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Shijie Huaren Xiaohua Zazhi

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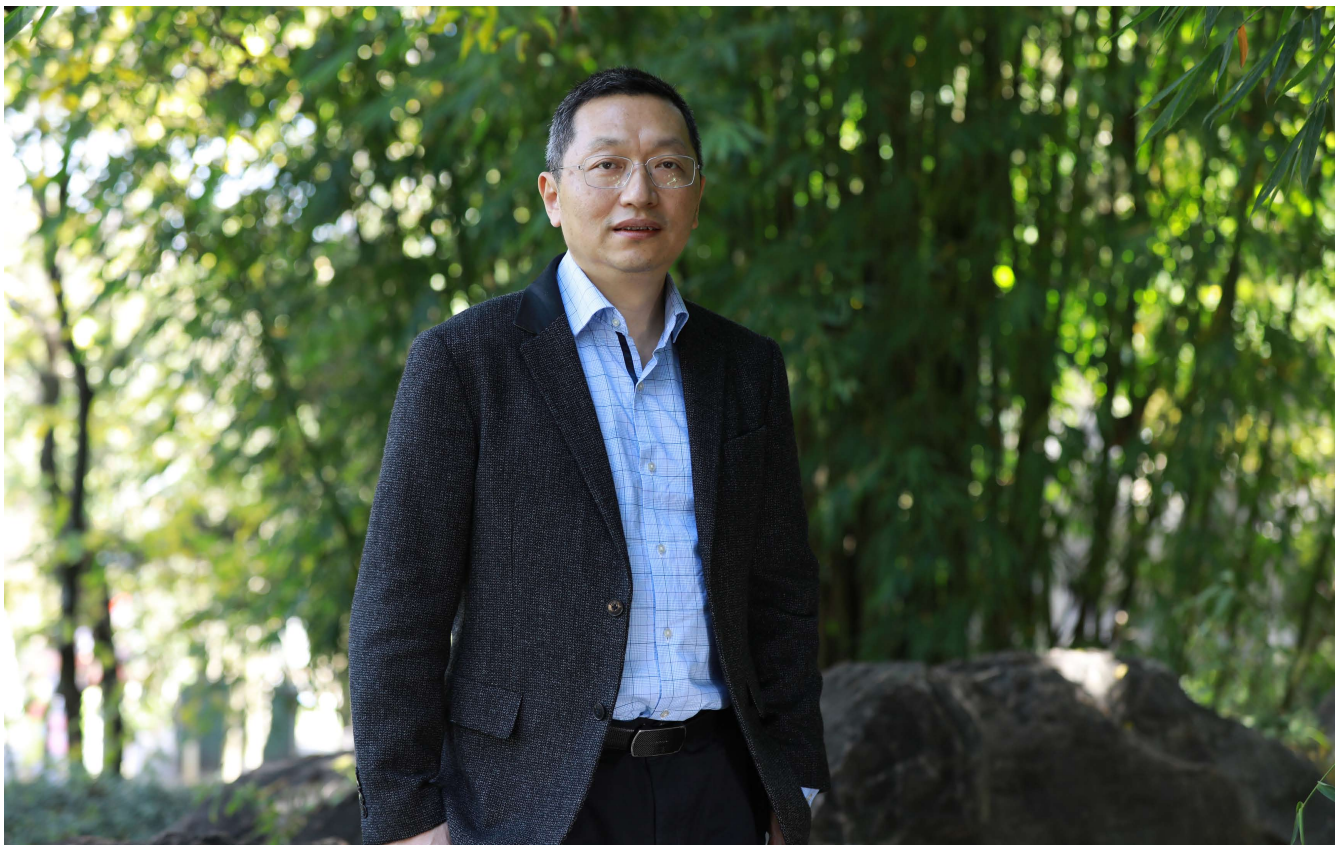

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文献综述 REVIEW

调控胰腺癌侵袭和转移分子靶点研究新进展

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Molecular targets regulating invasion and metastasis of pancreatic cancer

