

综述

环状RNA在前列腺癌治疗抵抗中的作用

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摘要: 环状RNA(circRNA)是共价闭合的RNA分子, 在各种肿瘤中起着重要的调节作用。CircRNA在前列腺癌(PCa)的发展和治疗中扮演着重要的角色。PCa对新型内分泌治疗、多西他赛化疗以及放疗等治疗手段常产生治疗抵抗, 是导致前列腺癌治疗失败的原因之一。研究表明, circRNA可通过多种信号通路影响PCa细胞的生物学行为, 进而调节其增殖、迁移以及治疗抵抗等过程。因此, 研究circRNA在PCa治疗抵抗中的调控作用对于逆转治疗抵抗以及提高治疗效果具有重要意义。本文总结了circRNA对PCa产生治疗抵抗的重要调控作用, 介绍了circRNA在PCa治疗抵抗中的具体作用机制, 旨在为未来靶向circRNA从而逆转PCa治疗抵抗提供新的思路。

关键词: 环状核糖核酸; 前列腺癌; 药物治疗; 放射治疗; 治疗抵抗

The role of circRNA in prostate cancer treatment resistance

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Abstract: Circular RNA (circRNA) is a covalently closed RNA molecule that plays a crucial regulatory role in various tumors. With further research, circRNA plays an important role in the development and treatment of prostate cancer (PCa). PCa often produces therapeutic resistance to new hormone therapy (NHT), docetaxel chemotherapy, and radiation therapy, which is one of the reasons for the failure of prostate cancer treatment. Researches have shown that circRNA can affect the biological behavior of PCa cells through various signaling pathways, thereby regulating their proliferation, migration and treatment resistance processes. Therefore, studying the regulatory role of circRNA in PCa treatment resistance is of great significance for reversing treatment resistance and improving treatment efficacy. This review summarizes the important regulatory role of circRNA in the development of therapeutic resistance to PCa, and introduces the specific mechanism of circRNA in the treatment resistance of PCa. The aim is to provide new ideas for targeting circRNA in the future to reverse the therapeutic resistance of PCa.

Key Words: circRNA; prostate cancer; drug therapy; radiation treatment; treatment resistance

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前列腺癌(prostate cancer, PCa)是泌尿生殖系统中最常见的肿瘤类型之一,也是导致男性肿瘤死亡的第二大原因^[1]。PCa在临床上可定义为局限性PCa和转移性PCa,治疗方法包括手术、放疗、雄激素剥夺疗法(androgen deprivation therapy, ADT)、化疗等。尽管这些疗法在一定程度上取得了成功,但随着治疗抵抗的不断产生,患者总生存期(overall survival, OS)仍然逐渐降低,给PCa的治疗带来巨大挑战^[2]。因此,了解PCa治疗抵抗的相关机制尤为重要。

近年来,随着RNA深度测序技术和生物信息学的发展,越来越多的环状RNA(circular RNA, circRNA)被发现在PCa中存在异常表达,并且与PCa的许多临床病理学特征如肿瘤分级、淋巴结转移及远处转移相关。此外, circRNA还参与了PCa的增殖、凋亡、药物耐药和放疗抵抗等多种病理现象^[3]。本文系统地总结了目前circRNA在PCa治疗抵抗中的作用,对其在PCa新型内分泌治疗、化学治疗与放射治疗中与治疗抵抗的相关性进行综述。

