环状RNA对自噬和癌症进展的影响

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摘要 环状RNA(circular RNA, circRNA)是近年来引起广泛关注的非编码RNA。由于其独特的闭环结构, circRNA在细胞中具有高度稳定性。自噬是一种分解代谢过程, 有助于细胞中有害或无关紧要的生物大分子的降解和再循环, 并使细胞能够适应内外环境的压力和变化。有证据表明, circRNA通过调节自噬来影响癌症的进程, 这表明自噬参与各种癌症的发生和发展, 并可能影响耐药性。该文总结了circRNAs在自噬中的作用及其对肿瘤发生和进展以及耐药性的影响。

关键词 circRNA; 自噬; 肿瘤

Effects of CircRNA on Autophagy and Cancer Progression

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Abstract CircRNA (circular RNA) is a non-coding RNA that has attracted much attention in recent years. circRNAs are highly stable in cells due to their unique closed-loop structure. Autophagy is a catabolic process that contributes to the degradation and recirculation of harmful or insignificant biomolecules in cells and enables cells to adapt to stresses and changes in the internal and external environments. There is evidence that circRNAs influence cancer progression by regulating autophagy, suggesting that autophagy is involved in the development and progression of various cancers and may influence drug resistance. The role of circRNAs in autophagy and its effects on tumorigenesis, progression and drug resistance were reviewed.

Keywords circRNA; autophagy; tumour

由于环状RNA(circular RNA, circRNA)和自噬在癌症的发生和进展中都起着至关重要的作用, 它们之间的调控关系正受到越来越多的关注。随着生物学和医学的发展, 越来越多的circRNA通过竞争内源性RNA(competitive endogenous RNA, ceRNA)机制或非ceRNA机制影响自噬进而促进或抑制肿瘤发生、发展。因此, 在本综述中, 我们重点介绍了circRNA在调节癌症自噬中的功能和机制最新进展。这些自噬相关的circRNA通过激活或抑制自噬, 影响各种癌症发生和发展。

1 circRNA概述

circRNA属于特殊的非编码RNA, 不具有5′末端帽子和3′末端ploy(A)尾, 呈封闭环状结构, 不受

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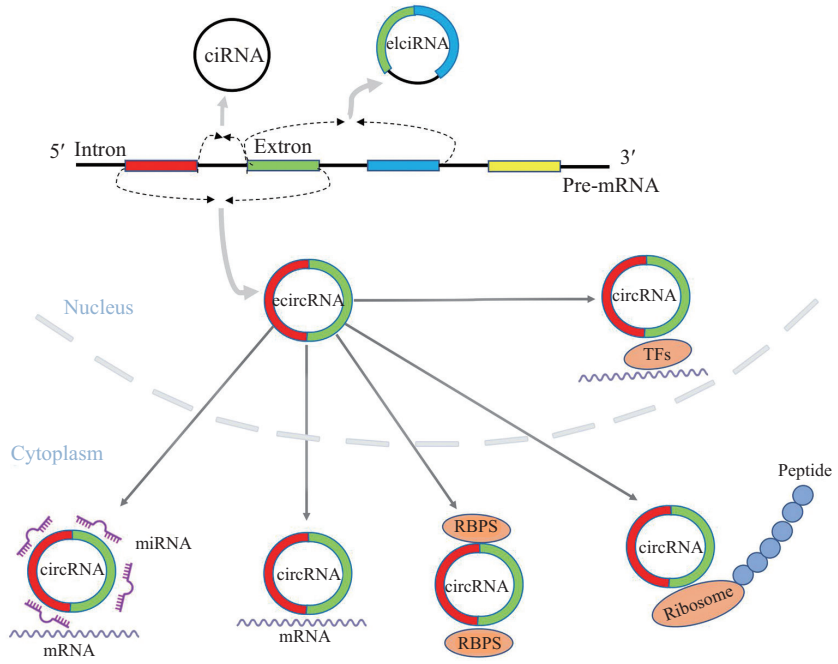

图1 circRNAs的生物学功能示意图

Fig.1 Schematic diagram of biological function of circRNAs

RNA外切酶的影响, 表达更稳定, 不易被降解[1]。根据其组成, circRNA可分为三种不同类型: 外显子circRNA(exon circular RNA, ecircRNA)、内含子circRNA(intron circular RNA, ciRNA)、外显子–内含子circRNA(exon-intron circular RNA, elciRNA)[2]。circRNA以前被认为是转录副产物, 无功能[3], 随着研究的深入和技术的发展, circRNA已被证明在癌症生物学中具有关键的调节作用[4-5]。目前已知circRNA主要功能为miRNA海绵功能、结合亲本基因、结合转录因子、与蛋白质之间的相互作用和编码蛋白质等[6](图1)。有研究表明, circRNA介导的自噬对肿瘤的发生、发展和耐药性至关重要[7]。尽管如前所述, circRNA可通过多种机制驱动其生物学功能, 但目前的研究主要集中在通过ceRNA机制调节自噬。