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Abstract

Pancreatic cancer is one of the most malignant tumors of the digestive system. Invasion and metastasis are important biological characteristics of pancreatic cancer and contribute greatly to the poor prognosis of the patients. Many lines of evidence have recently revealed that many molecules, genes and proteins regulate the invasion and metastasis of pancreatic cancer cells. Therefore, exploration and a deep understanding of the molecular mechanism accounting for the invasion and metastasis of pancreatic cancer can help find novel pancreatic cancer biomarkers, improve early diagnosis, develop novel and effective treatment strategies, and predict the prognosis. This review summarizes the latest progress in the research of molecular targets for pancreatic cancer and the mechanisms by which they participate in the invasion and metastasis of this aggressive malignancy.

Key Words: Pancreatic cancer; Invasion; Metastasis; Molecular targets; Regulatory mechanism.

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摘要

胰腺癌是恶性程度最高的消化道肿瘤之一. 侵袭和转移是胰腺癌的重要生物学特性, 也是导致胰腺癌预后不良的重要因素. 近年来, 大量研究证明多种分子、基因和蛋白参与调控胰腺癌细胞的侵袭和转移. 因此, 深入揭示和研究胰腺癌侵袭转移的分子机制, 不仅有助于发现新的肿瘤标志物和胰腺癌早期诊断, 还可以用来制定新的有效治疗策略以及判断预后. 本文就影响胰腺癌侵袭和转移的分子靶点和机制的

最新进展作一综述.

关键词: 胰腺癌; 侵袭; 转移; 分子靶点; 调控机制

核心提要: 胰腺癌是恶性程度最高的消化道肿瘤之一, 侵袭和转移是胰腺癌的重要生物学特性, 涉及因素众多. 大量实验研究使得影响胰腺癌侵袭和转移的相关基因、蛋白逐渐进入人们视野.深入揭示和理解胰腺癌侵袭转移的分子机制,不仅能发现新的肿瘤标志物, 帮助诊断早期胰腺癌, 还可以用来制定新的有效的治疗策略以及判断预后, 提高患者的生存率. 多靶点、个体化、综合治疗将是未来胰腺癌治疗的发展方向.

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0 引言

胰腺癌是恶性程度最高的消化道肿瘤之一. 根据我国国家癌症中心发布的最新数据, 我国胰腺癌的发病率已达第10位, 死亡率升高到第6位; 在一些大城市中,胰腺癌的发病率和死亡率甚至高达第7位和第5位[1]. 据报道, 胰腺癌患者的平均生存期少于6 mo, 5年生存率小于5%[2]. 侵袭和转移是恶性肿瘤的重要生物学特性, 也是导致胰腺癌患者预后不良的主要原因. 然而, 由于胰腺癌早期症状不明显, 且缺乏用于胰腺癌早期诊断的有效而特异的生物标志物, 大部分患者就诊时已出现局部侵袭甚至远处转移, 失去了最佳的治疗时机. 因此, 探究调控胰腺癌发生发展以及侵袭转移的分子靶点, 寻找有效的用于早期诊断及治疗的生物标志物是亟待解决的关键问题. 本文就调控胰腺癌侵袭和转移的分子靶点及其机制进行综述如下, 希望为胰腺癌的早期诊断以及分子治疗提供新的思路.

1 上皮-间充质转化

肿瘤转移和侵袭是一个由多阶段多层次组成的过程. 肿瘤细胞首先获得迁移能力并脱离原组织, 在远隔部位建立起新的肿瘤微环境[3]. 上皮-间充质转化(epithelial-mesenchymal transformation, EMT)被认为是促进肿瘤转移的主要因素之一[4]. EMT是肿瘤细胞的一种转录和表观遗传程序, 可以使上皮细胞获得间充质特性, 如细胞-细胞间的连接丢失、增加细胞的运动能力, 使其离开原发肿瘤并转移至远隔器官[5]. 转化生长因子-β通路、丝裂原活化蛋白激酶通路、Hedgehog通路等细胞内信号转导通路在EMT过程中发挥非常重要的作用, 调节EMT相关因子Snail、Twist、ZEB等的表达, 最终引起细胞的一系列形态和功能的变化[6].

