胆管癌中非编码 RNA 的调控作用研究

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摘　要：胆管癌是起源于胆管上皮细胞的恶性肿瘤，该疾病具有高度致死性且发病率逐年增加。机制及病因不清使该病诊疗困难。随着生物信息学的发展，越来越多的研究发现非编码 RNA（ncRNA）与胆管癌病理生理过程密切相关并且作为潜在的肿瘤标志物和治疗位点而备受关注。全文将胆管癌中非编码 RNA 的研究成果作以综述。
关键词：胆管肿瘤；非编码 RNA；微小 RNA；长链非编码 RNA；环状 RNA
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Regulatory Role of ncRNAs in Cholangiocarcinoma

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Abstract：Originating from bile ducts，cholangiocarcinoma is an epithelial malignant cancer with high mortality and rising incidence. Less understanding of its etiology and pathogenesis makes the diagnosis and treatment difficult. With the development of bioinformatics，more and more studies have found that ncRNA were closely related to its tumorigenesis. And the potential of ncRNA to be biomarkers and therapy targets is great attractive. In this article，we summarize the latest advances of ncRNAs in cholangiocarcinoma.
Key words：cholangiocarcinoma；ncRNA；microRNA；lncRNA；circular RNA

胆管癌（cholangiocarcinoma）是起源于胆管上皮细胞的恶性肿瘤。根据其发生位置的不同可分为肝内胆管癌和肝外胆管癌两类。作为发病率第一的胆道肿瘤，胆管癌约占消化系统肿瘤的 3%[1]。目前胆管癌治疗主要依靠外科手术切除，但胆管癌发病隐匿，诊断方法敏感性差，多数患者在确诊之时已错过手术时机；使用指南推荐的吉西他滨联合顺铂化疗方式，平均生存期也不足 12 个月[2]。因此在医疗水平逐步发展、各种癌症生存率普遍得到提高的今天，胆管癌 5 年生存率仍小于 5%[3]，且发病率和死亡率呈逐年提高趋势[4]。原因则是我们对于其病理生理机制认识不清，难以进行早期诊断及有效治疗，对该问题的研究成为了我们破解此项难题的重点。

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非编码 RNA 是指一类虽经转录却不编码蛋白质的 RNA 总称，包括微小 RNA（microRNA，miRNA）、长链非编码 RNA（long non-coding RNA，lncRNA）、环状 RNA（circularRNA，circRNA）、假基因（pseudogene）、siRNA、piRNA 等。在人类基因组中占比 98%，远高于编码基因[5]。长期被认为是无用序列而不受重视，随着研究的不断深入，越来越多的证据显示 miRNA、lncRNA、circRNA 等在人类疾病特别是肿瘤中起着巨大作用，其作为未来靶向药物作用位点以及新型肿瘤标志物的潜质越来越得到研究者的青睐。全文将胆管癌中非编码 RNA 的研究成果作以综述。

1　miRNA 和胆管癌

miRNA 是由 RNA 聚合酶Ⅱ转录的长度约为 19~25nt 的非编码 RNA。其发挥作用通常在转录后

水平通过碱基互补配对与靶基因形成 RNA 诱导沉默复合体(RNA-induced silencing complex,RISC)。通过该结构,miRNA 既可紧密结合靶基因使其降解[6];也可通过非紧密结合锁定靶基因阻止其转录[7],最终达到负向调控的作用。由于第二种机制的存在,某个特定 miRNA 可能对应数个乃至数百个 mRNA,同样某个特定 mRNA 可能对应数个乃至数百个 miRNA[8]。这就从理论上解释了为什么一种 miRNA 能通过调控诸多蛋白表达从多种细胞生物学行为上影响疾病的进程。