1 CircRNA的生物学特性和功能

CircRNA是一种由RNA聚合酶Ⅱ转录的内源性

非编码RNA分子,由前体信使RNA(precursor mRNA, pre-mRNA)通过独特的反向剪接过程产生。根据组成结构,主要可将其分为外显子 circRNA(exonic circRNAs, EcircRNAs)、内含子 circRNA(circular intronic RNAs, CiRNAs)和外显子-内含子 circRNA(exon-intron circRNAs, EIciRNAs)^[4]。与传统的线性RNA不同, circRNA缺乏5'端帽子结构和3'端poly A尾,不易被RNA外切酶降解,具有更高的稳定性。已经有大量的研究探索了circRNA的生物学功能,如图1所示:(1) circRNA作为竞争性内源RNA,可通过吸附功能性miRNA(microRNA),间接调控miRNA下游靶基因的表达,因此它被视为miRNA海绵^[5]; (2) circRNA的产生依赖于典型的剪接位点和剪接体机制,并与pre-mRNA剪接竞争,表明circRNA在发育和疾病过程中具有调控基因转录和表达的能力^[6]; (3) RNA结合蛋白(RNA binding protein, RBP)是功能广泛的调节因子,参与多个转录后调控过程, circRNA可以与许多RBP相互作用,从而阻断或增强蛋白质功能^[7]; (4)有研究表明, circRNA可以编码蛋白质,但由于不存在翻译所需的游离5'帽或3'多聚(A),需要在初始密码子上游插入合成的内部核糖体进入位点(internal ribosome entry site, IRES)

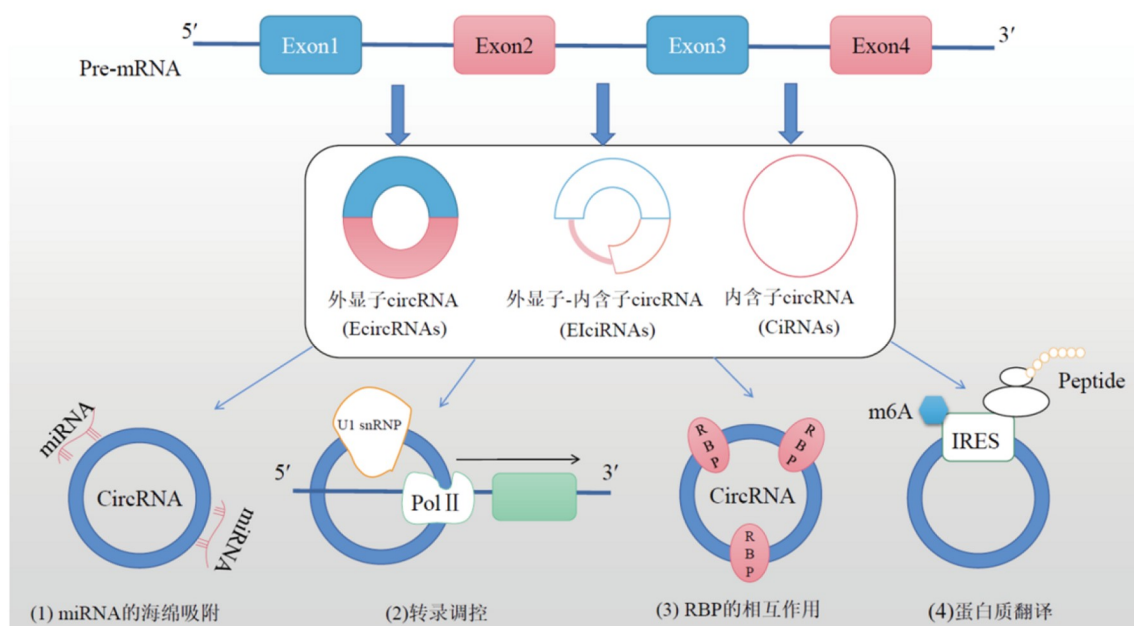


图1 CircRNA的生物学功能

或者以N6-甲基腺苷(m^6A)形式存在的甲基化腺苷核苷酸,从而驱动circRNA的翻译^[8]。由于circRNA的高稳定性、广泛表达和组织特异性,正在成为潜在的癌症生物标志物和治疗靶点。