E-钙黏素可以调节肿瘤细胞的运动能力、侵袭能力以及肿瘤细胞的迁移能力[7], 其表达下降被认为是胰腺癌发生EMT和转移的主要指标[8]. 生理情况下, E-钙黏素与β-连接蛋白结合维持组织结构的稳定. E-钙黏素表达降低使细胞间的相互黏着力下降, 引起肿瘤细胞浸润性生长以及迁移[9]. 许多细胞内信号转导通路和蛋白在E-钙黏素的亚细胞定位以及调控过程中发挥重要作用[10,11]. 例如, EGFR可以增加EMT相关转录因子Snail, Twist和Slug的表达, 促进EMT的发生[12]. Snail/HDAC1/HDAC2复合体可以抑制E-钙黏素的表达, 促进EMT, 增加胰腺癌细胞的侵袭能力和免疫抑制[13]. Snail, Snail2(Slug), ZEB-1, ZEB-2以及Twist通过结合基因启动子, 抑制E-钙黏素的表达[14]. Snail还可以提高胰腺癌细胞抗凋亡能力和对5-FU及吉西他滨的耐药性, 间接促进胰腺癌细胞的增殖及转移[15]. 因此, 对EMT发生的分子机制的深入研究, 对于降低胰腺癌转移具有非常重要的应用前景.

2 基因组学

基因组变异是恶性肿瘤发生和发展的主要原因之一. 近些年来, 随着基因测序技术的发展和对胰腺癌组织基因突变研究的深入, 越来越多的基因突变被证实与胰腺癌侵袭和转移密切相关.

Waddell等[16]通过对100例胰腺癌组织样本的分析, 绘制出胰腺癌基因突变景观图, 发现胰腺癌组织主要突变基因有KARS、TP53、SMAD4、CDKN2A、ARID1A和ROBO2, 同时还发现2个新的候选驱动基因的突变(KDM6A和PREX2)[16]. 阿特拉斯癌症基因组研究小组通过对150例胰腺癌样本外显子深度测序分析, 发现胰腺癌主要的驱动突变基因包括KRAS、TP53、CDKN2A、SMAD4、RNF43、ARID1A、TGFbR2、GNAS、RREB1和PBRM1[17]. 然而, 尽管胰腺癌组织基因突变的研究进展迅速, 对于影响胰腺癌转移的遗传信息仍不十分明确.

原发肿瘤内存在特殊遗传异质性的癌细胞是导致肿瘤发生转移的重要因素. Yachida等[18,19]通过对原发胰腺癌肿瘤和转移肿瘤比较分析, 发现超过90%的胰腺癌病例中, 驱动基因的突变在原发肿瘤组织和转移组织中保持一致, 表明这些基因突变在胰腺癌的早期发挥作用. 同样有研究表明, 在胰腺癌原发肿瘤和转移肿瘤之间具有较低的基因异质性[20]. 因此, 可以推测出只有少

量基因的突变与胰腺癌的转移相关.

KARS、TP53、CDKN2A和SMAD4是胰腺癌最常见的突变基因[21]. 约94%的胰腺癌病人发生KRAS基因突变[22], 导致癌细胞异常增殖、抗凋亡、耐药和促进转移[23]. 抑制KRAS基因的突变或异常构象RAS蛋白的表达可以抑制胰腺癌细胞增殖, 甚至可以降低肿瘤的恶性程度[24]. ADAM9和MMP7是miR-489的靶基因, 在胰腺癌组织中高表达, 可以促进细胞外基质重塑和细胞远处转移[25]. KRAS还可以通过NF-κB通路激活转录因子YY1, 抑制miR-489的表达, 增加ADAM9和MMP7的表达, 从而促进胰腺癌细胞的远处转移[25]. RKIP是一种抑癌基因, 在胰腺癌组织中与KRAS的表达呈负相关, 敲除KRAS基因可以通过调节MAPK-ERK通路, 增加RKIP基因的表达, 抑制胰腺癌细胞的转移和耐药[26].

