRNAs(miRNAs)是一类小分子非编码RNA, 通过与靶基因序列的相互作用调控细胞增殖、分化和凋亡过程, 在BE化生(Barrett's metaplasia, BM)-EAC的进程中起重要作用[62]. 作为分子标志物, miRNAs在BE和EAC中的不同表达有助于识别BE并发EAC的风险, 对于BE和EAC的诊断、治疗乃至预后评估均有重要意义[62,63]. Leidner等[63]对BM-HGD-EAC进程中的26个候选miRNAs评估发现, 23个miRNAs于BM初期下调, 2个miRNAs(miR-31、miR-31*)仅在HGD和EAC频繁下调, 而第3个miRNA(miR-375)仅在EAC显著下调, 提示miR-31和miR-375分别与BE恶性进程的早期和晚期密切相关. Saad等[64]发现, miR-194、miR-200a、miR-192的过表达仅于EAC早期显著升高, 说明这些miRNAs可能只涉及EAC肿瘤发生, 而与其进展无关[64], 此结果与Fassan等[65]研究相似. 此外, BE组织中miR-192、miR-194、miR-196a、miR-196b的显著表达有助于识别EAC风险[66]. Sakai等[62]采用Meta分析对BE和EAC研究发现, 4种miRNAs(miR-25、miR-99a、miR-133a、miR-133b)有良好的诊断标志物潜能, 5种miRNAs(miR-21、miR-27b、miR-126、miR-143、miR-145)似乎可作为有效的诊断和预后标志物. EAC相关癌基因和抑癌基因的表达失衡可诱导EAC的发生、发展[67]. 在BE-EAC的进程中, 除miR-223表达显著上调外[67], 一些已知癌基因miRNAs(miR-21、miR-25、miR-223)和抑癌基因miRNAs(miR-205、miR-203、let-7c、miR-133a)的表达在逐渐发生变化, 而某些新被认定的miRNAs(miR-301b、miR-618、miR-23b)表达也在逐渐发生变化[68]. 研究显示, miR-375下调以及5种miR-17-92同源物上调仅见于EAC[68], miR-203下调也与EAC进展有关[64], 上述miRNAs有望成为EAC进展的生物学标志物. 此外, 有研究显示, miRNA-145通过GATA6间接调节BMP4信号通路[69], miRNA-221、miRNA-222过表达导致的CDX2降解[70]等因素均可能在EAC的致癌机制中起重要作用.

8 结论

BE的分子机制非常复杂, 涉及细胞起源、免疫机制、转录因子、DNA甲基化、一氧化氮、信号蛋白以及miRNAs等诸多因素. 部分miRNAs因具有癌基因或抑癌基因作用, 有望成为新的生物学标志物而用于EAC的诊断、预后评估及靶向治疗. 分子生物学技术的飞速发展为寻找EAC生物学标志物提供了途径, EAC患者血清miRNAs表达谱异常对其早期诊断及预后评估均有重要价值, 但目前尚缺乏大规模健康人群的血清miRNAs表达谱资料, 血清内源性miRNAs的参照体系也尚未建立, 这些均有待于进一步研究, 前景值得期待.

■应用要点
本文系统阐述了BE发生的分子生物学机制, 不仅对BE的基础研究有重要的指导意义, 也对BE的早期诊断、治疗及预防提供了新的思路.

9 参考文献

1 黄颖秋. Barrett's食管的研究现状. 世界华人消化杂志 2007; 15: 2567-2571
2 DeMeester SR. Letter to the editor regarding "Definition of Barrett's esophagus: time for a rethink-is intestinal metaplasia dead?". *Am J Gastroenterol* 2010; 105: 1201-1202; author reply 1202-1203 [PMID: 20445513 DOI: 10.1038/ajg.2010.6]
3 Vieth M, Langner C, Neumann H, Takubo K. Barrett's esophagus. Practical issues for daily routine diagnosis. *Pathol Res Pract* 2012; 208: 261-268 [PMID: 22513275 DOI: 10.1016/j.prp.2012.03.001]
4 Westerhoff M, Hovan L, Lee C, Hart J. Effects of dropping the requirement for goblet cells from the diagnosis of Barrett's esophagus. *Clin Gastroenterol Hepatol* 2012; 10: 1232-1236 [PMID: 22642957 DOI: 10.1016/j.cgh.2012.05.013]
5 Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association technical review on the management of Barrett's esophagus. *Gastroenterology* 2011; 140: e18-52; quiz e13 [PMID: 21376939]
6 Nemeth IB, Rosztoczy A, Izbeki F, Roka R, Gecse K, Sukosd F, Nyari T, Wittmann T, Tiszlavicz L. A renewed insight into Barrett's esophagus: comparative histopathological analysis of esophageal columnar