2 CircRNA与PCa对新型内分泌治疗的治疗抵抗

转移性去势抵抗性PCa(metastatic castration-resistant prostate cancer, mCRPC)是指PCa患者接受去势治疗后继续进展的状态。近年来,针对mCRPC的治疗取得了一些进展,如新型内分泌治疗(new hormone therapy, NHT)药物阿比特龙(Abiraterone, Abi)、恩扎卢胺(Enzalutamide, Enz)、阿帕他胺(Apalutamide, Apa)、达罗他胺(Darolutamide, Dar)等能显著延长患者OS。然而,大多数患者在接受NHT药物治疗后依然会出现治疗抵抗,这可能与雄激素受体(androgen receptor, AR)基因扩增、AR剪接变体-7(AR-V7)的表达、点突变、葡萄糖代谢等多种机制有关^[9-11]。本文拟以Enz为例,讨论circRNA在NHT治疗抵抗中发挥的重要作用。

2.1 CircRNA通过EZH2介导Enz治疗抵抗

组蛋白甲基化转移酶EZH2(enhancer of Zeste homolog 2)是多梳抑制复合体2(polycomb repressive complex 2, PRC2)的核心催化亚基,通过调节组蛋白H3上的赖氨酸27的甲基化修饰(H3K27me3)来影响多种基因的表达。在PCa中,EZH2的过度表达能抑制抑癌基因的表达,同时会增加AR的转录活性,从而促进PCa的生长和转移^[12,13]。

Circ0006357是一种源自EZH2外显子2和3的circRNA(因此被命名为circEZH2^{E2/E3}),它在PCa中的表达显著上调,且与PCa的进展和不良预后相关。CircEZH2^{E2/E3}作为miR-363和miR-708的双重抑制剂,可以上调EZH2,从而降低EZH2抑制基因的表达,促进PCa的进展^[14]。另一项研究表明,circTRPS1(hsa_circ_0006950)在高级别PCa组织中显著上调,其可通过与miR124-3p竞争结合位点,导致miR-124-3p无法正常抑制EZH2的表达,从而促进PCa细胞增殖和转移^[15]。因此,对EZH2及其相关circRNA的研究有助于深入理解PCa的发生和发展,并为该疾病的治疗提供新的靶点。

2.2 CircRNA通过EMT介导Enz治疗抵抗

上皮-间充质转化(epithelial-mesenchymal transition, EMT)是一种转录调控和表观遗传修饰驱动的转分化过程,能使细胞失去上皮特征并转变为间充质表型。EMT在肿瘤中的作用已逐渐被认识和探索,通过抑制EMT,可以使癌细胞恢复上皮特征,减少其侵袭和转移能力,并增加对化学治疗的敏感性,从而提高治疗效果^[16,17]。

B细胞特异性莫洛尼鼠白血病病毒插入位点-1(B-lymphoma moloney murine leukemia virus insertion region-1, BMI-1)是多梳抑制复合体1(polycomb repressive complex 1, PRC1)的重要组成部分,它通过抑制特定基因的转录来维持干细胞的自我更新能力,因此,它的高表达与肿瘤的侵袭、转移和治疗抵抗密切相关^[18,19]。研究发现,circ0016068作为miRNA海绵与miR-330-3p结合,并通过抑制miR-330-3p的功能来促进BMI-1的表达,从而增强EMT以及PCa细胞的生长、迁移和侵袭^[20]。

2.3 CircRNA通过糖酵解介导Enz治疗抵抗

对于肿瘤细胞而言,其代谢特点与快速增殖和生存能力密切相关^[21]。跟正常细胞通过线粒体氧化磷酸化产生能量不同,肿瘤细胞在缺氧环境下通常倾向于采用糖酵解途径获取能量,这种现象被称为Warburg效应^[22]。