1.1 增殖和抗凋亡

增殖迅速、抗凋亡是癌症细胞的重要特点,很多 miRNA 与这些特点密切相关。有学者通过对胆管癌组织中多种 miRNA 进行定量分析,首次发现 miR-141、miR-21 和 miR-200b 在胆管癌组织中高表达,随后下调 miR-141 表达水平使得胆管癌细胞增殖速率显著下降,从实验方面验证了 miR-141 的促增殖作用,首次将 miRNA 引入胆管癌的研究中[9]。Mott 等[10]发现 miR-29 在胆管癌中呈低表达,其抑癌机制为 miR-29 抑制 Mcl-1 促进肿瘤坏死因子引起的凋亡。该团队随后证实 miR-29 表达下调可能与 c-Myc、Hedgehog 及 NF-kappaB 等通路的开放相关[11]。Olaru 等[12]报道 miR-494 在胆管癌中呈低表达,细胞学实验结果证实 miR-494 是细胞周期 G_1/S 的重要负性调控因子,进一步行荧光素实验认为其作用靶点可能为 CDK6。随后 Yamanaka 等[13]验证了 miR-494 在 G_1/S 期中的作用并进一步发现其在 G_2/S 期中同样发挥重要作用,其作用位点可能为 Top2A、pttG1。Wang 等[14]运用 qPCR 技术对多种胆管癌细胞系及肿瘤标本发现 miR-138 在胆管癌中呈低表达状态,细胞学实验发现 miR-138 表达增高抑制了肿瘤细胞增殖、G_1/S 期的转化及细胞的侵袭转移;通过荧光素分析实验认为 RhoC 可能是其作用位点,Rhoc 表达的增高促进了 p-ERK、MMP-2、MMP-9 的表达从而发挥促癌作用。miR-31 在胆管癌中高表达,生物信息学预测及免疫荧光报告实验证实 RASA1 促生长及抑制凋亡作用[15]。miRNA 在发挥促癌作用时,其在细胞中的表达水平是否随时间变化呢?Chen 等[16]通过实时动态监测癌组织中 miRNA 表达水平发现多种 miRNA 均随时间发生显著变化,其变化可能与胆管癌的某些病理生理过程相关,为研究 miRNA 和胆管癌的关系提供了新的思路。

1.2 侵袭和转移

肿瘤侵袭转移与肿瘤微环境密切相关,许多研究发现多种 miRNA 与肿瘤侵袭相关。有学者研究肝吸虫相关性胆管癌发现 miR-21 通过 PDCD4、TIMP3 实现促增殖作用[17],在另一个仓鼠模型实验认为,RECK 也可能是 miR-21 促转移的靶点[18]。同时,He 等[19]发现 miRNA 的一种合成原料 Ars2 的缺乏可导致 miR-21 的低表达从而抑制其促癌作用,实验上调 Ars2 的表达水平却不能促使 miR-21 合成增多而起促癌作用,提示了肿瘤病理生理过程的复杂性。EMT 作为肿瘤微环境中的特殊病理生理过程增强细胞侵袭和转移能力越来越成为研究热点。2012 年,Oishi 等[20]发现,miR-200c 作用于 NCAM1 从而发挥抑制 EMT 发挥抑癌作用。Mizuguchi 等[21]发现 miR-200c/141 同样具有抑制 EMT 进程保持胆管细胞稳定性的作用。随后诸如 miR-214 等 miRNA 也被证明与 EMT 过程相关。Li 等[22]发现 miR-221 作用于 PTEN 形成 β-catenin/c-Jun 形成闭环通路,正反馈加强胆管癌的侵袭转移作用。