■同行评价
本文详尽综述了BE分子机制领域的最新研究进展，内容新颖，对BE的基础研究及临床工作有重要的参考价值.

metaplasia. *Dis Esophagus* 2012; 25: 395-402 [PMID: 22035281 DOI: 10.1111/j.1442-2050.2011.01270.x]

7 Pohl H, Wrobel K, Bojarski C, Voderholzer W, Sonnenberg A, Rösch T, Baumgart DC. Risk factors in the development of esophageal adenocarcinoma. *Am J Gastroenterol* 2013; 108: 200-207 [PMID: 23247577 DOI: 10.1038/ajg.2012.387]

8 Anaparthy R, Gaddam S, Kanakadandi V, Alsop BR, Gupta N, Higbee AD, Wani SB, Singh M, Rastogi A, Bansal A, Cash BD, Young PE, Lieberman DA, Falk GW, Vargo JJ, Thota P, Sampliner RE, Sharma P. Association Between Length of Barrett's Esophagus and Risk of High-grade Dysplasia or Adenocarcinoma in Patients Without Dysplasia. *Clin Gastroenterol Hepatol* 2013; 11: 1430-1436 [PMID: 23707463 DOI: 10.1016/j.cgh.2013.05.007]

9 Spechler SJ. Barrett's esophagus: the American perspective. *Dig Dis* 2013; 31: 10-16 [PMID: 23797117 DOI: 10.1159/000347099]

10 Huang Q, Fang DC, Yu CG, Zhang J, Chen MH. Barrett's esophagus-related diseases remain uncommon in China. *J Dig Dis* 2011; 12: 420-427 [PMID: 22118690 DOI: 10.1111/j.1751-2980.2011.00535.x]

11 Huang Q. Carcinoma of the gastroesophageal junction in Chinese patients. *World J Gastroenterol* 2012; 18: 7134-7140 [PMID: 23326117 DOI: 10.3748/wjg.v18.i48.7134]

12 Agarwal A, Polineni R, Hussein Z, Vigoda I, Bhagat TD, Bhattacharyya S, Maitra A, Verma A. Role of epigenetic alterations in the pathogenesis of Barrett's esophagus and esophageal adenocarcinoma. *Int J Clin Exp Pathol* 2012; 5: 382-396 [PMID: 22808291]

13 Zhai R, Zhao Y, Su L, Cassidy L, Liu G, Christiani DC. Genome-wide DNA methylation profiling of cell-free serum DNA in esophageal adenocarcinoma and Barrett esophagus. *Neoplasia* 2012; 14: 29-33 [PMID: 22355271]

14 Sinicrope FA, Broaddus R, Joshi N, Gerner E, Half E, Kirsch I, Lewin J, Morlan B, Hong WK. Evaluation of difluoromethylornithine for the chemoprevention of Barrett's esophagus and mucosal dysplasia. *Cancer Prev Res* (Phila) 2011; 4: 829-839 [PMID: 21636549 DOI: 10.1158/1940-6207.CAPR-10-0243]

15 Akagi T, Ito T, Kato M, Jin Z, Cheng Y, Kan T, Yamamoto G, Olaru A, Kawamata N, Boult J, Soukiasian HJ, Miller CW, Ogawa S, Meltzer SJ, Koeffler HP. Chromosomal abnormalities and novel disease-related regions in progression from Barrett's esophagus to esophageal adenocarcinoma. *Int J Cancer* 2009; 125: 2349-2359 [PMID: 19670330 DOI: 10.1002/ijc.24620]