作为一种抑癌基因, TP53基因突变有两种表现形式, 一是TP53突变基因不表达, 使野生型P53基因功能失活; 二是P53突变基因过表达, 获得致癌功能[27]. 在胰腺癌组织中, TP53突变过表达可以通过上调Cavin-1的表达, 促进胰腺癌细胞的侵袭和转移[27].

SMAD4也称DPC4, 其突变与胰腺癌细胞的远处转移相关[21]. 然而, 有Meta分析结果提示, 胰腺癌SMAD4基因的缺失与肿瘤的大小、分级以及淋巴结转移无明显相关, 但与患者的预后密切相关[28]. Whittle等[29]研究发现, 杂合突变体DPC4/SMAD4抑制$KRAS^{G12D/+}$细胞的转移能力, 增加$TP53R^{172H/+}$胰腺癌细胞的增殖能力. DPC4杂合突变体还可降低RUNX3基因表达, 抑制胰腺癌细胞的转移, 但是却促进细胞增殖; 相反, 当DPC4为纯合子时, RUNX3基因表达增加, 抑制癌细胞增殖, 却促进癌细胞的转移[29]. 因此, RUNX3与DPC4两者可协作控制胰腺癌细胞的分裂和扩散间的平衡; RUNX3作为胰腺癌转移的开关, 调控DPC4/SMAD4信号通路相关基因的表达, 进而影响胰腺癌细胞增殖和转移.

另有研究发现, 在胰腺癌细胞中, 抑癌基因HIC1与STAT3结合, 抑制其DHA结合能力, 进而降低STAT3靶基因包括c-myc、VEGF、 CyclinD1、MMP2和MMP9的表达, 抑制胰腺癌细胞的侵袭和转移[30]. TUFT1基因表达增加可以通过HIF1/Snail信号通路, 调节EMT相关蛋白的表达, 促进胰腺癌细胞EMT的发生, 进而促进胰腺癌的远处转移[31].

近年来, 随着基因测序技术的不断升级, 更多的基因突变被证实与胰腺癌转移相关. Robinson等[32]对500例发生胰腺癌转移的患者进行全外显子组和转录组序列分析, 发现胰腺癌转移组织中主要基因发生突变, 包括KRAS、TP53、CDKN2A、PTEN、PIK3CA、AR和RB1等. 有研究发现CNTN5、DOCK2、MEP1A和LMTK2基因的突变和重排仅在胰腺癌IV期病人的转移灶中出现[19,33], 认为这些基因可能与胰腺癌的侵袭和转移相关. Zhou等[34]通过外显子组序列分析证实KRASG12V和TP53Y163C在胰腺癌转移癌组织中存在高等位基因频率; 说明KRAS和TP53基因突变是引起胰腺癌转移的主要原因之一. ADRB1、DCLK1、KCNH2、NOP14、SIGLEC1和 ZC3H7A基因的异常表达与胰腺癌细胞的增殖和迁徙密切相关. Stratford等[35]通过对无转移和伴有转移的胰腺原发肿瘤比较分析, 发现FosB、 KLF6、NFKBIZ、ATP4A、GSG1和SIGLEC11这6种基因与胰腺癌的转移相关. 然而, 目前尚缺乏直接证据证明这些基因的突变可直接促使胰腺癌细胞的转移, 还需要进一步研究.

3 L1细胞黏附分子

L1细胞黏附分子(L1 cell adhesion molecule, L1CAM)是免疫球蛋白超家族的成员之一, 最初被认为在神经系统的发育过程中起重要作用[36]. 近年来研究发现L1CAM的过度表达在肿瘤的发生和增殖过程中同样具有重要作用. L1CAM在胰腺癌细胞中高表达, 并且通过激活STAT3/NF-κB信号转导通路促进癌细胞的增殖和迁移[37]. 抑制L1CAM的表达通过p38/ERK1/2信号通路抑制胰腺癌细胞侵袭以及使细胞周期停滞[38]. L1CAM同样在肿瘤的血管生成过程扮演重要角色, 在胰腺癌患者的血管内皮细胞中L1CAM的表达明显增加, 通过IL-6/JAK/STAT信号通路促进血管内皮细胞的增殖和迁移[39].