最近的研究揭示了一种被称为circMID1的circRNA(hsa_circ_0007933)通过海绵吸附miR-330-3p,从而调节YTHDC2/IGF1R/AKT轴促进PCa的增殖、迁移、侵袭以及糖酵解^[23]。其中,胰岛素样生长因子1受体(insulin-like growth factor 1 receptor, IGF1R)作为一种细胞表面受体,也参与了肿瘤恶性进展的调控^[24]。除了circMID1,circ0057553也扮演着重要的角色。研究发现,circ0057553通过吸附miR-515-5p,阻止其对YES1基因的靶向作用。Yes原癌基因1(Yes proto-oncogene 1, YES1)是一种酪氨酸激酶,其过度活化与多种癌症的发生和进展相关。进一步实验结果显示,circ0057553通过促进YES1的表达,增加了PCa细胞的糖酵解,从而为肿瘤细胞的生存和增殖提供了更多的能量和代谢物质^[25]。

由于升高的糖酵解活性能确保癌细胞有足够的

ATP供应,以满足ATP结合盒转运蛋白介导药物外排及耐药性的需要^[26]。这些circRNA有可能通过促进PCa糖酵解,从而导致PCa细胞对Enz的治疗抵抗。

2.4 CircRNA通过氧化磷酸化介导Enz治疗抵抗

除了糖酵解以外,线粒体氧化磷酸化也是一种重要的代谢途径。该过程能够将葡萄糖、脂肪酸和氨基酸氧化成二氧化碳和水,并生成大量ATP^[27]。研究表明,在肿瘤发展和转移中,肿瘤细胞会增加线粒体氧化磷酸化的活性,以满足其快速生长和增殖的能量需求,这种能力使肿瘤细胞能够更有效地利用营养物质,并产生足够的能量来维持其异常的代谢需求^[28,29]。

CircRBM33是一种经过m⁶A修饰的RNA,在PCa细胞中表达上调。m⁶A修饰使circRBM33具有生物学活性。进一步研究发现,circRBM33会与脆性X智力低下蛋白1(fragile X mental retardation 1, FMR1)相互作用,形成一个二元复合物(circRBM33-FMR1),并通过维持下游靶基因丙酮酸脱氢酶A1(pyruvate dehydrogenase alpha 1, PDHA1)的mRNA稳定性来激活线粒体氧化磷酸化,从而促进PCa细胞的生长和侵袭。研究还发现,敲低circRBM33能够显著增加PCa对NHT治疗(包括Enz、Apa和Dar)的反应敏感性^[30]。这一发现表明,在PCa治疗中,除了针对糖酵解的干扰,干扰肿瘤细胞的线粒体氧化磷酸化也可能是一种有效的策略。然而,需要注意的是,干扰线粒体氧化磷酸化也可能对正常细胞造成影响,因为该代谢途径在正常细胞中同样重要。因此,在开发针对线粒体氧化磷酸化的治疗策略时,需要密切考虑其选择性和对正常细胞的毒性。

2.5 CircRNA通过AR-V7介导Enz治疗抵抗

AR-V7是AR的剪接变体,它缺乏正常AR所具有的雄激素结合结构域,因此AR-V7无法与雄激素结合。然而,AR-V7仍能够激活下游基因表达,从而绕过正常AR信号通路的调控,促进PCa细胞的增殖和存活,并且影响Enz疗效^[31,32]。

Circ0004870在调控基因表达方面具有重要作用,当抑制circ0004870的表达时,会导致宿主基因RBM39(一种富含丝氨酸/精氨酸的RNA结合蛋白编码基因)的表达降低,从而调控AR-V7,增加对

Enz的治疗抵抗^[33]。与circ0004870的作用不同,circRNA17(hsa_circ_0001427)是一种特殊的RNA分子,它可以改变miR-181c-5p的表达,而miR-181c-5p能够直接结合AR-V7的3'UTR,因此circRNA17可以被视为一种抑制因子,通过调控miR-181c-5p/AR-V7轴,增加PCa细胞对Enz敏感性^[34]。