16 Zhang HY, Spechler SJ, Souza RF. Esophageal adenocarcinoma arising in Barrett esophagus. *Cancer Lett* 2009; 275: 170-177 [PMID: 18703277 DOI: 10.1016/j.canlet.2008.07.006]

17 Goldman A, Chen HD, Roesly HB, Hill KA, Tome ME, Dvorak B, Bernstein H, Dvorak K. Characterization of squamous esophageal cells resistant to bile acids at acidic pH: implication for Barrett's esophagus pathogenesis. *Am J Physiol Gastrointest Liver Physiol* 2011; 300: G292-G302 [PMID: 21127259]

18 Quante M, Bhagat G, Abrams JA, Marache F, Good P, Lee MD, Lee Y, Friedman R, Asfaha S, Dubeykovskaya Z, Mahmood U, Figueiredo JL, Kitajewski J, Shawber C, Lightdale CJ, Rustgi AK, Wang TC. Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. *Cancer Cell* 2012; 21: 36-51 [PMID: 22264787 DOI: 10.1016/j.ccr.2011.12.004]

19 Quante M, Abrams JA, Lee Y, Wang TC. Barrett esophagus: what a mouse model can teach us about human disease. *Cell Cycle* 2012; 11: 4328-4338 [PMID: 23095673 DOI: 10.4161/cc.22485]

20 Pan Q, Nicholson AM, Barr H, Harrison LA, Wilson GD, Burkert J, Jeffery R, Alison MR, Looijenga L, Lin WR, McDonald SA, Wright NA, Harrison R, Peppelenbosch MP, Jankowski JA. Identification of lineage-uncommitted, long-lived, label-retaining cells in healthy human esophagus and stomach, and in metaplastic esophagus. *Gastroenterology* 2013; 144: 761-770 [PMID: 23266557 DOI: 10.1053/j.gastro.2012.12.022]

21 Vega KJ, May R, Sureban SM, Lightfoot SA, Qu D, Reed A, Weygant N, Ramanujam R, Souza R, Madhoun M, Whorton J, Anant S, Meltzer SJ, Houchen CW. Identification of the putative intestinal stem cell marker doublecortin and CaM kinase-like-1 in Barrett's esophagus and esophageal adenocarcinoma. *J Gastroenterol Hepatol* 2012; 27: 773-780 [PMID: 21916995 DOI: 10.1111/j.1440-1746.2011.06928.x]

22 Stamp LA, Braxton DR, Wu J, Akopian V, Hasegawa K, Chandrasoma PT, Hawes SM, McLean C, Petrovic LM, Wang K, Pera MF. The GCTM-5 epitope associated with the mucin-like glycoprotein FCGBP marks progenitor cells in tissues of endodermal origin. *Stem Cells* 2012; 30: 1999-2009 [PMID: 22761039 DOI: 10.1002/stem.1167]

23 Hutchinson L, Stenstrom B, Chen D, Piperdi B, Levey S, Lyle S, Wang TC, Houghton J. Human Barrett's adenocarcinoma of the esophagus, associated myofibroblasts, and endothelium can arise from bone marrow-derived cells after allogeneic stem cell transplant. *Stem Cells Dev* 2011; 20: 11-17 [PMID: 20677919 DOI: 10.1089/scd.2010.0139]

24 Upton MP, Pai RK, Vieth M, Neumann H, Langner C. Esophageal disease and pathology. *Ann N Y Acad Sci* 2011; 1232: 376-380 [PMID: 21950829 DOI: 10.1111/j.1749-6632.2011.06063.x]

25 Barbera M, Fitzgerald RC. Cellular origin of Barrett's metaplasia and oesophageal stem cells. *Biochem Soc Trans* 2010; 38: 370-373 [PMID: 20298185 DOI: 10.1042/BST0380370]

26 Aikou S, Aida J, Takubo K, Yamagata Y, Seto Y, Kaminishi M, Nomura S. Columnar metaplasia in a surgical mouse model of gastro-esophageal reflux disease is not derived from bone marrow-derived cell. *Cancer Sci* 2013; 104: 1154-1161 [PMID: 23734763 DOI: 10.1111/cas.12213]

