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非小细胞肺癌Wnt/β-catenin信号通路相关ncRNAs: 多维机制解析与诊疗转化研究

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摘要 Wnt/β-catenin信号通路是维持肺组织稳态的核心通路, 其异常激活则赋予肺癌恶性表型. 该通路复杂的调控机制已成为精准医疗的研究焦点. 大量研究表明, 非编码RNAs(non-coding RNAs, ncRNAs)是该通路的关键调控因子, 参与调控Wnt/β-catenin通路靶基因的表达, 在非小细胞肺癌(non-small-cell lung cancer, NSCLC)发生发展中扮演了重要角色. 本文通过系统解析不同类型ncRNAs在Wnt/β-catenin通路配体分泌、受体激活、信号转导及转录调控中的功能分工与协同网络, 揭示ncRNAs/Wnt/β-catenin轴驱动NSCLC发生发展的多维调控机制, 并进一步探讨了ncRNAs作为NSCLC早期诊断、疗效预测、预后评估的新型生物标志物以及开发为新型治疗靶点的临床诊疗转化研究进展与挑战. 本研究为深入理解NSCLC分子机制认知提供新视角, 并为推动其机制导向的精准诊疗转化奠定理论框架.

关键词 Wnt/β-catenin, ncRNAs, 非小细胞肺癌, 作用机制, 生物标志物

肺癌(lung cancer, LC)是全球癌症相关死亡的主要原因[1]. 非小细胞肺癌(non-small-cell lung cancer, NSCLC)是LC最常见的亚型, 约占全部LC病例的85%[2]. 对NSCLC分子机制认知不足、早期高灵敏/特异检测技术瓶颈及广泛耐药性仍是攻克NSCLC的主要障碍[3]. Wnt/β-catenin信号通路的异常激活已被证实是驱动NSCLC发生发展和治疗耐药的关键通路枢纽[4]. 近年研究发现, 以微小RNA(microRNA, miRNA)、长链非编码RNA(long non-coding RNA, lncRNA)和环状RNA(circular RNA, circRNA)为代表的非编码RNAs (non-coding RNAs, ncRNAs)通过靶向调控Wnt/β-catenin信号通路的配体、受体、信号转导分子、通路负调控因子及转录复合物层面, 在转录、转录后及表观遗传修饰水平影响NSCLC的恶性演进[5,6]. 然而, 目前不同类型ncRNAs在Wnt/β-catenin信号通路中的多水平、多层面的调控网络尚未系统解析, ncRNAs从基础发现到临床转化的系统路径亟待建立[7,8]. 本文系统阐述NSCLC发生发展中miRNA/lncRNA/circRNA调控Wnt/β-catenin通路的多层面分子调控网络, 展望靶向ncRNAs/Wnt/β-catenin轴的新型小分子药物及天然药物在临床ncRNAs药物开发中的前景, 并讨论Wnt/β-catenin通路相关ncRNAs作为NSCLC生物标志物的潜力, 以期为NSCLC的精准诊疗提供重要的理论基础和新方向(图1).

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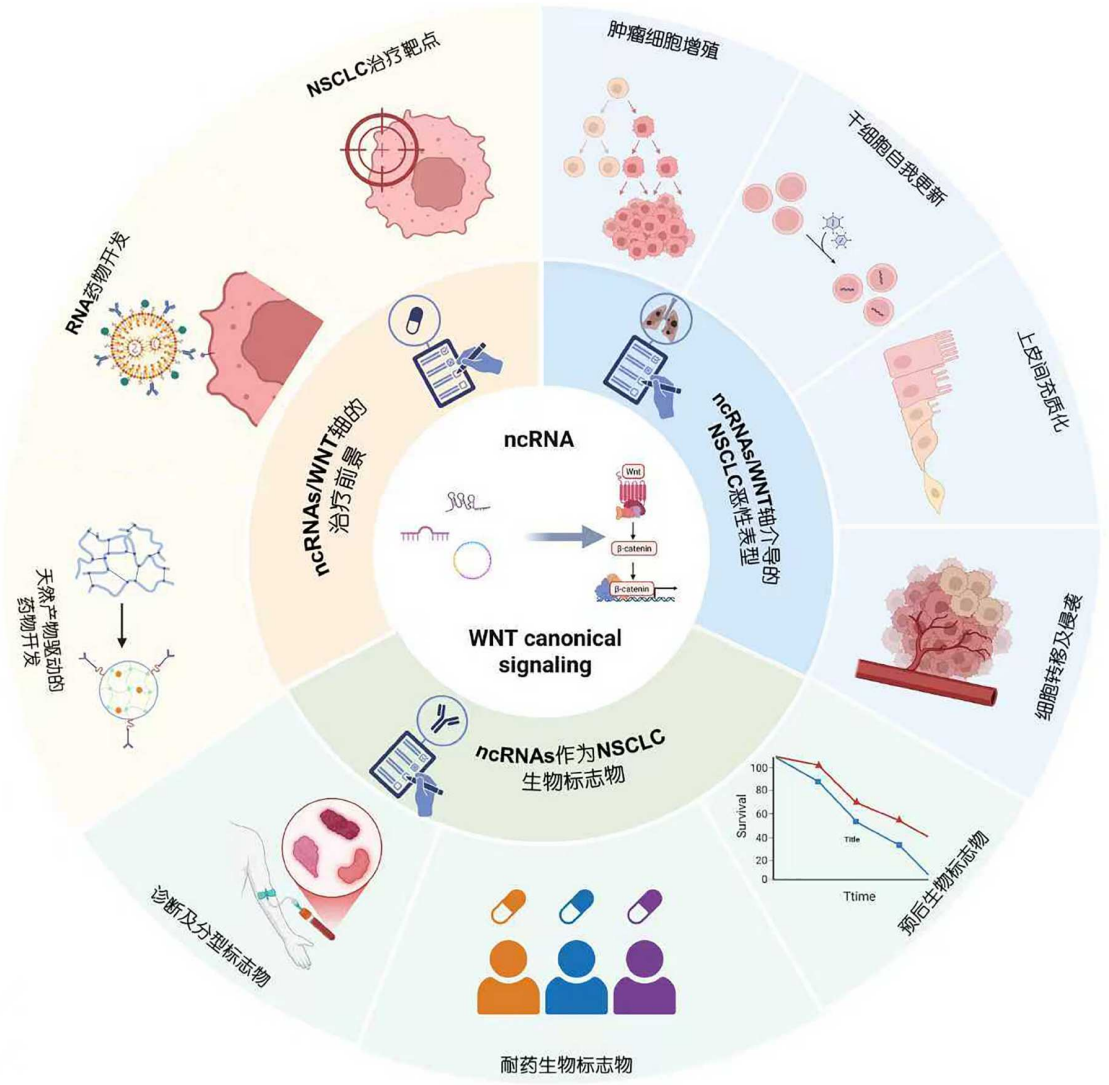

图 1 (网络版彩色)非小细胞肺癌Wnt/β-catenin通路中ncRNAs的层级化调控: 从机制到诊疗转化. 图片素材来源于BioRender.com
Figure 1 (Color online) Hierarchical regulation of ncRNAs in the Wnt/β-catenin pathway in NSCLC: from mechanisms to translational medicine. Created with BioRender.com

1 NSCLC中的Wnt/β-catenin信号通路

1.1 Wnt/β-catenin信号通路

Wnt/β-catenin信号通路又称作经典Wnt信号通路, 在包括发育、组织稳态和细胞增殖等各种生理过程中起着至关重要的作用[9]. 然而, 持续的Wnt/β-catenin信号通路激活赋予癌细胞持续的自我更新生长特性, 并与治疗耐药性相关[10]. 当Wnt/β-catenin信号通路处于失活状态时, 细胞质中两种支架蛋白AXIN(axis inhibition, AXIN)、APC(adenomatous polyposis coli, APC)以及两种激酶GSK-3β(glycogen synthase kinase 3 beta, GSK-3β)、CK-1α(casein kinase 1 alpha, CK-1α)所组成的β-catenin破坏复合物(β-catenin destruction complex, DC)诱导β-catenin磷酸化. 磷酸化的β-catenin通过与E3泛素连接酶β-TrCP(beta-transducin repeats-containing proteins, β-Trcp)结合而被泛素化, 最终被蛋白酶体(proteasome)降解, 维持胞内β-catenin的低水平状态[11,12]. 当Wnt/β-catenin通路处于激活状态时, WNT配体通过自分泌/旁分泌机制激活卷曲蛋白(frizzled, FZD)受体及低密度脂蛋白受体相关蛋白5/6(LDL-receptor-related protein 5/6, LRP5/6)共受体. 随后, FZD-LRP复合物磷酸化蓬乱蛋白(dishevelled, DVL), 募集支架蛋白AXIN和

APC到质膜上, 导致DC解离. 细胞质中积累的β-catenin经过细胞质-核穿梭, 与核内的T细胞因子/淋巴增强因子(T cell factor/lymphoid enhancer factor, TCF/LEF)结合[13], 激活*c-Myc*、*Cyclin D1*等促癌基因表达[14](图2).