2.6 CircRNA通过Wnt/ β -catenin通路介导Enz治疗抵抗

Wnt信号通路在PCa中具有复杂的作用,并可能成为药物治疗的靶点。Wnt信号通路的激活需要Wnt配体与跨膜受体卷曲蛋白和辅助受体形成复合物,从而诱导Wnt信号传导。在信号传导过程中, β -catenin易位到细胞核,刺激并参与癌症进展的下游靶点。在正常情况下,糖原合成酶激酶-3 β (glycogen synthase kinase-3 β , GSK-3 β)会参与降解 β -catenin,抑制其向细胞核易位,进而抑制Wnt信号通路的激活^[35,36]。然而,在某些情况下,Wnt信号通路会被过度激活,导致 β -catenin在细胞核中积累,进而影响PCa细胞的增殖、分化和EMT^[37]。

CircPHF16是一种分布在细胞质和细胞核中的circRNA,与正常组织相比,它在PCa细胞中表达下调。CircPHF16可以海绵吸附miR-581以调节RNF128(一种E3泛素连接酶)的表达。通过这种方式,circPHF16可以抑制Wnt/ β -catenin途径,从而影响PCa细胞对Enz的敏感性。这表明circPHF16可能作为克服Enz治疗抵抗的新治疗靶点^[38]。

2.7 CircRNA通过自噬介导Enz治疗抵抗

自噬是一个高度保守的分解代谢过程,对细胞的生存和稳态起着至关重要的作用。它通过回收细胞内的蛋白质和细胞器来提供能量和物质,帮助细胞在缺氧、饥饿和药物应激等不利环境下存活。然而,过度激活的自噬也会消耗细胞内的物质,导致细胞死亡^[39-41]。在肿瘤治疗中,有研究显示,自噬可通过激活AMP活化蛋白激酶和抑制mTOR途径减少药物的积累或增加药物的泵出,从而减少药物对细胞的效应,这可能是一种细胞对抗药物应激的适应机制^[42]。

Zhong等^[43]发现,在PCa中,所有自噬相关的circRNA的表达水平均下调。进一步的实验证明,circ0001747能通过抑制自噬激活来抑制PCa细胞的增殖。然而,对于circ0001747调节自噬的特异性

机制, 仍然需要进一步的研究。这可能涉及分子信号通路和调控因子, 以便更好地理解circ0001747的作用机制。

2.8 CircRNA通过海绵miRNA介导Enz治疗抵抗

在肿瘤中, 某些circRNA通过与特定的miRNA结合, 抑制miRNA对关键基因的调控作用, 从而对肿瘤细胞的治疗敏感性产生影响。

由EIF4A3和LEF1介导的circRAB3IP通过吸附miR-133a-3p和miR-133b来调节血清和糖皮质激素诱导蛋白激酶1(serum and glucocorticoid-regulated kinase 1, SGK1)的表达, 促进Enz的治疗抵抗^[44]。CircUCK2已被发现通过海绵化miR-767-5p, 减少了miR-767-5p与TET1的结合效率, 导致TET1的表达上调, 抑制PCa耐药细胞的增殖和侵袭^[45]。此外, 研究发现, circ0001275在Enz耐药细胞系中高度上调, 其过表达可增加PCa细胞对Enz的治疗抵抗^[46]。然而, 关于circ0001275在Enz耐药机制中的具体作用和调控机制目前尚不完全清楚。

3 CircRNA与前列腺癌对多西他赛化疗的治疗抵抗

多西他赛(Docetaxel, DTX)是紫杉烷家族的第二代化疗药物, 它的作用机制主要是抑制微管的分解和调节AR的转录。此外, DTX还可以干扰雄激素和配体依赖的信号通路来阻止AR向细胞核易位, 并通过结合基因启动子降低AR的表达和上调AR的转录抑制因子FOXO1的表达, 从而抑制雄激素介导的PCa细胞的生长和转移^[47-49]。尽管DTX的作用机制多样, 但仍然存在患者对该药物产生耐药的情况, 因此了解DTX治疗抵抗的潜在机制对于改善PCa患者的预后至关重要。