4 缺氧诱导因子

实体肿瘤组织内存在缺氧微环境, 肿瘤细胞在适应低氧环境过程中激活一系列低氧相关的分子, 其中最为重要的就是缺氧诱导因子(hypoxia-inducible factors, HIFs)[40]. HIFS由对氧敏感的α亚基和稳定表达的β亚基组成; 在低氧环境下, HIF-α结构会变得稳定, 向细胞核移动, 并与HIF-1β结合成为具有转录因子作用的二聚体. HIF-1的过表达在胰腺癌的侵袭及转移过程中具有重要作用[41]. HIF-3α的过表达通过激活HIF-3α/RhoC-ROCK1信号通路, 促进胰腺癌细胞的侵袭和转移[42].

HIF还可以促进胰腺癌细胞EMT的发生, 如HIF-1α-HDAC1复合体会结合miR-548an启动子上的缺氧反应原件, 抑制miR-548an转录, 从而上调其下游靶蛋白vimentin的表达, 促进胰腺癌细胞的增殖和侵袭[43]. HIF-2α调节Twist1与E-钙黏素启动子的结合, 促进胰腺癌细胞的EMT[44], 进而促进胰腺癌细胞的增殖和侵袭、增加肿瘤血管生成和有氧酵解[45]. 但是, 有学者报道HIF-2α

表 1 调控胰腺癌侵袭及转移的miRNAs

miRNA	靶基因	对胰腺癌侵袭以及转移的作用
miRNA-216b[47]	*ROCK1*	抑制
miRNA-652[48]	*ZEB1*	抑制
miRNA-146a[49]	*EGFR*、*MTA-2*	抑制
miRNA-141[51]	*MAP4K4*	抑制
miRNA-218[74]	*ROBO-1*	抑制
miRNA-34b[75]	*SMAD3*	抑制
miRNA-29c[76]	*MMP2*	抑制
miR-124[77]	*Rac1*	抑制
miR-148a[78]	*DNMT1*	抑制
miR-148b[79]	*AMPKα1*	抑制
miR-548an[43]	*vimentin*	抑制
miR-615-5p[80]	*AKT2*	抑制
miR-323-3p[81]	*SMAD2*、*SMAD3*	抑制
miR-367[82]	*Smad7*	促进
miRNA-31[83]	*ARID1A*	促进
miR-10a[84]	*HOXB1 and HOXB3*	促进
miR-224、miR-486[85]	*CD40*	促进
miR-27a[86]	*Spry2*	促进
miRNA-1178[53]	*Stub1*	促进

表达增加对胰腺癌细胞的侵袭作用起到负向调节作用, HIF-2α高表达患者的生存期较HIF-1α高表达者明显延长; 从而认为HIF-1α和HIF-2α在胰腺癌中起相反的作用[40]. 因此, HIFs在胰腺癌中的作用仍存有争议, 其具体机制需进一步研究.