1.2 NSCLC中Wnt/β-catenin信号通路异常激活的临床-分子特征

Wnt/β-catenin通路在正常肺组织中维持呼吸道上皮稳态与修复, 该通路异常激活是驱动NSCLC恶性演进的关键事件, 其复杂的调控机制已成为NSCLC精准医疗的研究焦点[5,15,16]. 越来越多的证据表明, Wnt/β-catenin信号通路组分与NSCLC临床-分子特征密切关联. WNT配体、β-catenin、FZD受体及通路负调控因子的表达水平与NSCLC患者预后、肿瘤亚型、肿瘤分期以及肿瘤微环境(tumor microenvironment, TME)中的免疫细胞浸润状态密切相关[17~20]. 此外, 异常的Wnt/β-catenin通路激活在NSCLC中广泛存在. 据估计, 大约35%~70%中的NSCLC具有异常的Wnt信号通路激活, 并且在76%的NSCLC中检测到异常β-catenin蛋白表达[21]. 多种WNT配体(如WNT1、WNT2B以及WNT5A)、FZD受体(如FZD2、FZD8)表达水平相较于癌旁正常组织显著上调[22~24], 并参与NSCLC的干性、增殖、血管生成、转移侵袭、治疗耐药性和其他关键肿瘤发展过程[25~28]. 然而, NSCLC中Wnt/β-catenin通路的激活模式不同于其他经典Wnt信号通路驱动的肿瘤. 多项研究表明NSCLC中的通路基因突变很少见[29,30], *APC*和*CTNNB1*基因特定位点突变在NSCLC中的发生率仅为10.4%和1.04%[31]. 这些证据表明, NSCLC中Wnt/β-catenin通路的激活并非主要依赖于高频驱动基因突变, 而是一个涉及多因素的复杂过程. 既存在部分基因的低频突变, 但更广泛地表现为通路组分的异常表达, 提示存在其他关键的调控机制.

2 ncRNAs: Wnt/β-catenin通路的多样性调控因子

ncRNAs是一类不编码蛋白质的功能性RNA分子, 其中miRNA、lncRNA和circRNA已被证明通过Wnt/β-catenin通路促进肿瘤发生、上皮-间充质转化(epithelial-mesenchymal transition, EMT)、血管生成、肿瘤发展、侵袭、转移及治疗耐药[32~34]. 不同类型ncRNAs调

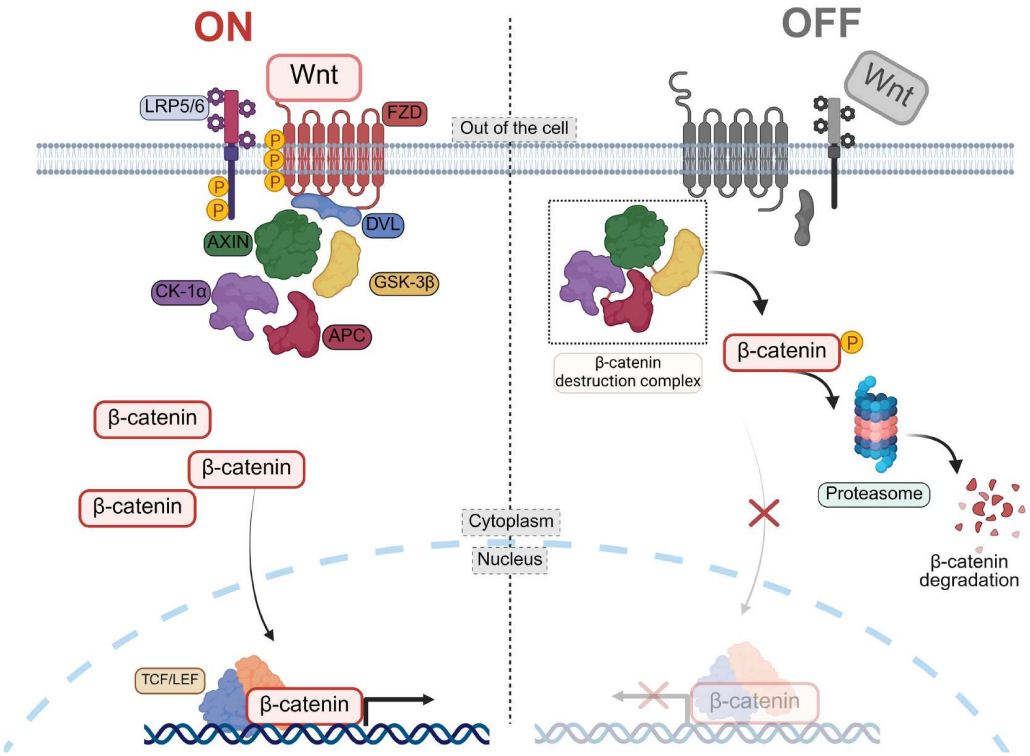

图 2 (网络版彩色)Wnt/β-catenin信号通路. 图片素材来源于BioRender.com
Figure 2 (Color online) Wnt/β-catenin signaling pathway. Created with BioRender.com

控Wnt/β-catenin通路的分子模式存在显著差异.

2.1 miRNA/Wnt/β-catenin调控模式

miRNA的生物合成途径与作用机制在进化中高度保守. 其成熟依赖双链RNA前体经Drosha和Dicer (RNase III型酶)逐步加工, 进而与AGO(argonaute, AGO)蛋白结合形成RNA沉默复合体(RNA-induced silencing complex, RISC), 最终通过抑制靶mRNA翻译或促使其降解实现转录及转录后调控[35,36]. 如miR-200a既靶向EMT转录因子Zeb1/2, 又可直接阻断β-catenin mRNA翻译, 抑制Wnt/β-catenin通路激活, 其抑癌功能在胃腺癌和肝癌中得到进一步证实[37]. 此外, miRNA主要通过其5′端的种子序列与靶mRNA的3′非翻译区(3′ untranslated region, 3′UTR)进行部分碱基配对[38]. 这种不完全配对使miRNA可靶向多个mRNA. 例如miR-128-3p可同时靶向负调控AXIN1、分泌型卷曲相关蛋白2(secreted frizzled-related protein 2、SFRP2)和Wnt抑制因子1(Wnt inhibitory factor 1, WIF1)等多种通路关键组分发挥致癌作用[39](图3). 综上, 致癌/抑癌miRNA通过精准靶向Wnt/β-catenin通路核心元件, 以转录抑制、翻译阻断或mRNA降解等方式, 在肿瘤发生发展中起关键作用.