27 Wang X, Ouyang H, Yamamoto Y, Kumar PA, Wei TS, Dagher R, Vincent M, Lu X, Bellizzi AM, Ho KY, Crum CP, Xian W, McKeon F. Residual embryonic cells as precursors of a Barrett's-like metaplasia. *Cell* 2011; 145: 1023-1035 [PMID: 21703447 DOI: 10.1016/j.cell.2011.05.026]

28 von Holzen U, Enders GH. A surprise cell of origin for Barrett's esophagus. *Cancer Biol Ther* 2012; 13: 588-591 [PMID: 22549156 DOI: 10.4161/cbt.20088]

29 Somja J, Demoulin S, Roncarati P, Herfs M, Bletard N, Delvenne P, Hubert P. Dendritic cells in Barrett's esophagus carcinogenesis: an inadequate microenvironment for antitumor immunity? *Am J Pathol* 2013; 182: 2168-2179 [PMID: 23619476 DOI: 10.1016/j.ajpath.2013.02.036]

30 Bobryshev YV, Tran D, Killingsworth MC, Buckland M, Lord RV. Dendritic cell-associated immune inflammation of cardiac mucosa: a possible factor in the formation of Barrett's esophagus. *J Gastrointest Surg* 2009; 13: 442-450 [PMID: 19015928 DOI: 10.1007/s11605-008-0746-x]

31 Lind A, Siersema PD, Kusters JG, Van der Linden JA, Knol EF, Koenderman L. The immune cell composition in Barrett's metaplastic tissue resembles that in normal duodenal tissue. *PLoS One* 2012; 7: e33899 [PMID: 22509265 DOI: 10.1371/journal.pone.0033899]

32 Kavanagh ME, O'Sullivan KE, O'Hanlon C, O'Sullivan JN, Lysaght J, Reynolds JV. The esophagitis to adenocarcinoma sequence; the role of inflammation. *Cancer Lett* 2013 Aug 27. *[Epub ahead of print]* [PMID: 23994342 DOI: 10.1016/j.canlet.2013.08.017]

33 Trowbridge R, Kizer RT, Mittal SK, Agrawal DK. 1,25-dihydroxyvitamin D in the pathogenesis of Barrett's esophagus and esophageal adenocarcinoma. *Expert Rev Clin Immunol* 2013; 9: 517-533 [PMID: 23730883 DOI: 10.1586/eci.13.38]

34 DiMaio MA, Kwok S, Montgomery KD, Lowe AW, Pai RK. Immunohistochemical panel for distinguishing esophageal adenocarcinoma from squamous cell carcinoma: a combination of p63, cytokeratin 5/6, MUC5AC, and anterior gradient homolog 2 allows optimal subtyping. *Hum Pathol* 2012; 43: 1799-1807 [PMID: 22748473 DOI: 10.1016/j.humpath.2012.03.019]

35 Gen Y, Yasui K, Nishikawa T, Yoshikawa T. SOX2 promotes tumor growth of esophageal squamous cell carcinoma through the AKT/mammalian target of rapamycin complex 1 signaling pathway. *Cancer Sci* 2013; 104: 810-816 [PMID: 23510069 DOI: 10.1111/cas.12155]

36 Lefort K, Dotto GP. p63 and epithelial metaplasia: a gutsy choice. *Cell* 2011; 145: 1003-1005 [PMID: 21703442 DOI: 10.1016/j.cell.2011.06.008]

37 Zhao J, Gregersen H. Relationships of CDXs and apical sodium-dependent bile acid transporter in Barrett's esophagus. *World J Gastroenterol* 2013; 19: 2736-2739 [PMID: 23687410 DOI: 10.3748/wjg.v19.i18.2736]

38 Liu T, Zhang X, So CK, Wang S, Wang P, Yan L, Myers R, Chen Z, Patterson AP, Yang CS, Chen X. Regulation of Cdx2 expression by promoter methylation, and effects of Cdx2 transfection on morphology and gene expression of human esophageal epithelial cells. *Carcinogenesis* 2007; 28: 488-496 [PMID: 16990345 DOI: 10.1093/carcin/bgl176]