3.1 CircRNA通过糖酵解介导DTX治疗抵抗

肿瘤细胞在糖酵解过程中会产生过量的乳酸, 这可能与肿瘤细胞的干性(干性是指细胞具有干性的特征: 细胞增殖能力强、耐受外界环境变化能力强)有关。研究发现, 过量的乳酸积累在肿瘤微环境中会导致酸化, 并参与调节肿瘤细胞的生物学行为和化疗耐药性^[50]。其中, 乳酸脱氢酶A(lactate dehydrogenase A, LDHA)被认为是催化乳酸生成的关键酶。有研究已经证明, 抑制LDHA表达可增加PCa细胞对DTX的敏感性^[51]。

CircARHGAP29是一种由ARHGAP29基因环化产生的circRNA, EIF4A3通过结合circARHGAP29的后剪接连接位点和下游侧链序列, 诱导其环化和胞质输出。环化后的circARHGAP29在细胞中发挥多个功能。首先, 它通过加强与IGF2BP2蛋白(胰岛素样生长因子2-mRNA结合蛋白2)的相互作用, 增强LDHA的稳定性, 从而增加了PCa细胞对DTX的治疗抵抗和糖酵解代谢。此外, circARHGAP29还可以稳定c-Myc基因的mRNA和蛋白质水平, 使LDHA基因的表达增加^[52]。

3.2 CircRNA通过有丝分裂机制介导DTX治疗抵抗

DTX能以高亲和力与 β -微管蛋白结合, 破坏微管动力学, 从而影响有丝分裂期间的细胞骨架功能。最近, 染色体移动复合体(chromosomal passenger complex, CPC)被证实有助于纠正有丝分裂过程中的染色体错位, 并且还能增加微管靶向药物的作用, 表明有丝分裂纠错机制可能是参与DTX治疗抵抗的机制之一^[53]。

Chen等^[54]研究发现, circ0004087能与转录共激活因子SND1结合, 刺激MYB的反式激活, 进一步增强下游靶点BUB1的表达。BUB1是一个重要的调节因子, 参与了有丝分裂过程中的染色体错位纠正。增加BUB1的表达有助于将CPC招募到着丝粒, 确保PCa细胞的无错误有丝分裂。这个过程最终导致了PCa细胞对DTX的治疗抵抗, 因为CPC的强化和正常有丝分裂的发生使细胞能够更好地应对DTX的杀伤作用。

3.3 CircRNA表达上调介导DTX治疗抵抗

小脑锌指蛋白2(Zinc finger of the cerebellum 2, ZIC2)的水平降低可抑制PCa细胞的转化, 包括EMT以及血管生成^[55,56]。CircDPP4(hsa_circ_0056881)的上调可使PCa细胞中的miR-564脱离与ZIC2的结合, 导致细胞过度增殖和迁移/侵袭, 同时降低DTX细胞毒性^[57]。乙醛脱氢酶家族1-A3(aldehyde dehydrogenase 1-A3, ALDH1A3)是乙醛脱氢酶家族的重要成员之一, 它可将乙醛氧化为乙酸, 参与醛类物质的解毒过程。CircCYP24A(has_circ_0060927)是一种能调节ALDH1A3表达的circRNA, 它通过海绵化miR-1301-3p调节ALDH1A3的表达。另外, circCYP24A还通过激活

PI3K/AKT/mTOR信号通路来调节ALDH1A3的表达。最后,这项研究表明,circCYP24A通过上调ALDH1A3表达来增加PCa细胞对DTX的治疗抵抗^[58]。

肿瘤蛋白D52(tumor protein D52, *TPD52*)作为促癌基因,在包括PCa在内的许多肿瘤中均表达上调。据报道,TPD52可通过抑制LKB1/AMPK介导的自噬来增加PCa细胞对DTX的治疗抵抗^[59]。而circXIAP已被证实通过海绵miR-1182来调节TPD52的表达,促进DTX治疗抵抗^[60]。另一项研究表明,circ0000735在抗DTX的PCa组织和细胞中上调,通过抑制circ0000735的表达,可以降低其对miR-7的吸附能力,提高PCa细胞对DTX的敏感性^[61]。此外,circ0057558通过海绵化miR-206,正向调控泛素特异性蛋白酶33(ubiquitin-specific peptidase 33, USP33)的转录。USP33作为一种去泛素化酶,能够结合和去泛素化c-Myc,从而促进PCa细胞的增殖和细胞周期转变,降低其对DTX的敏感性^[62]。