2.2 lncRNA/Wnt/β-catenin调控模式

lncRNA通过信号、支架、诱饵及引导等多种机制, 在转录、转录后、翻译后以及表观遗传水平参与染色质重塑、转录调控、生物分子凝聚物形成及蛋白质或RNA招募等过程[40,41]. lncRNA/Wnt/β-catenin信号转导贯穿肿瘤发生发展的各个阶段, 其作用模式具有高度多样性. 在转录水平, lncFZD6结合染色质重塑复合物SWI/SNF核心组分BRG1, 将其募集至FZD6启动子区, 激活肝癌起始细胞的Wnt/β-catenin通路[42]; 在转录后水平, lncRNA广泛作为竞争性内源RNA(competing endogenous RNA, ceRNA)结合特定miRNA, 解除

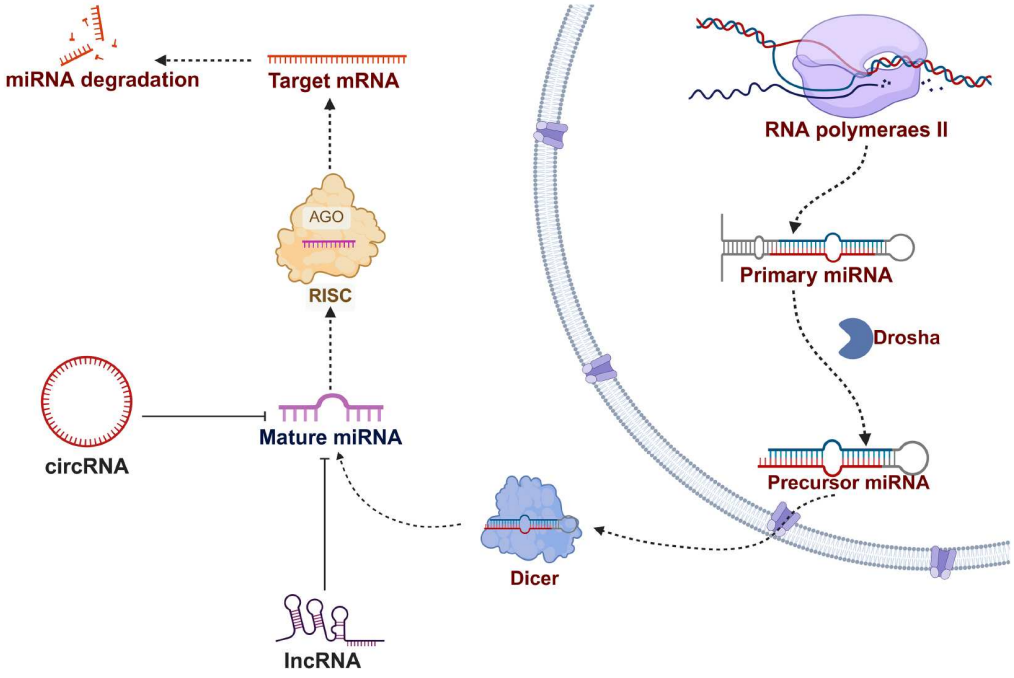

图 3 (网络版彩色)MiRNA生成及作用机制. Primary miRNA由RNA polymeraes II转录产生. Drosha将primary miRNA加工成precursor miRNA. 随后, precursor miRNA通过核转运蛋白进入细胞质, 与Dicer结合后被加工为成熟miRNA, 并装载至RISC复合体中, 其中一条链被降解, 另一条与RISC整合, 最终与靶mRNA互补结合并调控基因表达. lncRNA和circRNA也可与成熟的miRNA结合, 作为竞争性内源RNA抑制其活性. 图片素材来源于BioRender.com. AGO: argonaute蛋白; RISC: RNA沉默复合体

Figure 3 (Color online) MiRNA biogenesis and mechanism of action. Primary-miRNA is transcribed by RNA polymeraes II. Drosha processes primary-miRNA into precursor-miRNA. Subsequently, pre-miRNA is transported to the cytoplasm via nuclear transport proteins. In the cytoplasm, precursor-miRNA binds to Dicer and is processed into mature miRNA, which is loaded into RISC. One strand of the miRNA duplex is degraded, while the other integrates into RISC to ultimately bind complementary target mRNAs and regulate gene expression. Notably, both lncRNA and circRNA can also bind to mature miRNAs and act as competing endogenous RNAs to inhibit miRNA activity. Created with BioRender.com. AGO: argonaute; RISC: RNA-induced silencing complex

靶基因的表达抑制, 发挥转录后调控作用. 在翻译后水平, lncTIC1结合β-catenin N端结构域, 抑制GSK-3β介导的β-catenin磷酸化, 从而激活肝癌Wnt/β-catenin信号通路[43]. 在表观遗传水平, LINC01133通过诱导Wnt信号通路拮抗剂Dickkopf相关蛋白1(Dickkopf-1, DKK1)启动子甲基化, 激活Wnt/β-catenin通路, 促进胰腺癌进展[44](图4).

2.3 circRNA/Wnt/β-catenin调控模式

circRNA具有闭合环状结构, 主要定位于细胞质或外泌体中, 不易被RNA外切酶降解, 表达稳定性高[45,46]. 其功能机制与lncRNA类似: 一方面可作为miRNA海绵, 通过结合位点阻断miRNA与靶mRNA 3′UTR的相互作用, 解除下游基因的表达抑制[47]; 另一方面, circRNA通过结合并隔离特定蛋白干扰其功能; 或作为蛋白支架, 通过募集RNA结合蛋白(RNA-binding protein, RBP)或转录因子等, 进而调控复合体组装与蛋白活性[48,49]. 值得注意的是, 部分circRNA含内部核糖体进入位点, 可翻译为功能性多肽调控Wnt/β-catenin信号通路[50,51]. 例如, circAXIN1编码的AXIN1-295aa多肽竞争性结合APC破坏DC复合物结构[52], 而circβ-catenin则翻译生成β-catenin-370aa, 随后其作为分子诱饵竞争性拮抗GSK3β与β-catenin的结合, 从而抑制β-catenin磷酸化[53], 二者均通过干扰通路关键组分激活Wnt/β-catenin信号, 分别驱动胃癌与肝癌的恶性表型(图5).

3 ncRNAs作用于Wnt/β-catenin信号通路调控NSCLC发生发展

3.1 配体与受体层面的调控

3.1.1 靶向WNT的ncRNAs

WNT配体作为通路关键起始信号, 通过与细胞膜受体特异性结合, 激活下游Wnt/β-catenin通路传导, 从而调控细胞增殖、分化和稳态维持[54]. 在NSCLC发生发展中, ncRNAs通过直接或间接调控WNT配体的表达与功能, 成为Wnt/β-catenin通路异常激活的关键驱动因素[7,55,56]. 多项研究揭示了不同ncRNAs分别靶向WNT1、WNT2B及WNT5A等核心配体调控NSCLC恶