39 Burnat G, Majka J, Konturek PC. Bile acids are multifunctional modulators of the Barrett's carcinogenesis. *J Physiol Pharmacol* 2010; 61: 185-192 [PMID: 20436219]

40 Castillo D, Puig S, Iglesias M, Seoane A, de Bolós C, Munitiz V, Parrilla P, Comerma L, Poulsom R, Krishnadath KK, Grande L, Pera M. Activation of the BMP4 pathway and early expression of CDX2 characterize non-specialized columnar metaplasia in a human model of Barrett's esophagus. *J Gastrointest Surg* 2012; 16: 227-237; discussion 237 [PMID: 22076569 DOI: 10.1007/s11605-011-1758-5]

41 Clemons NJ, Wang DH, Croagh D, Tikoo A, Fennell CM, Murone C, Scott AM, Watkins DN, Phillips WA. Sox9 drives columnar differentiation of esophageal squamous epithelium: a possible role in the pathogenesis of Barrett's esophagus. *Am J Physiol Gastrointest Liver Physiol* 2012; 303: G1335-G1346 [PMID: 23064761 DOI: 10.1152/ajpgi.00291.2012]

42 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]

43 Tomizawa Y, Wu TT, Wang KK. Epithelial mesenchymal transition and cancer stem cells in esophageal adenocarcinoma originating from Barrett's esophagus. *Oncol Lett* 2012; 3: 1059-1063 [PMID: 22783391 DOI: 10.3892/ol.2012.632]

44 Wu W, Bhagat TD, Yang X, Song JH, Cheng Y, Agarwal R, Abraham JM, Ibrahim S, Bartenstein M, Hussain Z, Suzuki M, Yu Y, Chen W, Eng C, Greally J, Verma A, Meltzer SJ. Hypomethylation of noncoding DNA regions and overexpression of the long noncoding RNA, AFAP1-AS1, in Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterology* 2013; 144: 956-966. e4 [PMID: 23333711 DOI: 10.1053/j.gastro.2013.01.019]

45 Alvi MA, Liu X, O'Donovan M, Newton R, Wernisch L, Shannon NB, Shariff K, di Pietro M, Bergman JJ, Ragunath K, Fitzgerald RC. DNA methylation as an adjunct to histopathology to detect prevalent, inconspicuous dysplasia and early-stage neoplasia in Barrett's esophagus. *Clin Cancer Res* 2013; 19: 878-888 [PMID: 23243219 DOI: 10.1158/1078-0432.CCR-12-2880]

46 Kaz AM, Luo Y, Dzieciatkowski S, Chak A, Willis JE, Upton MP, Leidner RS, Grady WM. Aberrantly methylated PKP1 in the progression of Barrett's esophagus to esophageal adenocarcinoma. *Genes Chromosomes Cancer* 2012; 51: 384-393 [PMID: 22170739 DOI: 10.1002/gcc.21923]

47 Kaz AM, Wong CJ, Luo Y, Virgin JB, Washington MK, Willis JE, Leidner RS, Chak A, Grady WM. DNA methylation profiling in Barrett's esophagus and esophageal adenocarcinoma reveals unique methylation signatures and molecular subclasses. *Epigenetics* 2011; 6: 1403-1412 [PMID: 22139570 DOI: 10.4161/epi.6.12.18199]

48 黄颖秋, 张德中, 萧树东. 一氧化氮与消化道动力. 国外医学•消化系疾病分册 1997; 17: 23-27

49 黄颖秋, 王昕, 李嗯, 刘丽. 一氧化氮在胃食管反流病发病机制中的作用. 世界华人消化杂志 2000; 8: 253-255

50 McAdam E, Haboubi HN, Forrester G, Eltahir Z, Spencer-Harty S, Davies C, Griffiths AP, Baxter JN, Jenkins GJ. Inducible nitric oxide synthase (iNOS) and nitric oxide (NO) are important mediators of reflux-induced cell signalling in esophageal cells. *Carcinogenesis* 2012; 33: 2035-2043 [PMID: 22826608 DOI: 10.1093/carcin/bgs241]