5 MicroRNA

MicroRNA(miRNA)指约18-25个核苷酸序列的非编码微小RNA, 它们靶向结合mRNA的3'端非编码区, 沉默相应的mRNA和调控转录后基因表达[46]. 细胞内miRNA的表达异常在胰腺癌的侵袭和转移过程中发挥重要作用(表1). 大量研究表明, 许多miRNA在胰腺癌的发生发展过程中扮演抑癌基因的角色. miRNA-216b是miRNA-216家族的一员, 位于染色体2p16.1. 胰腺癌细胞中miRNA-216b的表达明显减少, miRNA-216b模拟物下调其靶基因ROCK1的表达, 抑制胰腺癌细胞的增殖、侵袭和迁移[47]. miRNA-652与ZEB1结合抑制胰腺癌肿瘤细胞EMT所需的酸性微环境, miRNA-652过表达下调ZEB1的表达, 抑制胰腺癌细胞的增殖和转移; 因此, 酸性环境/miR-655/ZEB1/EMT轴可能是胰腺肿瘤发生发展的新机制[48]. 增加胰腺癌组织中miRNA-146a的表达, 可以抑制表皮生长因子受体、白介素受体联合激酶-1、NF-κB的表达, 从而抑制胰腺癌细胞的侵袭[49]. 抑制胰腺癌细胞中miRNA-99a的表达,通过mTOR抑制E-钙黏素的表达, 进而促进胰腺癌细胞的增殖和转移[50]. MiRNA-141可以抑制MAP4K4的表达, 在胰腺癌细胞中扮演抑癌基因的角色[51]. 因此, 靶向上述miRNA可下调胰腺癌相关基因的表达, 进而抑制胰腺癌细胞的增殖和迁移.

另外, 许多miRNA在胰腺癌细胞中表达增加, 具有促进胰腺癌细胞增殖和转移的作用. MiRNA-373在胰腺癌细胞中表现出原癌基因的活性, miRNA-373可抑制TP53INP1、LATS2和CD44的表达, 促进胰腺细胞的增殖和侵袭[52]. 有学者报道, miRNA-1178在胰腺癌中的表达明显增加, 通过上调FAK/MMP-9信号通路抑制Stub1的表达, 促使胰腺癌细胞的侵袭[53]. 由上述可知, miRNA在胰腺癌细胞中具有原癌基因和抑癌基因双重特性, 深入了解这些miRNA在胰腺癌细胞中的作用及分子机制, 有助于胰腺癌的早期诊断和治疗.

6 长链非编码RNA

长链非编码RNA(Long non-coding RNA, lncRNA)是指RNA分子长度大于200个核苷酸的非编码RNA. LncRNA虽不编码蛋白质, 但在细胞生长、分化以及增殖等过程中扮演重要角色. 利用在疾病中具有高特异性表达的LncRNA可以对疾病进行分类并协助精确诊断[54]. LncRNA在多种肿瘤组织中调节异常, 表现出高表达状态和组织特异性, 使得它们成为理想的诊断标志物和潜在的治疗靶点[55]. 有大量研究表明, LncRNA在胰腺癌的侵袭和转移过程中具有重要调节作用[56](表2).

表 2　调控胰腺癌侵袭及转移的LncRNAs

LncRNA	相关表达	分子机制	对胰腺癌侵袭和转移的作用
AFAP1-AS1[87]	增加	调控细胞周期和EMT	促进
H19[39]	增加	拮抗let-7、促进HMGA2调节的EMT	促进
HOTAIR[88]	增加	调控细胞周期	促进
HOTTIP[57]	增加	激活HOX基因、沉默抑癌基因的表达	促进
HULC[89]	增加	促进肿瘤血管侵袭	促进
MALAT1[90,91]	增加	下调E-钙黏素, 上调N-钙黏素和纤链蛋白的表达, 促进EMT	促进
ANRIL[92]	增加	通过ATM-E2F1信号通路调节EMT	促进
CCAT1[93]	增加	调控细胞周期, 增加cyclin D1的表达	促进
ROR[94]	增加	上调ZEB1的表达、促进EMT	促进
ZFP91-P[95]	增加	上调β-连环蛋白表达, 促进EMT	促进
Linc00675[96]	增加	调控细胞周期和EMT	促进
LncRNA-ATB[61]	降低		促进

EMT: 上皮-间充质转化.