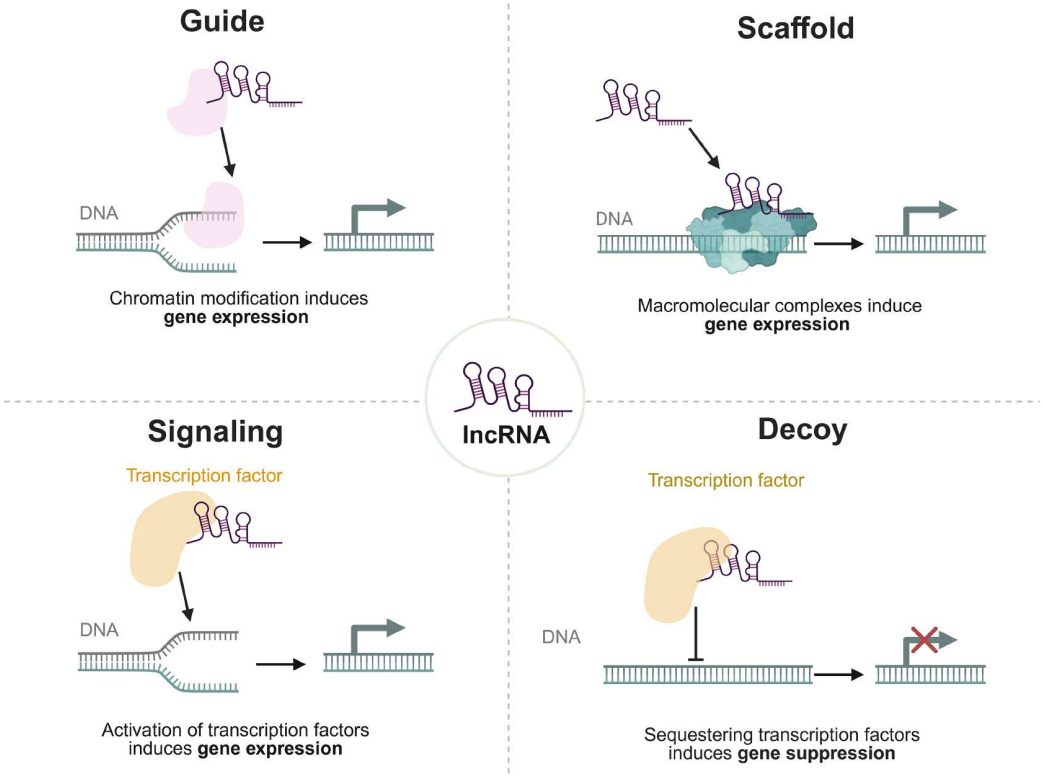

图 4 (网络版彩色)LncRNA作用机制. LncRNA可以通过信号、支架、诱饵和引导等作用机制参与细胞过程的各个方面. 图片素材来源于BioRender.com

Figure 4 (Color online) LncRNA mechanism of action. LncRNA can participate in various aspects of cellular processes through mechanisms of action such as signaling, scaffolding, decoy, and guiding. Created with BioRender.com

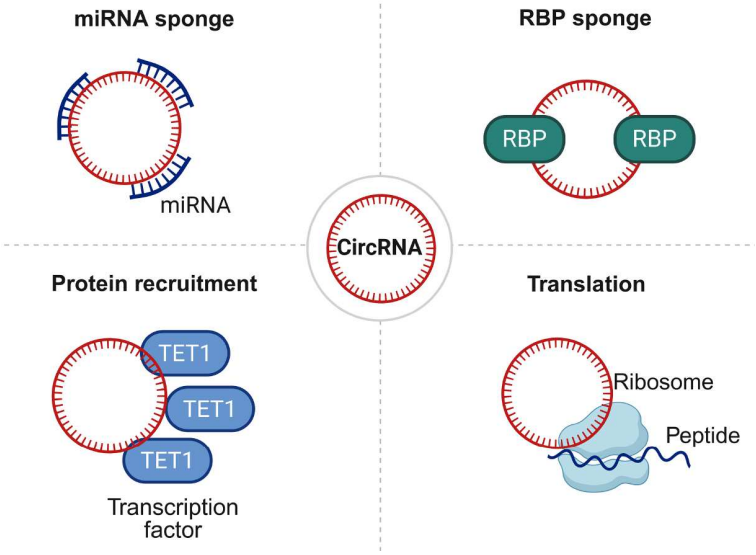

图 5 (网络版彩色)CircRNA作用机制. 图片素材来源于BioRender.com
Figure 5 (Color online) CircRNA mechanism of action. Created with BioRender.com

性进展. 其中miR-148a、miR-383可直接结合WNT1 mRNA 3′UTR区, 抑制Wnt/β-catenin通路活化, 降低NSCLC细胞迁移侵袭能力并诱导凋亡[57,58]. 在WNT2B调控中, miR-577通过下调WNT2B配体转录活性及蛋白表达水平, 抑制NSCLC细胞增殖和EMT过程[59]. 而WNT5A则表现出双重调控作用, 如miR-1253通过负调控WNT5A表达, 抑制NSCLC细胞增殖及转移[60]. 与之相反, miR-374a、circVAPA则通过靶向WNT5A, 促进NSCLC细胞EMT与干性维持[61,62]. 目前在哺乳动物中已发现19个独特的WNT配体并表现出组织特异性, 然而目前研究主要集中在少数几个WNT配体上. 针对其他多数WNT配体的特异性调控ncRNAs及其功能仍有待深入探索.

3.1.2 靶向FZD的ncRNAs

FZD受体构成Wnt/β-catenin通路的分子枢纽, 主导配体识别与跨膜信号转导过程[63]. ncRNAs对FZD家族成员的异常调控已被广泛证实[64,65], 并在Wnt/β-catenin通路的配体-受体互作层面表现出促癌或抑癌特性[66]. 在抑癌调控层面, 多种ncRNAs通过靶向FZD抑制Wnt/β-catenin通路激活[67]. 如miR-203直接结合FZD2 mRNA并阻断其翻译, 抑制Wnt/β-catenin通路活性[68]; lncRNA AK126698可通过负调控FZD8表达阻断通路信号转导, 诱导肿瘤细胞凋亡[69]; miR-3127-5p则通过抑制FZD4/β-catenin轴阻断NSCLC的EMT进程[70]. 与之相反, 促癌ncRNAs如circ_0017109吸附miR-671-5p, 解除其对FZD4 mRNA的翻译抑制, 进而激活Wnt/β-catenin通路并加速NSCLC进展[71]. 临床前研究表明, 针对FZD家族的靶向干预策略已展现出明确的抗肿瘤效应[72,73]. 系统阐释ncRNAs/FZD调控网络, 可能为NSCLC靶向治疗策略的创新提供分子基础.

3.1.3 靶向DVL的ncRNAs

DVL是一种支架蛋白, 帮助维持经典与非经典Wnt信号传导[74]. 尽管DVL蛋白是致癌Wnt/β-catenin通路的重要驱动因素, 然而DVL生物学活性调控仍知之甚少[75]. 近年来, ncRNAs对DVL磷酸化的调控机制逐渐阐明. 研究表明, LINC00673-v4在肺腺癌(lung adenocarcinoma, LUAD)中异常高表达, 其作为分子支架促进DDX3与CK1ε形成激酶复合体, 进而诱导DVL磷酸化, 最终激活Wnt/β-catenin通路, 驱动LUAD早期发生及转移[76]. 这一发现揭示了lncRNA通过激酶复合物调控DVL修饰的新致癌机制. 然而, DVL的泛素化、乙酰化等修饰机制及其生物学意义仍待阐明[77]. 新证据指向ncRNAs可能调控上述的翻译后修饰过程参与肿瘤等疾病进展[78,79], 全面解析DVL修饰机制有望拓展NSCLC靶向策略.

3.2 胞内信号转导节点的调控

3.2.1 直接靶向β-catenin的ncRNAs

ncRNAs通过ceRNA机制和翻译后修饰等方式直接调控β-catenin的表达与功能. 在ceRNA网络调控层

面，ncRNAs作为分子海绵作用解除靶miRNA对β-catenin mRNA的抑制，驱动NSCLC恶性进展. 研究表明，lncRNA SNHG11既竞争性结合miR-4436a，解除CTNNB1 mRNA的翻译抑制，又直接结合β-catenin促进其核转位，展现出双重作用机制[80]. 类似地，LINC01006[81]、lncRNA DANCR[82]以及lncRNA PKMYT1AR[83]均通过ceRNA模式激活Wnt/β-catenin通路. 在翻译后修饰层面，circRNA通过编码功能肽调控β-catenin稳定性. 其中，circFBXW7-185翻译为短肽circFBXW7-185AA，并以m6A依赖方式诱导β-catenin泛素化降解，进而逆转奥希替尼耐药及NSCLC干细胞特性[84]. 已有研究表明circRNA或lncRNA编码的功能肽通过介导特定分子的磷酸化和泛素化，在多癌种中调控Wnt/β-catenin信号通路[85]. 部分circRNA编码的肽或蛋白可作为肿瘤生物标志物，用于NSCLC的早期筛查与预后评估[86,87].