2 自噬概述

自噬是细胞吞噬和自我消化的过程, 可分为宏观自噬(巨自噬)、微自噬和伴侣介导的自噬, 其中巨自噬是最常见的自噬类型[8]。自噬过程取决于膜上不同复合物的形成, 可分为起始、成核、伸长、自噬体–溶酶体融合和降解[9]。调节自噬的细胞内信号通路可以抑制或激活自噬, AMPK[10-12]、PI3K-AKT-mTOR[13]、MAPK/ERK[14]、BCL2[15]通过影响关键蛋白如ULK1复合物、PI3K复合物, ATG蛋白家族和LC3-II的表达来调节自噬[16](图2)。迄今为止, 自噬在癌症发展中的作用仍然存在争议。一方面, 自噬通过维持基因组稳定性和细胞代谢的稳态来抑制肿瘤发生。另一方面, 它参与癌症建立后的细胞微环境重编程, 并保护癌细胞免受各种生存应激[17]。此外, 越来越多的证据表明circRNA在自噬调节中起着双重作用。因此, 阐明circRNA如何调节自噬以及circRNA介导的自噬如何影响肿瘤发生和进展有助于开发新的基于circRNA的癌症治疗策略。

3 环状RNA介导自噬在消化系统恶性肿瘤中的作用

3.1 胃癌

近几年研究发现, circRNA通过海绵化miRNA来调节靶基因, 从而参与胃癌(gastric cancer, GC)发展。例如, circUBE2Q2可以通过海绵miR-370-3p和激活信号转导及转录激活蛋白3(signal transducer and activator of transcription 3, STAT3)途径抑制自噬并促进胃癌细胞增殖和迁移[18]。hsa_circ_0006470通过靶向miR-27b-3p上调磷脂酰肌醇-3-激酶催化亚单位α(phosphatidylinositol-3-kinase catalytic subunit α, PI3KCA)和抑制自噬来促进GC细胞增殖和迁移[19]。circRELL1通过circRELL1/miR-637/肌酐蛋白B受体3(recombinant ephrin type B receptor 3, EPHB3)轴激