3.4 CircRNA表达下调介导DTX治疗抵抗

Krüppel样因子5(Krüppel-like factor 5, KLF5)是一种位于细胞核的锌指转录因子,可调控多种基因的表达,影响肿瘤细胞的多种功能。研究发现,KLF5可通过抑制细胞自噬来增强PCa细胞对DTX的敏感性^[63]。CircCRKL(*hsa_circ_0001206*)被证实PCa细胞中表达下调,然而,当circCRKL过表达时,它能够作为miR-141的海绵,上调KLF5表达,从而增加PCa细胞对DTX敏感性,表明CircCRKL可能是PCa治疗的潜在治疗靶点^[64]。

CircFoxo3(*has_circ_0006404*)是目前研究最多的circRNAs之一,它在PCa中的表达增加可抑制肿瘤进展,而表达减少则促进肿瘤进展,表明circFoxo3可作为诊断PCa的生物标志物。Shen等^[65]研究发现,circFoxo3通过海绵miRNA增强Foxo3的表达,从而促进细胞凋亡并抑制PCa的进展,而沉默circFoxo3会通过增强EMT来增加PCa细胞对DTX的治疗抵抗。

4 CircRNA与前列腺癌对放射治疗的治疗抵抗

放射治疗是治疗PCa的一种重要手段。然而,

部分PCa患者在接受放疗后仍然出现复发,这可能是由于PCa细胞对放疗产生了抵抗。因此,有必要进一步了解PCa细胞对放疗产生治疗抵抗的机制。

4.1 CircRNA通过自噬介导放疗抵抗

自噬是调节细胞信号和维持体内平衡的细胞过程,它的调控与癌细胞的放疗敏感性密切相关^[66]。Cai等^[67]的研究表明,circCCNB2(*hsa_circ_0035483*)在抗辐射的PCa组织和细胞中过表达。下调circCCNB2可以通过miR-30b-5P/KIF18A轴抑制自噬过程,从而增强PCa细胞对放疗的敏感性。此外,该研究还表明,circCCNB2可能作为PCa细胞对放疗抵抗的预测标志物。因此,抑制circCCNB2的表达被认为具有放射增敏作用,可以提高PCa患者对放疗的治疗效果。

4.2 CircRNA通过糖酵解介导放疗抵抗

CircRNA的异常表达与放疗抵抗和糖酵解之间存在一定的关联。Du等^[68]发现,沉默circZNF609可以提高放疗的敏感性,而且在使用2-DG(糖酵解抑制剂)抑制有氧糖酵解的同时,也能改善放疗抵抗。该研究还发现,circZNF609能作为miR-501-3p的分子海绵,上调糖酵解关键酶己糖激酶2(HK2)的表达,提高PCa细胞的放疗抵抗。而在另一项研究中,circLPAR3也被证实与放疗和糖酵解密切相关,circLPAR3通过结合和抑制miR-513b-5p的活性,导致*JPTI*(一种影响细胞凋亡和信号转导的蛋白编码基因)过度表达,进而增强PCa细胞对糖酵解的依赖性,并减弱了放疗的敏感性^[69]。

4.3 CircRNA通过miRNA介导放疗抵抗

CircABCC4在PCa中作为癌基因发挥作用(表1)。它在PCa患者体内富集并与临床病理特征密切相关,提示circABCC4可以作为一种新的预后指标。CircABCC4通过海绵miR-1253和增加SRY-box转录因子4(SRY-box transcription factor 4, SOX4)表达,促进了PCa细胞的增殖、侵袭和放疗抵抗,并阻碍细胞凋亡。因此,高表达的circABCC4和SOX4可能成为PCa细胞放疗抵抗的新标志物^[70]。与circABCC4作用途径不同,circ0062020通过miR-615-5P/TRIP13轴调节PCa细胞对放疗的敏感性^[71]。