3.2.2 间接靶向β-catenin的ncRNAs

同时，β-catenin的表达与功能也受到多种ncRNAs的多层级间接调控. 在转录层面，抑癌因子miR-185通过抑制SRY-盒转录因子9(SRY-box transcription factor 9, SOX9)表达，下调β-catenin mRNA水平[88]，而lncRNA PVT1则通过吸附miR-361-3p解除对SOX9的抑制，诱导β-catenin转录激活，从而促进NSCLC增殖与侵袭[89]. 在表观遗传层面，部分ncRNAs调控甲基化修饰抑制β-catenin功能，例如miR-708-5p通过抑制DNA甲基转移酶DNMT3A，降低细胞间黏附分子(E-Cadherin, CDH1)启动子甲基化，促进CDH1/β-catenin复合体形成，诱导Wnt/β-catenin通路失活[90]；lncRNA ITGB1-DT则通过竞争性结合增强子蛋白锌指同源物2，从而上调ITGB1表达并形成ITGB1/β-catenin/MYC正反馈回路，持续激活Wnt/β-catenin通路[91]. 在翻译后修饰层面，ncRNAs调控乙酰化、泛素化修饰过程参与Wnt/β-catenin通路激活. 如circCDR1as通过抑制富含丝氨酸/精氨酸的剪接因子1泛素化降解，促进β-catenin表达[92]；circRACGAP1则通过募集多聚嘧啶区结合蛋白1，并诱导下游的诱导复制时间调节因子1脱乙酰化，激活Wnt/β-catenin通路并促进CSC特性[93]. 以上机制共同揭示了ncRNAs多水平、多途径调控网络在NSCLC进展中的核心作用.

3.2.3 靶向DC复合物的ncRNAs

DC复合物介导的β-catenin磷酸化和泛素化降解过程失调是Wnt/β-catenin通路过度激活的核心[94]，而ncRNAs通过干预DC组装与激酶活性，驱动NSCLC恶性进展. 其中促癌因子miR-3607和miR-4326分别靶向APC及APC2的3′UTR区域阻断DC复合物组装，导致β-catenin核累积[95,96]；miR-17-92簇则通过抑制p38α激酶活性，间接促进GSK3β磷酸化，介导Wnt/β-catenin通路激活，以维持CSC特性[97]；同时，促癌因子miR-19[98]和miR-1246[99]直接抑制GSK3β表达，促进NSCLC细胞的CSC活性及EMT进程；另外，miR-20b可通过抑制APC表达，并形成正反馈循环加速NSCLC进展[100]. 相反，部分ncRNAs靶向DC复合物发挥抑癌作用，如circ-GSK3B竞争结合FK506结合蛋白51，阻断GSK3β磷酸化，从而增强DC介导的β-catenin降解[101]；LINC00222则直接激活GSK3β，抑制Wnt/β-catenin通路活性，最终抑制LUAD细胞的增殖、迁移和CSC特性[102].

3.3 靶向TCF/LEF转录复合物的ncRNAs

Wnt/β-catenin通路的终末效应依赖于β-catenin与核内TCF/LEF转录复合物的结合并激活下游靶基因转录，而这一关键过程受ncRNAs调控[103]. 研究发现，在LUAD中，细胞核内的lncRNA UPLA1通过与桥粒斑蛋白(desmoplakin, DSP)结合，解除DSP对TCF/LEF转录活性的抑制，最终激活Wnt/β-catenin信号传导，促进LUAD的进展[104]. 与之相反的是，抑癌因子chromobox蛋白同源物7(chromobox protein homolog 7, cbx7)通过阻断TCF4与β-catenin的结合抑制转录复合物形成，而lncRNA-SNHG7与miRNA-181相互作用，上调cbx7表达水平，进而破坏细胞核内的TCF4和β-catenin复合物形成，阻断Wnt/β-catenin通路激活，抑制LUAD细胞增殖和迁移[105]. 可见，ncRNAs通过直接或间接干预TCF/LEF-β-catenin转录复合物的形成与活性，在Wnt/β-catenin通路中发挥关键作用.

3.4 靶向通路负调控因子的ncRNAs

Wnt/β-catenin通路的稳态由分泌型拮抗蛋白如DKK、SFRP、WIF家族与胞内调控元件共同维持[106]. ncRNAs通过直接或间接干预负调控因子表达驱动NSCLC恶性转化[107]. 在直接调控方面，miR-1275通过抑制DKK3、SFRP1增强LUAD干细胞特性及转移[108]. 同样，miR-582-3p通过抑制AXIN2、DKK3、SFRP1维持CSC特性[109]，miR-128-3p则同时靶向Axin1、SFRP2、WIF1等通路负调控因子，诱导CSC干性、EMT编程以及化疗耐药相关转移[39]. 在间接调控方面，

LINC00326竞争结合miR-657，解除其对DKK2抑制作用，从而激活Wnt/β-catenin通路[110]；LINC01089则通过吸附miR-27a上调SFRP1，阻断Wnt/β-catenin通路传导[111]；此外，circ_0006427经miR-6783-3p/DKK1轴抑制LUAD增殖侵袭[112](图6)．这些发现表明ncRNAs通过多层面、多靶点调控通路负调控因子的表达，参与Wnt/β-catenin通路的稳态维持，为理解NSCLC发生发展的分子机制提供了新视角(表1)．

4 ncRNAs/WNT轴的治疗前景

4.1 ncRNAs/Wnt/β-catenin轴: NSCLC治疗耐药和靶向药物开发中的潜在靶点

Wnt/β-catenin通路相关ncRNAs在NSCLC治疗耐药中发挥核心调控作用[6]．目前越来越多的研究聚焦于ncRNAs介导的化疗抵抗机制，最新研究表明，hsa_circ_0125356通过miR-582-5p/FGF9轴调节WNT经典和非经典信号通路，诱导吉西他滨治疗耐药[113]．两种小分子拮抗剂WAY 316606和XAV-939可抑制hsa_circ_0125356诱导的Wnt/β-catenin通路的激活，为确定治疗NSCLC吉西他滨耐药的治疗靶点提供了新的方向[113]．此外，miR-130b通过抑制抑癌因子磷酸酶和张力蛋白同系物表达，降低β-catenin磷酸化水平，驱动Wnt/β-catenin通路介导的化疗耐药[114]．此外，lncRNA SNHG1通过miR-140-5p/Wnt轴促进顺铂(cisplatin, DDP)耐药[115]，而lncRNA RPPH1则通过miR-326/WNT2B轴加速NSCLC进展并诱导DDP抵抗[116]．这些发现系统揭示了ncRNAs通过不同分子机制调控Wnt/β-catenin通路驱动化疗耐药的共性特征，为开发新型联合治疗策略提供了理论依据．

在靶向药物开发方面，靶向ncRNAs为克服表皮生长因子受体酪氨酸激酶抑制剂(epidermal growth factor receptor-tyrosine kinase inhibitor, EGFR-TKI)耐药提供了新路径．多项研究揭示了ncRNAs的动态调控机制．