HOXA末端转录本反义RNA(HOXA transcript at the distal tip, HOTTIP)基因位于HOXA位点(染色体7p15.2), 通过募集组蛋白修饰酶来激活HOX基因, 沉默肿瘤抑制基因的表达[57]. HOTTIP在胰腺导管腺癌中呈现高表达状态, 沉默HOTTIP可以抑制胰腺癌细胞的增殖和转移, 促进癌细胞的凋亡[58]. 有趣的是, 上调HOTTIP的表达还可增加胰腺癌细胞对化疗药物吉西他滨的敏感性[57]. 因此, HOTTIP在胰腺癌细胞中可能具有双向调节作用. 被转换因子β激活的长链非编码RNA(LncRNA-ATB)基因位于人类染色体14:19, 858667-19941024区间, 具有2个长度超过80 kb的外显子, 在许多肿瘤中过度表达, 它竞争性结合miRNA, 促进EMT的发生, 促进肿瘤的发展和转移[59]. 一项Meta分析结果证明LncRNA-ATB的表达增加可作为评估预后的有效生物标志物[60]. 然而, 也有学者报道, LncRNA-ATB在胰腺癌组织低表达, 上调LncRNA-ATB可抑制胰腺癌细胞的侵袭和转移[61]. 由上述可知, LncRNA-ATB在胰腺癌和其他肿瘤细胞中可能发挥着不同的作用.

LncRNA还可作为竞争性内源RNA(competitive endogenous RNA, ceRNA)在胰腺癌的发生发展中发挥作用. ceRNA是一些lncRNA的特殊表现形式, 可以竞争性地结合相应的miRNA, 抑制miRNA的活性, 调控其下游靶向基因的表达, 从而调节细胞内一系列的病理生理变化[62,63]. 例如, Linc00511作为竞争性内源RNA, 竞争性结合hsa-miR-29b-3p, 从而上调VEGFA的表达[64]. VEGF使磷酸化的Smad转移至细胞核内, 进而上调N-钙黏素、Snail1、Snail2和Vimentin等蛋白的表达, 下调E-钙黏素的表达, 促进胰腺癌细胞EMT的发生、增殖与侵袭[64]. PVT1位于染色体8q24, 可竞争性结合miRNA-448, 调节其靶基因SERBP1的表达, 促进胰腺癌细胞的增殖和迁移[65,66]. LncRNA-CRNDE通过与miRNA-384靶向结合, 促进miRNA-384靶基因IRS1的表达, 促进胰腺癌细胞的增殖和转移[67].

总之, LncRNA作为胰腺癌的潜在分子靶点以及新型生物标志物具有十分广阔的前景. 然而, 目前存在的主要问题是其发挥作用的分子机制尚不十分明确, 而且LncRNA对于靶基因的调控受多种因素多分子的影响.

7 其他

Song等[68]研究发现, 磷酸甘油酸脱氢(phosphoglycerate dehydrogenase, PHGDH)在胰腺癌细胞中表达增加, 敲除PHGDH 可抑制cyclin B1、cyclin D1、MMP-2和MMP-9的表达, 从而抑制胰腺癌细胞的增殖、侵袭以及转移; 因此, PHGDH被认为是促进胰腺癌转移的因素. 此外, 高尔基蛋白73、神经轴突导向分子-5A、黏着斑激酶、微管不稳定蛋白1、黏蛋白1和苏氨酰tRNA合成酶等也可促进胰腺癌细胞的增殖、侵袭以及远处转移[69-73].

8 结论

胰腺癌是恶性程度最高的消化道肿瘤之一. 侵袭和转移是胰腺癌的重要生物学特性, 涉及因素众多. 大量的研究发现, 多种基因和蛋白调控胰腺癌侵袭和转移, 这一由多阶段多层次组成的过程. 然而, 它们的作用机制尚不十分明确; 并且它们的表达和激活受到多种分子和通路的调节. 深入揭示和理解胰腺癌侵袭转移的分子机制, 不仅有助于发现新的肿瘤标志物和胰腺癌的早期诊断, 也有助于用来制定新的有效治疗策略以及判断预

后, 提高患者的生存率. 因此, 多靶点、个体化、综合治疗将是未来胰腺癌治疗的发展方向.

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• 消息 •

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