1.3 炎 症

大量研究表明,肿瘤起源于慢性炎症,炎症中重要的细胞因子 IL-6 有强烈的促癌作用。Meng 等[23]发现在 IL-6 高表达使得 let-7a 的水平增高,进一步实验发现 let-7a 可能作用于 NF2 降低 Stat3 磷酸化速率从而发挥促癌作用。随后该团队还发现肿瘤组织通过 IL-6/miR-370/MAP3K8 抵抗化疗药物 5-氮杂胞嘧啶[24]。COX-2 作为炎症中另一重要因子,也被认为与 miRNA 相关。Zhang 等[25]通过动物实验发现高表达的 miR-101 通过降低了 COX-2 及 VEGF 水平,抑制肿瘤中血管形成从而显著抑制了肿瘤的生长。Lu 等[26]发现 miR-21 通过 15-PGDH 激活 PGE2,PGE2 活化后进一步促进 miR-21 表达形成闭环正反馈通路,发挥不可逆转的促癌作用。作者认为该位点可能成为优良的药物靶点:靶向药物在毒副作用上明显低于传统药物并且该药物能通过 miRNA 影响多种蛋白的表达抑制肿瘤多种生物学行为,更加有效地发挥抗癌作用。胆汁淤积和炎症同为胆管癌病理生理过程的两大特性[27],淤积胆汁中胆汁酸等物质可能破坏胆管结构并加速胆管癌病理生理过程。Yang 等[28]在小鼠淤胆模型中运用免疫共沉淀等

技术，提出其促癌作用可能为 miR-34a 的减少及 miR-210 的扩增激活 *c-Myc* 基因，从而增强细胞周期蛋白 D1 表达。

1.4 耐药性

Meng 等首次指出 miRNA 与胆管癌关系时同时指出降低 miR-21 和 miR-200b 水平能恢复肿瘤细胞对化疗药物吉西他滨的敏感性，并通过裸鼠成瘤实验认为其可能作用于 PI3k/PTEN 通路发挥作用[9]。同时 Okamoto 等[29]研究发现恢复 miR-29B、miR-205 和 miR-221 表达水平使得抵抗吉西他滨的肿瘤细胞对该药重新敏感，同时行生物信息学预测认为 miR-29b、miR-221 作用位点可能为 PIK3R1；miR-205 作用位点可能为 MMP-2。Peng 等[30]行细胞学实验发现 miR-200b/c 在胆管癌组织中低表达且其表达水平的增高显著提高了肿瘤细胞对氟尿嘧啶的敏感性，其作用位点可能为 SUZ12/ROCK2。Toyota 等[31]对吉西他滨处理的胆管癌细胞系进行基因芯片定量，发现多种 miRNA 水平在吉西他滨处理后发生变化，包括 miR-222、miR-210 等。

2 LncRNA 和胆管癌

长链非编码 RNA 是一类长度超过 200nt 的非编码 RNA 分子[56]；相比于 miRNA，lncRNA 长度较长并且拥有类似 mRNA 的 5'端帽子、3'端多聚核苷酸尾结构等结构，但同样缺乏开放阅读框[57]。相比于 miRNA，lncRNA 有更多样更复杂的机制来直接调控基因，因此也存在类似的一对多和多对一的可能性。LncRNA 经典的调控机制为通过 ceRNA 机制吸附相应 miRNA，阻止其与 mRNA 结合而发挥调控作用[58]。

Wang 等[59]通过基因芯片技术对肝内胆管癌组织进行研究，共测定 2392 种异常表达的 lncRNA 并推断了可能的 lncRNA-mRNA 作用途径；进一步结合临床数据分析发现高表达 CYP2D6 和 RNA40057 的患者拥有较好的预后。Ma 等[60]对肝内胆管癌组织进行实验，发现 CPS1 及其 LncRNACPS1-IT1 在癌组织中高表达，随后在体外实验发现该基因的主要作用是促进增殖和抑制凋亡；进一步结合临床数据发现该 RNA 表达升高与不良的肝功能和较短的生存期显著相关。Wang 等[61]发现胆管癌细胞通过炎症反应促进自身增殖和侵袭，其作用机制可能为 H19 和 HULC 吸附 let-7b/let-7a 和 miR-373/miR-372。