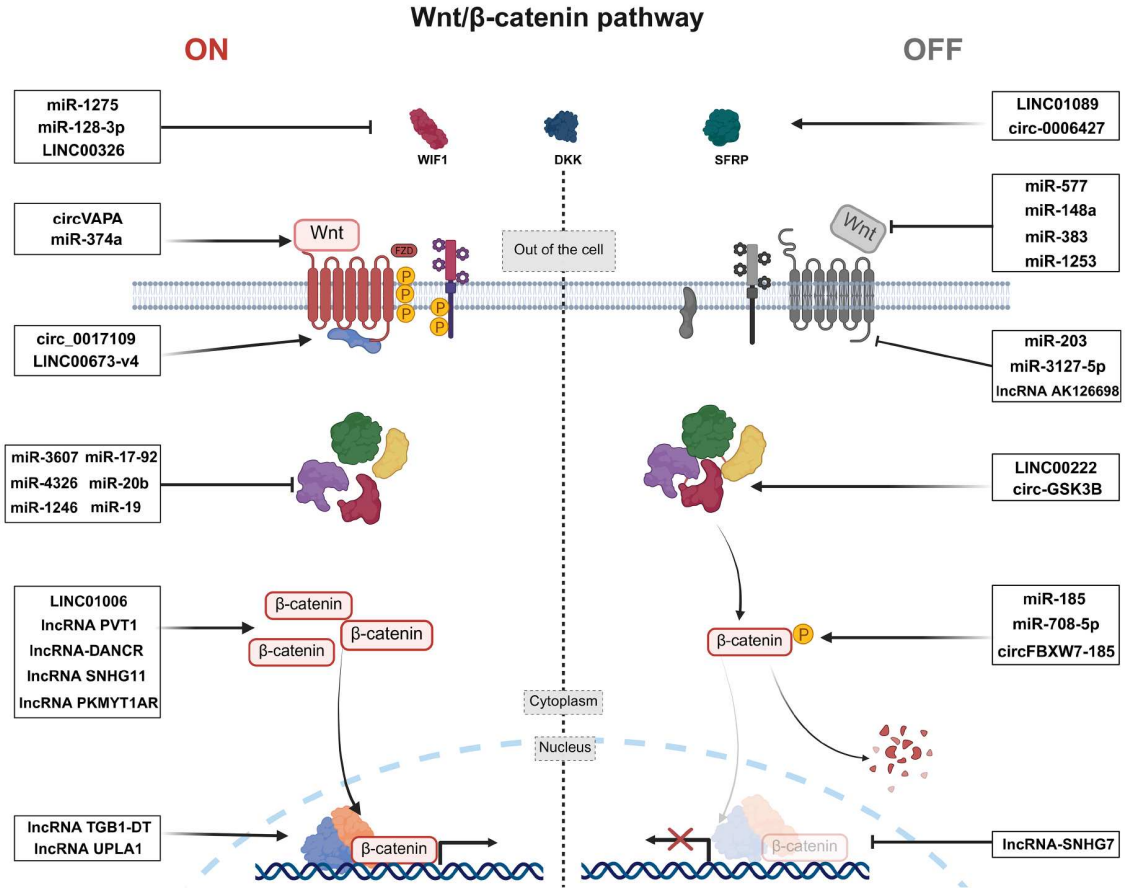

图 6 (网络版彩色)NSCLC中ncRNAs作为Wnt/β-catenin通路调控的分子开关. 图片素材来源于BioRender.com

Figure 6 (Color online) NcRNAs act as molecular switches governing Wnt/β-catenin signaling regulation in NSCLC. Created with BioRender.com

表 1　NSCLC中的ncRNAs/Wnt/β-catenin轴

Table 1　The ncRNAs/Wnt/β-catenin functional axis in NSCLC

作用位点	ncRNAs	细胞系	生物学功能	ncRNAs表达	参考文献
靶向WNT配体	miRNA-148a	NSCLC细胞系(A549、H1299)	抑制NSCLC细胞迁移和侵袭	下调	[57]
	miR-383	NSCLC细胞系(H1299、A549、和SW900)	抑制NSCLC细胞的细胞活力并诱导细胞凋亡	下调	[58]
	miR-577	NSCLC细胞系(H650、A549、H522、H1299和H1155)	抑制NSCLC细胞增殖和EMT过程	下调	[59]
	miR-1253	非小细胞细胞系(A549、NCI-H1299、NCI-H157、ANIP-973和GLC-82)	抑制NSCLC细胞的增殖、迁移和侵袭	下调	[60]
	miR-374a	NSCLC细胞系(HCC827和Calu1/HCC827-Gef抗性细胞系)	促进NSCLC细胞EMT、干性和吉非替尼耐药性	上调	[61]
	circVAPA	LC细胞系(H1299、H1975、A549和HCC827)	促进LC细胞增殖、迁移、侵袭和干性	上调	[62]
靶向FZD	miR-203	NSCLC细胞系h1299	抑制NSCLC细胞增殖、转移	下调	[68]
	lncRNA AK126698	NSCLC细胞系(A549、NCI-H520和H1299)	抑制NSCLC细胞增殖和迁移,诱导细胞凋亡	下调	[69]
	miR-3127-5p	LC细胞系(A549、H1299和HEK-293T)	抑制NSCLC中EMT, 细胞迁移、侵袭和黏附	下调	[70]
	circ_0017109	NSCLC细胞系(CALU3、CALU6、A549、H1229)	促进NSCLC细胞增殖、迁移、侵袭和干性	上调	[71]
靶向DVL	LINC00673-v4	LUAD细胞系(HCC827、NCI-H1650、A549、NCI-H596、NCI-H1975、NCI-H1299、SK-LU-1、NCI-H358、NCI-H2009、HCC4006、NCI-H2030和PC9)	促进LAD细胞侵袭、迁移和转移	上调	[76]
直接靶向β-catenin	lncRNA SNHG11	LUAD细胞系(A549、H1299、H460和SPCA1)	促进LUAD进展	上调	[80]
	LINC01006	LUAD细胞系(PC9、H1650、H1975和A549)	促进LUAD细胞增殖、迁移和EMT	上调	[81]
	lncRNA DANCR	LUAD细胞系(A549、H1975、H1755、H1944、H2087和H358NSCLC)大细胞癌细胞系(H661和H1299)	促进CSC的自我更新	上调	[82]
	lncRNA PKMYT1AR	LC细胞系(H358、H1975、H1299、H1650、A549和SPC-A1)	维持CSC特性	上调	[83]
	circFBXW7	奥希替尼耐药细胞系(HCC827OR和H1975OR)	抑制CSC特性, 逆转奥希替尼耐药	下调	[84]
间接靶向β-catenin	miR-185	NSCLC细胞系(A549、H1299、H1650和SK-MES-1)	抑制NSCLC细胞增殖和侵袭	下调	[88]
	lncRNA PVT1	NSCLC细胞系(H1650、H1975、H460和A549)	促进NSCLC细胞增殖、迁移、侵袭	上调	[89]
	miR-708-5p	LC细胞系(A549、Calu-3和95D)	抑制CSC特性	下调	[90]
	lncRNA ITGB1-DT	LUAD细胞系A549(ATCC CCL-185)、NCI-H1975(ATCC CRL-5908)	促进LUAD进展	上调	[91]
	circCDR1as	NSCLC细胞系(H1299、A549和H460)	促进NSCLC细胞增殖、迁移和侵袭	上调	[92]
	circRACGAP1	NSCLC细胞系(A549、H1299H1975、H460和PC-9)	维持CSC特性和转移	上调	[93]
靶向DC复合物	miR-3607	LC细胞系(NCI-H1650、5D、A549、NCI-H460、NCI-H358、NCI-H1975和NCI-H1299)	促进LC细胞增殖	上调	[95]
	miR-4326	LC细胞系(95D、NCI-H1299、NCI-H460、NCI-H1650、NCI-H358、NCI-H1975和A549)	促进LC细胞增殖	上调	[96]

(续表1)