51 Kusaka G, Uno K, Iijima K, Endo H, Asano N, Koike T, Imatani A, Shimosegawa T. The role of nitric oxide in the induction of caudal-type homeobox 2 through epidermal growth factor receptor in the development of Barrett's esophagus. *Scand J Gastroenterol* 2012; 47: 1148-1158 [PMID: 22834965 DOI: 10.3109/00365521.2012.703232]

52 Goldman A, Shahidullah M, Goldman D, Khailova L, Watts G, Delamere N, Dvorak K. A novel mechanism of acid and bile acid-induced DNA damage

involving Na+/H+ exchanger: implication for Barrett's oesophagus. *Gut* 2010; 59: 1606-1616 [PMID: 20876775 DOI: 10.1136/gut.2010.213686]

53 Clemons NJ, Shannon NB, Abeyratne LR, Walker CE, Saadi A, O'Donovan ML, Lao-Sirieix PP, Fitzgerald RC. Nitric oxide-mediated invasion in Barrett's high-grade dysplasia and adenocarcinoma. *Carcinogenesis* 2010; 31: 1669-1675 [PMID: 20584750 DOI: 10.1093/carcin/bgq130]

54 Streppel MM, Montgomery EA, Maitra A. New Advances in the Pathogenesis and Progression of Barrett's Esophagus. *Curr Mol Med* 2013 Jul 16. *[Epub ahead of print]* [PMID: 23865431]

55 Clemons N, Phillips W, Lord RV. Signaling pathways in the molecular pathogenesis of adenocarcinomas of the esophagus and gastresophageal junction. *Cancer Biol Ther* 2013 Jun 17. *[Epub ahead of print]* [PMID: 23792587]

56 Mendelson J, Song S, Li Y, Maru DM, Mishra B, Davila M, Hofstetter WL, Mishra L. Dysfunctional transforming growth factor-β signaling with constitutively active Notch signaling in Barrett's esophageal adenocarcinoma. *Cancer* 2011; 117: 3691-3702 [PMID: 21305538 DOI: 10.1002/cncr.25861]

57 Chen X, Jiang K, Fan Z, Liu Z, Zhang P, Zheng L, Peng N, Tong J, Ji G. Aberrant expression of Wnt and Notch signal pathways in Barrett's esophagus. *Clin Res Hepatol Gastroenterol* 2012; 36: 473-483 [PMID: 22889748 DOI: 10.1016/j.clinre.2012.06.001]

58 Moyes LH, McEwan H, Radulescu S, Pawlikowski J, Lamm CG, Nixon C, Sansom OJ, Going JJ, Fullarton GM, Adams PD. Activation of Wnt signalling promotes development of dysplasia in Barrett's oesophagus. *J Pathol* 2012; 228: 99-112 [PMID: 22653845 DOI: 10.1002/path.4058]

59 Dvorak K, Dvorak B. Role of interleukin-6 in Barrett's esophagus pathogenesis. *World J Gastroenterol* 2013; 19: 2307-2312 [PMID: 23613623 DOI: 10.3748/wjg.v19.i15.2307]

60 Gibson MK, Dhaliwal AS, Clemons NJ, Phillips WA, Dvorak K, Tong D, Law S, Pirchi ED, Räsänen J, Krasna MJ, Parikh K, Krishnadath KK, Chen Y, Griffiths L, Colleypriest BJ, Farrant JM, Tosh D, Das KM, Bajpai M. Barrett's esophagus: cancer and molecular biology. *Ann N Y Acad Sci* 2013; 1300: 296-314 [PMID: 24117650 DOI: 10.1111/nyas.12252]

61 Zhang Q, Yu C, Peng S, Xu H, Wright E, Zhang X, Huo X, Cheng E, Pham TH, Asanuma K, Hatanpaa KJ, Rezai D, Wang DH, Sarode V, Melton S, Genta RM, Spechler SJ, Souza RF. Autocrine VEGF Signaling Promotes Proliferation of Neoplastic Barrett's Epithelial Cells Through a PLC-Dependent Pathway. *Gastroenterology* 2013 Oct 8 *[Epub ahead of print]* [PMID: 24120473 DOI: 10.1053/j.gastro.2013.10.011]