3 circRNA 和胆管癌

环状 RNA 作为 ncRNA 家族中的“新成员”，结构上以共价闭合连续环形式替代了 5′末端帽子和 3′末端的多聚腺苷酸尾结构[62]。circRNA 典型的机制同样是通过吸附 miRNA 来调控转录[63]。已有证据证明 circRNA 在疾病中也起着重要作用。例如 ciRS-7(又称为 CDR1as)可通过吸附 miR-7 等方式在心肌梗死[64]、系统性红斑狼疮[65]、肝癌[66]等发挥重要作用。虽然目前其与胆管癌的关系尚未被报道。但 Kulcheski 等[67]利用生物信息学预测 ciR-SRY 可能通过 miR-138/RhoC 影响胆管癌病理过程。我们完全有理由相信在未来会有更多的实验证实 circRNA 与胆管癌的关系。

4 结　语

对胆管癌中非编码 RNA 的研究不仅有助于我们了解胆管癌的病理生理过程，还对我们临床大有裨益。首先，非编码 RNA 作为潜在的新型肿瘤标志物，为胆管癌的诊断提供了新的思路，诸多能在血液中稳定存在的 miRNA 例如 miR-21、miR-221 作为肿瘤标志物被证明有较高的敏感性及特异性[68]。胆管癌患者术前多需胆汁引流，获取胆汁较为容易，对胆汁囊泡中 miRNA 的分析同样有助于胆管癌的诊断[69]。其次非编码 RNA 可以作为药物的靶点。非编码 RNA 的靶向治疗可以通过调节非编码 RNA 这一位点，准确并有效地控制多个细胞生物学行为。相比于普通药物，肝脏的“首过效应”可能使药物更多地停留于肿瘤部位更好地发挥其抑癌效果[70]。因此针对胆管癌中非编码 RNA 的研究有可能成为胆管癌的诊疗带来新的革命。

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附录：

表达水平	miRNA	相关疾病	作用通路	生物学功能	参考文献
上调	miR-21	胆管癌 肝内胆管癌	PI3k、PDCD4、TIMP3、RECK、TPM1、15-PGDH、PTPN14、PTE	耐药性、增殖、转移、侵袭、凋亡、EMT 过程	[9] [17 ~19] [26] [29] [32~34]
	miR-25	胆管癌	DR4		[35]
	miR-26a	胆管癌	GSK-3b、TGFβ1、KRT19	增殖、EMT	[36][54][55]
	miR-31	肝内胆管癌	RASA1	增殖、凋亡	[15]
	miR-106a	胆管癌		转移	[37]
	miR-141	胆管癌	CLOCK	增殖、生理节律	[38]
	miR-200b	胆管癌	PTPN12	耐药性	[38]
	miR-210	胆管癌	Mnt	增殖	[39]
	miR-421	胆管癌	FXR	增殖、转移	[40]
下调	Let-7a	胆管癌	NF2	细胞生存能力	[41]
	miR-29b	胆管癌	Mcl1、MMP-2	凋亡、耐药性	[10] [29]
	miR-34a	胆管癌	Smad4	细胞周期、增殖	[42]
	miRNA-101		VEGF	肿瘤血管生成	[25]
	miR-124	肝内胆管癌	SMYD3	侵袭转移	[43]
	miR-138	胆管癌	RHOC	增殖、细胞周期、侵袭转移	[14]
	miR-144	胆管癌	LIS1	增殖、侵袭转移	[44]
	miR-148a	胆管癌	DNMT-1	增殖	[45]
	miR-200b/c	胆管癌	rho-kinase2，SUZ12	侵袭、转移 耐药性	[30]
	miR-204	肝内细胞癌	Slug，Bcl-2	EMT、侵袭转移凋亡	[46][47]
	miR-214	肝内胆管癌	Twist	EMT、肿瘤转移	[48]
	miR-320	肝内胆管癌	Mcl-1/Bcl-2	凋亡	[49]
	miR-370	胆管癌	MAP3K8	细胞增殖	[50]
	miR-373	肝门部胆管癌	MBD2	表观遗传	[51]
	miR-376c	肝内胆管癌	GRB2	转移、增殖	[52]
	mir-494	胆管癌	CDK6pttG1top2A	增殖、细胞周期	[12][13]
	miR-410	胆管癌	XIAP	增殖	[24]

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