作用位点	ncRNAs	细胞系	生物学功能	ncRNAs表达	参考文献
靶向DC复合物	miR-17-92	Lgr6+人肺干细胞	维持CSC特性	上调	[97]
	miR-19	NSCLC细胞系(A549和H1299)	促进CSC活性	上调	[98]
	miR-1246	NSCLC细胞系A549	促进EMT	上调	[99]
	miR-20b	LUAD细胞系(PC-9、H1975和A549) 非小细胞LC细胞系H1299	促进NSCLC细胞增殖、 迁移和侵袭	上调	[100]
	circ-GSK3B	LUAD细胞系(PC9、H2073、H-1975和A549)	抑制LUAD细胞的增殖、 迁移和干性	下调	[101]
	LINC00222	LUAD细胞系(SPC-A-1和LTEP-A-2)	抑制LUAD细胞迁移和侵袭	下调	[102]
靶向TCF/LEF转录复合物	LNCRNA UPLA1	LUAD细胞系(A549和H1299)	促进LUAD的迁移、侵袭	上调	[104]
	lncRNA-SNHG7	LUAD细胞系	抑制LUAD细胞增殖, 抑制细胞凋亡	下调	[105]
靶向通路负调控因子	miR-1275	LC细胞系(L78、H460、A549、GLC-82、 SPC-A1、PC9、H1299、H1975和H2228)	诱导LUAD细胞的干细胞样性状, 促进肿瘤发生、复发和转移	上调	[108]
	miR-128-3p	LC细胞系(A549、Calu-3、SK-MES-1、 PAa、NCI-H292、NCI-H520(H520)、 NCI-H596、NCI-H1299、NCI-H1650、 NCI-H1975、HLAMP和95D)	维持EMT和CSC编程以及诱导 NSCLC细胞耐药	上调	[39]
	LINC00326	NSCLC细胞系(A549、NCI-H1299、 HCC827、NCI-1650和NCI-H358)	抑制NSCLC进展	下调	[110]
	LINC01089	NSCLC细胞系	抑制NSCLC细胞的EMT	下调	[111]
	circ_0006427	LUAD细胞系(H1299、A549、 SPC-A1和Calu3)	抑制LUAD进展	下调	[112]

例如, circ-FBXW7通过拮抗Wnt/β-catenin通路活性, 抑制CSC自我更新能力, 提示其作为逆转EGFR-TKI耐药的潜在靶点[84]; lncRNA NEAT1敲除可增强安罗替尼的促凋亡效应, 表明其可能成为联合治疗的增敏剂[117]; 此外, 外泌体miR-214通过激活Wnt/β-catenin通路, 赋予吉非替尼耐药性, 而靶向miR-214的antagomi可有效逆转耐药表型[118]. 值得注意的是, miR-374a与miR-548b通过协同作用调控NSCLC耐药细胞恶性表型, 前者通过抑制*WNT5a*阻断EMT及干细胞特性, 后者通过靶向*CCNB1*基因诱导细胞周期停滞, 这为多靶点干预策略提供了理论依据[119].

NSCLC治疗的复杂性不仅源于肿瘤细胞自身特性, 更与其所处的动态微环境密切相关, TME与ncRNAs/Wnt/β-catenin轴的调控网络正在成为突破现有治疗瓶颈的新方向[120,121]. 缺氧作为TME的核心特征, 可通过HIF-1α依赖性方式上调miR-1275, 协同激活Wnt/β-catenin通路, 显著增强LUAD干细胞特性并促进转移复发, 提示miR-1275可能成为治疗新靶点[108]. 在肿瘤细胞与TME的动态交流中, 外泌体介导的细胞间通讯发挥着关键作用. 研究发现外泌体转运的miR-4739同时激活肿瘤细胞及血管内皮细胞的Wnt/β-catenin通路, 促进"驱动基因阴性"NSCLC的恶性进展, 为开发针对此类难治性NSCLC的创新疗法提供了分子基础[122]. 另外, Wnt/β-catenin通路在肿瘤免疫微环境调控中同样具有重要作用. 研究表明, miR-23a/27a/24-2簇激活NSCLC中的β-catenin/TCF4轴驱动免疫逃逸以及PD-1/PD-L1抑制剂的耐药, 阻断该反馈回路可能是治疗miR-23a/27a/24-2簇中高表达的NSCLC的有用策略[123]. 针对ncRNAs/Wnt/TME轴的联合干预策略具有重要的临床转化价值, 有望突破当前NSCLC治疗的局限性.

4.2 临床ncRNAs药物开发及递送策略

RNA药物的靶向设计与递送系统开发是当前RNA疗法研究的核心热点及技术难点. 基于RNA疗法的临床转化可能受到与RNA药物靶向特异性、递送效率和体内耐受性等问题的阻碍, 但不可否认的是, 该领域为传统"不可成药"分子靶点及复杂疾病治疗开辟了独特机遇窗口[124]. 从分子优化层面而言, 针对RNA结构的化学修饰技术已取得显著进展, 通过对RNA分子的帽部结构、多聚腺苷酸尾部、核苷酸碱基(如假尿嘧啶替代尿嘧啶)及空间构象进行系统性修饰, 可有效提升

RNA稳定性、降低免疫原性并增强翻译效率[125~127]. 与此同时，基因编辑技术的革新为精准调控RNA功能提供了新维度[128]. CRISPR-Cas13系统通过特异性识别circRNA分子(如致癌性circFAM120A)实现精准编辑，而无需干扰同源线性mRNA，这为NSCLC相关ncRNAs干预提供了高特异性工具[129,130]. 在递送系统开发方面，外泌体、脂质纳米颗粒(lipid nanoparticle, LNP)、pH响应型聚合物载体等多元化递送平台已逐步成熟[131~133]. 已成功开发的各种纳米载体，例如外泌体、微泡、聚合物纳米颗粒、1,2-二油基-3-三甲基氯化铵纳米载体和病毒样颗粒在临床试验中已用于lncRNA递送[134]. 此外，将LNP与物理治疗技术(如离子照射)相结合，已显示出改善lncRNA治疗效果的前景，目前使用多孔氧化铁纳米剂递送的lncRNA CRYBG3已用于NSCLC治疗[135]. 值得关注的是，这些技术突破正加速RNA疗法的临床转化. 靶向KRAS G12D突变的小干扰RNA药物NDT-05-1040通过LNP实现肿瘤特异性递送[136]；基于miR-16模拟物的TargomiRs微型细胞则通过EGFR靶向机制在NSCLC临床试验中展现出可控安全性及初步疗效[137]. 然而我们必须清醒认识到，RNA疗法仍面临递送脱靶引发的正常组织毒性、载体免疫原性导致的全身炎症反应，以及TME异质性阻碍药物蓄积等多重挑战，这要求未来研究需进一步整合组织特异性配体修饰、动态生物传感等技术以完善治疗体系[138,139].

4.3 天然药物驱动ncRNAs靶向疗法

中医药是天然药物的重要组成部分，其核心特征在于通过多成分、多靶点、多通路协同调控机体. 这种整体调节模式与ncRNAs在细胞内形成的复杂调控网络高度契合. 大量研究发现，中药成分可通过多靶点、多成分干预ncRNAs的表达与功能，调控Wnt/β-catenin通路活性[140~142]. 例如，黄芩素不仅通过促进lncRNA-NEF表达，从而抑制Wnt/β-catenin信号通路激活，显著降低肿瘤细胞侵袭与转移能力，同时还可通过上调miR-25靶向沉默Wnt/β-catenin通路相关基因，上述作用共同拓展了黄芩素作为泛癌种潜在治疗剂的分子基础[143]. 进一步研究发现，黄酮类成分如黄芩苷通过激活miR-217/DKK1轴诱导结直肠癌细胞凋亡[144]，而川陈皮素通过抑制miR-15-5p，上调Wnt/β-catenin通路负调控因子AXIN2、WIF1表达，从而抑制NSCLC增殖[145]. 此外，天然多酚类化合物没食子酸可靶向lncRNA MALAT1阻断Wnt/β-catenin信号传导，抑制肿瘤进展[146]；萜类化合物如齐墩果酸则通过调控miR-122/β-catenin轴降低癌细胞迁移侵袭能力[147]，而芍药苷则通过miR-3194-5p/β-catenin轴抑制CSC特性[148]；青蒿琥酯则通过下调lncRNA-RP11，抑制Wnt/β-catenin通路活性，进而逆转肝癌细胞的EMT进程[149]. 已有的诸多研究从“天然产物-表观网络-核心通路”的级联调控模式系统揭示了中医药成分的多维作用机制，为开发基于天然产物的靶向治疗策略提供了理论依据[150].