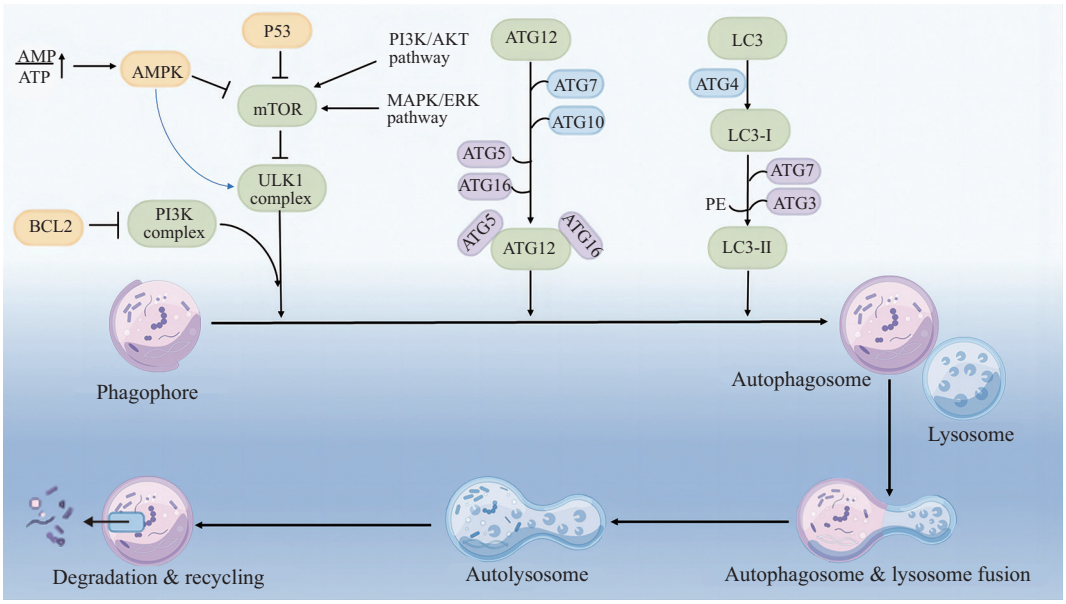

图2　自噬过程和调控的信号通路示意图

Fig.2　Schematic diagram of autophagy processes and regulatory signaling pathways

活自噬抑制GC的进展[20]。化学治疗是胃癌患者最主要的化疗策略之一, 化疗耐药是导致患者预后不良的主要原因。有研究表明, circCUL2作为miR-142-3p海绵来调节Rho相关卷曲螺旋蛋白激酶2(Rho associated coiled coil forming protein kinase 2, ROCK2), 进而抑制自噬, 增强肿瘤细胞顺铂敏感性[21]。另有研究发现, circCPM通过靶向miR-21-3p促进AMP激活蛋白激酶α2(AMP-activated protein kinase catalytic subunit alpha-2, *PRKAA2*)基因翻译来增强自噬水平, 从而增强体内GC 5-氟尿嘧啶(5-fluorouracil, 5-FU)化学耐药性。这些发现表明, circRNA可能是关键的自噬调节因子和GC的潜在治疗靶点, 并有望成为检测胃癌的生物标志物之一。

3.2　结直肠癌

研究表明, 一些自噬相关基因*LC3-II*、*Beclin1*、*ATG10*和*ATG5*在结直肠癌(colorectal cancer, CRC)中的过表达与CRC患者的癌症转移和预后不良有关[22-23]。例如, CircHADHA通过miR-361调节结肠上皮细胞和癌细胞中的ATG13来促进自噬, 抑制CRC的增殖[24]。circRNA_103948通过靶向miR-1236-3p/肿瘤翻译调控蛋白1(tumor protein translationally-controlled 1, TPT1)轴抑制自噬进而促进CRC细胞增殖、侵袭和转移[25]。circUBAP2在CRC组织和细胞系中上调, 通过circUBAP2/miR-582-5p/FOXO1轴诱导体外和体内自噬, 促进CRC增殖、侵袭和迁移[26]。因此, 预测更多与自噬通量相关的circRNA并深入了解其调控机制有助于为临床上CRC治疗策略奠定基础。

3.3　肝细胞癌

circRNA/自噬轴是肝细胞癌(hepatocellular carcinoma, HCC)进展的调节因子。circCBFB抑制miR-424-5p并上调自噬相关蛋白ATG14表达, 从而促进HCC细胞增殖和自噬[27]。circMDK可作为一种潜在的肿瘤生物标志物, 通过海绵miR-346和miR-874-3p上调ATG16L1, 导致PI3K/AKT/mTOR信号通路的激活, 以促进HCC细胞增殖、迁移和侵袭[28]。ZHANG等[29]发现, circ-SPECC1通过吸附miR-33a来调节氧化应激下的转化生长因子β2(transforming growth factor β2, TGFβ2)和自噬, 促进HCC细胞增殖。据报道circ-101280通过海绵miR-375促进HCC细胞中的细胞增殖[30]。在另一项研究中, miR-375在缺氧条件下抑制HCC细胞的自噬[31]。这表明, circ-101280的抗肿瘤作用可能通过促进自噬来实现, 还需要进一步研究支持此观点。这些研究提示靶向circRNA有利于HCC治疗, 例如, 芦荟素是一种新兴的抗肿瘤药物, 其抑制Circ-0011385的表达从而上调miR-149-5p。然后, 肾母细胞瘤基因(wilms tumor1, *WT1*)下调, 诱导细胞凋亡和自噬来延缓HCC进展。

3.4　胰腺癌

为了阐明胰腺癌(pancreatic cancer, PC)进展的机制, HE等[32]发现circATG7通过靶向miR-766-5p进

而上调亲本基因*ATG7*表达以促进PC增殖和转移, 所以, 靶向circATG7可能是PC患者的潜在治疗策略。另外, circRHOBTB3在胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)细胞系和组织中高表达, 在机制上, circRHOBTB3直接与miR-600结合, 随后其充当miRNA海绵以维持miR-600靶向转录因子伏隔核相关蛋白1(nucleus accumbens associated 1, NACC1)的表达水平, 从而促进PDAC细胞的自噬反应, 进而通过Akt/mTOR途径促进PDAC增殖[33]。因此, 调节自噬的circRNA在PC治疗领域具有重要意义。