62 Sakai NS, Samia-Aly E, Barbera M, Fitzgerald RC. A review of the current understanding and clinical utility of miRNAs in esophageal cancer. *Semin Cancer Biol* 2013; 23: 512-521 [PMID: 24013023 DOI: 10.1016/j.semcancer.2013.08.005]

63 Leidner RS, Ravi L, Leahy P, Chen Y, Bednarchik B, Streppel M, Canto M, Wang JS, Maitra A, Willis J, Markowitz SD, Barnholtz-Sloan J, Adams MD, Chak A, Guda K. The microRNAs, MiR-31 and MiR-375, as candidate markers in Barrett's esophageal carcinogenesis. *Genes Chromosomes Cancer* 2012; 51: 473-479 [PMID: 22302717 DOI: 10.1002/gcc.21934]

64 Saad R, Chen Z, Zhu S, Jia P, Zhao Z, Washington MK, Belkhiri A, El-Rifai W. Deciphering the unique microRNA signature in human esophageal adenocarcinoma. *PLoS One* 2013; 8: e64463 [PMID: 23724052 DOI: 10.1371/journal.pone.0064463]

65 Fassan M, Volinia S, Palatini J, Pizzi M, Fernandez-Cymering C, Balistreri M, Realdon S, Battaglia G, Souza R, Odze RD, Zaninotto G, Croce CM, Rugge Md Facg M. MicroRNA Expression Profiling in the Histological Subtypes of Barrett's Metaplasia. *Clin Transl Gastroenterol* 2013; 4: e34 [PMID: 23677165 DOI: 10.1038/ctg.2013.5]

66 Revilla-Nuin B, Parrilla P, Lozano JJ, de Haro LF, Ortiz A, Martínez C, Munitiz V, de Angulo DR, Bermejo J, Molina J, Cayuela ML, Yélamos J. Predictive value of MicroRNAs in the progression of barrett esophagus to adenocarcinoma in a long-term follow-up study. *Ann Surg* 2013; 257: 886-893 [PMID: 23059500 DOI: 10.1097/SLA.0b013e31826ddba6]

67 Streppel MM, Pai S, Campbell NR, Hu C, Yabuuchi S, Canto MI, Wang JS, Montgomery EA, Maitra A. MicroRNA 223 is upregulated in the multistep progression of Barrett's esophagus and modulates sensitivity to chemotherapy by targeting PARP1. *Clin Cancer Res* 2013; 19: 4067-4078 [PMID: 23757351 DOI: 10.1158/1078-0432.CCR-13-0601]

68 Wu X, Ajani JA, Gu J, Chang DW, Tan W, Hildebrandt MA, Huang M, Wang KK, Hawk E. MicroRNA expression signatures during malignant progression from Barrett's esophagus to esophageal adenocarcinoma. *Cancer Prev Res* (Phila) 2013; 6: 196-205 [PMID: 23466817 DOI: 10.1158/1940-6207.CAPR-12-0276]

69 van Baal JW, Verbeek RE, Bus P, Fassan M, Souza RF, Rugge M, ten Kate FJ, Vleggaar FP, Siersema PD. microRNA-145 in Barrett's oesophagus: regulating BMP4 signalling via GATA6. *Gut* 2013; 62: 664-675 [PMID: 22504665 DOI: 10.1136/gutjnl-2011-301061]

70 Matsuzaki J, Suzuki H, Tsugawa H, Watanabe M, Hossain S, Arai E, Saito Y, Sekine S, Akaike T, Kanai Y, Mukaisho K, Auwerx J, Hibi T. Bile Acids Increase Levels of MicroRNAs 221 and 222, Leading to Degradation of CDX2 During Esophageal Carcinogenesis. *Gastroenterology* 2013; 145: 1300-1311 [PMID: 23933602 DOI: 10.1053/j.gastro.2013.08.008]

编辑 田滢 电编 闫晋利