5 Wnt/β-catenin通路相关ncRNAs的NSCLC生物标志物潜力

Wnt/β-catenin通路相关ncRNAs在NSCLC全周期管理中展现出多维度临床应用潜力，为NSCLC动态监测提供新型生物标志物. 首先，Wnt/β-catenin通路相关ncRNAs在NSCLC早期诊断及分型中展现出高灵敏性与特异性. 例如，血清外泌体miRNA组合(如miR-20b-5p和miR-3187-5p)可显著提高早期NSCLC检测效能(AUC=0.838)[151]，而LINC00673-v4联合miR-150可有效区分LUAD与肺鳞状细胞癌(AUC=0.784，P=0.03)[76]. 在预后评估方面，多项研究表明ncRNAs表达水平与患者生存显著相关. 例如，miR-582-3p高表达与较短的无复发生存期(recurrence free survival, RFS)及总生存期(overall Survival, OS)独立相关(P<0.01)[109]；LINC00222低表达提示LUAD复发风险升高(P<0.05)[102]，而miR-1275高表达患者OS显著降低且复发率增加，凸显其预后预警价值[108]. 在疗效评估方面，ncRNAs同样展现出重要价值. miR-128-3p高表达与基于DDP的NSCLC治疗疗效呈负相关，提示其作为疗效分层标志物的潜力[39]. 此外，ncRNAs表达谱可有效预测NSCLC的复发转移. 其中，miR-1275与β-catenin构建的联合预测模型具有优异的LUAD转移预测功能[108]；LINC00326、circ_0017109等ncRNAs与NSCLC临床分期及TNM(Tumor Node Metastasis, TNM)分类显著相关，为NSCLC复发监测提供分子基础[110,139]. 这些发现表明,Wnt/β-catenin通路相关ncRNAs通过其在诊断、预后和治疗预测等方面的应用价值，为NSCLC的精准诊疗提供了新的工具链.

6 总结与展望

随着精准医学的快速发展，ncRNAs动态分析技术为NSCLC诊疗模式的革新提供了重要契机，其不仅可

推动个体化治疗策略的制定，更可能通过早期诊断与实时监测显著改善患者预后. 然而, 当前研究多聚焦单一ncRNA分子或孤立通路节点制约了对ncRNAs调控网络的系统性认知. 本文系统解析ncRNAs/Wnt/β-catenin轴在NSCLC恶性演进中的多维调控机制，通过阐明不同类型ncRNAs(miRNA/lncRNA/circRNA)在通路配体分泌、膜表面受体激活、胞内信号转导及通路负调控因子的功能分工与协同效应, 揭示ncRNAs作为致癌/抑癌因子驱动NSCLC发生发展的复杂动态网络. ncRNAs作为Wnt/β-catenin通路的动态调控枢纽，展现出突破当前NSCLC治疗瓶颈的潜力. 基于此，靶向ncRNAs/Wnt/β-catenin轴可为NSCLC诊疗临床转化提供方向; 在诊断层面, Wnt/β-catenin通路相关ncRNAs展现出作为多维度生物标志物的潜力，其表达谱特征有望构建NSCLC“诊断-预后-疗效预测”全周期临床决策体系, 从而实现对NSCLC患者的精准分层管理; 在治疗策略方面, ncRNAs相关药物的开发及递送为NSCLC临床治疗打开了更为广阔的前景. 此外, 天然化合物以其多靶点特性，不仅为调控该复杂网络提供了丰富的可能性，并且基于天然化合物开发的靶向特定ncRNAs的小分子药物有望实现对信号通路的精准干预，从而提升新药研发效率, 推动NSCLC个体化治疗的发展.

当前关于ncRNAs在NSCLC中的研究仍存在重要挑战. 首先，研究结果呈现显著的异质性与矛盾性. 其主要原因在于不同临床样本、实验设计及检测技术等关键因素存在差异，从而导致ncRNAs作为生物标志物的可重复性受限. 基于多中心队列的大规模验证研究及标准化检测平台的建立是确证其临床有效性的必要前提. 其次，现有研究多聚焦于单个ncRNAs/Wnt/β-catenin轴的线性调控作用, 未能揭示ncRNAs在NSCLC信号网络中的全局调控特性. 最新研究表明，特定ncRNAs可同时调控Wnt、Hedgehog及Notch等通路关键节点，通过介导跨通路信号级联串扰驱动肿瘤恶性进展[152,153]. 未来，采用多组学整合策略系统解析ncRNAs在NSCLC信号网络中的多维调控图谱, 并建立以“分子机制解析-靶向治疗开发-标志物临床验证”为核心的临床诊疗转化路径，推动ncRNAs研究成果向临床实践的高效转化, 最终实现NSCLC诊疗的技术进步.

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Summary for “非小细胞肺癌Wnt/β-catenin信号通路相关ncRNAs: 多维机制解析与诊疗转化研究”

NcRNAs in the Wnt/β-catenin signaling pathway: from multidimensional mechanisms to diagnostic and therapeutic translation in non-small-cell lung cancer

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Lung cancer (LC) is the leading cause of cancer-related deaths worldwide, with non-small-cell lung cancer (NSCLC) constituting the majority of cases. Effective treatment is hampered by an incomplete understanding of molecular mechanisms, insufficient early-detection tools, and widespread drug resistance. The Wnt/β-catenin signaling pathway, central to lung tissue homeostasis, is frequently dysregulated in NSCLC and drives malignant transformation and progression. Accumulating evidence indicates that non-coding RNAs (ncRNAs)—including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs)—are critical modulators of this pathway. However, the multilayered regulatory networks they form, as well as strategies for their clinical translation, remain incompletely defined.

This review synthesizes current knowledge on how diverse ncRNAs target the Wnt/β-catenin pathway in NSCLC, addressing their impacts on ligand secretion, receptor activation, intracellular signal transduction, and negative regulators. It outlines a multidimensional regulatory landscape in which ncRNAs collaboratively promote or suppress NSCLC by modulating Wnt/β-catenin signaling and evaluates their potential as biomarkers and therapeutic targets.

Mechanistically, ncRNAs operate at transcriptional, post-transcriptional, translational, and epigenetic levels to influence cancer stem cell maintenance, epithelial–mesenchymal transition, angiogenesis, proliferation, metastasis, and therapy resistance. miRNAs commonly bind the 3′ untranslated regions of mRNAs encoding pathway components–such as secreted frizzled-related proteins, Dickkopf family members, GSK-3β, AXIN1, and β-catenin–thereby fine-tuning their expression and directly influencing malignant behaviors. Many lncRNAs act as competing endogenous RNAs (ceRNAs), sequestering specific miRNAs to relieve repression of target transcripts and activate Wnt signaling; others function as signals, scaffolds, decoys, or guides to regulate transcription factors and pathway components. Owing to their covalently closed structure, circRNAs are stable and primarily function as miRNA sponges; a subset also encodes functional peptides that influence phosphorylation, ubiquitination, or stability of Wnt/β-catenin components.

Therapeutically, ncRNAs function as pivotal regulatory nodes and represent promising targets for intervention. They are centrally involved in mechanisms of drug resistance, indicating that targeting the ncRNA–Wnt/β-catenin axis could synergize with existing treatments. Advances in RNA delivery platforms and RNA-based therapeutics offer promising routes to reverse resistance and remodel the tumor microenvironment. Additionally, natural compounds with multi-target activity and small molecules that modulate specific ncRNAs provide complementary strategies to accelerate drug discovery and personalize therapy.

In diagnostics, Wnt/β-catenin-related ncRNAs show considerable promise as clinical biomarkers throughout the management of NSCLC, including early detection, molecular subtyping, metastasis surveillance, recurrence monitoring, prognosis, and resistance assessment. High-throughput sequencing and comprehensive expression profiling have identified candidate ncRNA biomarkers showing promise for high sensitivity and specificity in preliminary studies, which require rigorous clinical validation.

Integrated multi-omics and functional studies are needed to decode ncRNA regulatory networks in NSCLC systematically. Establishing a translational pipeline from “mechanistic discovery → targeted therapeutic development → biomarker validation” will be critical to moving ncRNA findings from bench to bedside and ultimately improving the diagnosis and treatment of NSCLC.

Wnt/β-catenin, ncRNAs, non-small-cell lung cancer (NSCLC), mechanism of action, biomarkers

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