4 环状RNA介导自噬在泌尿和生殖系统恶性肿瘤中的作用

4.1 前列腺癌和膀胱癌

最近的一项研究表明, 敲除ATG7可抑制前列腺癌(prostate cancer, PCA)进展, 这表明功能失调的自噬可能与前列腺癌的进展有关[34]。早期生长反应因子1(early growth response factor 1, *EGR1*)在前列腺癌中作为癌基因, 通过转录影响自噬相关基因(包括*LC3B*)的表达来调节自噬[35]。LU等[36]研究证实, circCSPP1通过miR-520h/EGR1轴促进前列腺癌细胞自噬、增殖、侵袭和转移。circ_0004585通过靶向miR-1248/跨膜9超族蛋白成员4(trans-membrane 9 superfamily protein member 4, TM9SF4)轴在PCA侵袭和转移过程中发挥致癌作用, TM9SF4通过mTOR磷酸化激活自噬, 促进PCA细胞抗性[37]。研究证明hsa_circ_0007813在膀胱癌中表达上调, 可以通过海绵miR-361-3p调节胰岛素样生长因子2受体(insulin-like growth factor 2 receptor, IGF2R)表达, IGF2R被发现参与自噬和肿瘤生物学, 因此, 敲低hsa_circ_0007813可以抑制膀胱癌的致瘤特性以及肿瘤细胞自噬[38]。

4.2 宫颈癌

在宫颈癌(cervical cancer, CC)中, E26转录因子1(E-twenty six transcription factor 1, *ELK1*)作为癌基因发挥作用, TANG等[39]强调hsa_circ_0000515能够作为miR-326的ceRNA上调ELK1, 导致CC细胞的增殖和侵袭能力增强, 但hsa_circ_0000515抑制了细胞的凋亡和自噬, 该研究为靶向hsa_circ_0000515治疗CC提供了证据。同样, circ_0000285通过靶向miR197-3p调节ELK1, 抑制CC细胞的自噬, 促进其增殖[40]。hsa_circ_0023404通过抑制自噬诱导的细胞凋亡来促进CC细胞的转移和化学耐药性, 其机制可能为hsa_circ_0023404与miR-5047相互作用, miR-5047通过调节转录因子进而调节血管内皮生长因子A(vascular endothelial growth factor A, VEGFA)、Beclin1及p62表达[41]。

4.3 卵巢癌

卵巢上皮癌(epithelial ovarian carcinoma, EOC)是最常见的妇科恶性肿瘤之一, 死亡率高。研究表明, circMUC16介导的自噬增加了细胞增殖和迁移的速度, 其通过海绵miR-199a-5p调节Beclin1或Runt相关转录因子1(Runt-associated transcription factor 1, RUNX1)表达[42]; 另有研究发现circRAB11FIP1通过海绵miR-129调节ATG7和ATG14促进EOC细胞自噬, 增加了SKOV3和A2780细胞的增殖和迁移速度[43]。circEEF2通过与miR-6881-3p和膜联蛋白A7(annexin A7, ANXA7)相互作用促进EOC的自噬、增殖和侵袭, 从机制上讲, circEEF2海绵miR-6881-3p, 上调靶基因*ATG5*和*ATG7*表达, 此外, circEEF2可直接与ANXA2结合抑制mTOR的磷酸化[44]。CircRNF144B通过海绵miR-342-3p提高了F-box和富含亮氨酸的重复蛋白11(F-box and leucine -rich repeat protein 11, FBXL11)水平, 而升高的FBXL11促进了Beclin-1的泛素化和蛋白质降解, 从而抑制了自噬通量, 促进了卵巢癌的进展[45]。总而言之, circRNA调控EOC增殖和侵袭与自噬的发生密切相关。

5 环状RNA介导自噬在其他恶性肿瘤中的作用

5.1 肺癌

非小细胞肺癌(non small cell lung cancer, NSCLC)是全球死亡率最高的癌症[46]。circ-FOXM1通过调节miR-149-5p/ATG5轴加速NSCLC的发展, 并促进NSCLC细胞自噬[47]。circHIPK3作为癌基因促进NSCLC增殖、侵袭和迁移, 并通过海绵miR-124-3p调节自噬诱导细胞系(A549和H838)中的STAT3/PRKAA途径抑制自噬[48]。Circ_0020123通过吸附miR-193a-3p上调干扰素调节因子4(interferon regulatory factor 4, IRF4)的表达, 在体外抑制NSCLC细胞凋亡和自噬并促进肿瘤细胞增殖、迁移和糖酵解[49]。circRNA_100565是NSCLC患者生存的独立预后因素, 通过miR-337-3p/去整合素–金属蛋白酶