5 总结与展望

本文综述了circRNA与PCa在NHT治疗、DTX

表 1 不同circRNA在PCa中的治疗抵抗作用

CircRNA	表达水平	影响	抵抗作用	作用途径	参考文献
CircEZH2 ^{E2/E3}	上调	Enz	促进	调控miR-363/miR-708轴	[14]
CircTRPS1	上调	Enz	促进	调控miR-124-3p/EZH2轴	[15]
Circ0016068	上调	Enz	促进	调控miR-330-3p/BMI-1轴	[20]
CircMID1	上调	Enz	促进	调控miR-330-3p/YTHDC2/IGF1R/AKT轴	[23]
Circ0057553	上调	Enz	促进	调控miR-515-5p/YES1轴	[25]
CircRBM33	上调	Enz	促进	调控PDHA1介导线粒体氧化磷酸化	[30]
Circ0004870	下调	Enz	促进	调控AR-V7表达	[33]
CircRNA17	下调	Enz	抑制	调控miR-181c-5p/AR-V7轴	[34]
CircPHF16	下调	Enz	抑制	调控miR-581/RNF128/Wnt/ β -catenin轴	[38]
Circ0001747	下调	Enz	抑制	抑制自噬活化	[43]
CircRAB3IP	上调	Enz	促进	调控miR-133a-3p/miR-133b/SGK1轴	[44]
CircUCK2	下调	Enz	抑制	调控miR-767-5p/TET1轴	[45]
Circ0001275	上调	Enz	促进	在Enz耐药细胞系中高度上调	[46]
CircARHGAP29	上调	DTX	促进	调控IGF2BP2/c-Myc/LDHA轴	[52]
Circ0004087	上调	DTX	促进	调控SND1/MYB/BUB1轴	[54]
CircDPP4	上调	DTX	促进	调控miR-564/ZIC2轴	[57]
CircCYP24A	上调	DTX	促进	上调ALDH1A3表达	[58]
CircXIAP	上调	DTX	促进	调控miR-1182/TPD52轴	[60]
Circ0057558	上调	DTX	促进	调控miR-206/USP33/c-Myc轴	[61]
CircCRKL	下调	DTX	促进	调控miR-141/KLF5轴	[64]
CircFoxo3	下调	DTX	抑制	调控Foxo3/EMT轴	[65]
CircCCNB2	上调	放疗	促进	调控miR-30b-5p/KIF18A轴	[67]
CircZNF609	上调	放疗	促进	调控miR-501-3P/HK2轴	[68]
CircLPAR3	上调	放疗	促进	调控miRNA-513b-5p/JPT1	[69]
CircABCC4	上调	放疗	促进	调控miR-1253/SOX4轴	[70]
Circ0062020	上调	放疗	促进	调控miR-615-5P/TRIP13轴	[71]

化疗以及放射治疗中产生治疗抵抗的相关研究，如表1所示。这些研究揭示了circRNA在PCa治疗抵抗中的作用。这些研究也许有助于改善PCa患者的临床诊治结果。例如，将circRNA作为PCa对治疗反应的生物标志物，可能有助于早期识别潜在的治疗抵抗类型，帮助临床医生选择合适的治疗方法。或者针对这些circRNA开展一些靶向治疗措施，也可能有助于逆转治疗抵抗的发生。然而，目前仍有诸多问题未能得到有效解决，如PCa存在较高的肿瘤异质性、多种抵抗机制可能同时存在、尚不清楚这些circRNA是否存在关键驱动因子等。虽然两者之间还存在许多挑战，但随着研究的深入，circRNA在PCa治疗抵抗中有望展现出更多的临床应用前景。

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