28(disintegrin and metallopro teinase 28, ADAM28)轴调节细胞增殖、凋亡和自噬, 增强NSCLC细胞对顺铂的耐药性, 为提高NSCLC化疗疗效的新型治疗策略提供了思路[50]。

5.2 乳腺癌

虽然circRNA和自噬都与乳腺癌(breast cancer, BC)的生物学行为有关, 但circRNA是否通过自噬调节BC进展仍在探索中。其中circCDYL通过自噬通量的增加促进BC的进展, 机制上, circCDYL通过miR-1275/ATG7/ULK1自噬轴调节乳腺癌细胞的增殖[51]。circSEPT9通过circSEPT9/miR-637/白血病抑制因子(leukemia inhibitory factor, LIF)信号通路抑制自噬并促进三阴性乳腺癌(triple negative breast cancer, TNBC)增殖、侵袭和迁移[52]。Circ-ABCB10通过let-7a-5p/双特异性磷酸酶(dual specificity phosphatase 7, DUSP7)轴介导BC细胞的紫杉醇抗性、凋亡、侵袭和自噬[53]。以上均提示, circRNA不仅可以作为潜在的预后标志物, 还可以作为BC的治疗靶点。

5.3 血液恶性肿瘤

最近两种类型白血病的研究也报道了circRNA和自噬之间的关系。在急性髓系白血病(acute myeloid leukemia, AML)中, circPAN3很可能是多柔比星耐药的关键调节剂, 其通过AMPK/mTOR途径调节自噬, 作为自噬诱导剂来促进AML细胞的耐药性[54]。在慢性粒细胞白血病(chronic myeloid leukemia, CML)中, 沉默circ_0009910导致*ULK1*下调, *ULK1*是一种在伊马替尼(imatinib, IM)抗性K562细胞中过表达的自噬启动子, 进一步证实circ_0009910可以通过海绵miR-34a-5p激活ULK1诱导的自噬, 从而促进CML细胞的IM抵抗[55]。虽然对肿瘤自噬中的circRNA的研究仍处于起步阶段, 但这将为未来血液恶性肿瘤的诊断和治疗带来新的机遇。

6 环状RNA的其他功能

circRNA除了有以上miRNA海绵功能外, 还有编码蛋白质功能。其中, circATG4B-222aa是circATG4B编码的一种新型蛋白质, circATG4B-222aa作为诱饵与跨膜emp24样运输蛋白10(transmembrane emp24-like trafficking protein 10, TMED10)竞争性相互作用并阻止TMED10与ATG4B结合, 从而导致自噬增加, 然后导致CRC对奥沙利铂耐药。因此, 外泌体circATG4B为CRC中化学耐药的潜在治疗靶点提供了新的依据[56]。circMUC16是潜在EOC的治疗靶点和诊断标志物, 其可直接与ATG13蛋白结合, 进而促进细胞自噬[42]。另外, circRNA可以与蛋白质相互作用, 例如, ZHU等[57]研究结果表明, circTICRR在宫颈癌中充当癌基因, 抑制自噬和细胞凋亡, 促进CC细胞增殖, circTICRR和人抗原R(human antigen R, HuR)蛋白之间的相互作用位点可能作为宫颈癌治疗的潜在靶标。circ-DNMT1可以结合并调节BC细胞中的致癌蛋白p53和AU碱基富集元件RNA结合因子1(AU-rich element RNA-binding factor 1, AUF1)的表达, 促进两种蛋白质的核易位, 诱导细胞自噬以促进BC细胞的增殖[58]。同时, circRNA的表达还受转录因子的调控, 例如, 在EOC中, RUNX1可以反过来促进circMUC16的转录, 进一步诱导EOC细胞自噬[42]。

7 总结与展望

本文总结了circRNA通过多种信号通路以及不同的生物学功能(miRNA海绵、结合转录因子、与蛋白质之间相互作用以及编码蛋白质)参与自噬的调节, circRNA介导的自噬在肿瘤进展的多个方面发挥着至关重要的作用, 表现出促进和抑制肿瘤作用。不难发现, 大多数促癌的circRNA也促进肿瘤细胞自噬, 而肿瘤抑制性circRNA通常抑制自噬, 但也有通过抑制自噬促进肿瘤进展和化学耐药性。所以, 自噬对肿瘤发生和进展的影响可能取决于肿瘤类型、细胞的遗传背景和特定类型的细胞应激。因此, 了解circRNA如何调节自噬过程以及自噬如何影响肿瘤发生的机制对于开发基于circRNA的癌症治疗策略非常重要。

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