环状RNA在阿霉素心脏毒性中的生物学作用

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摘要 环状RNA(circular RNA, circRNA)是一类具有环状结构的非编码RNA分子, 主要是由线性前体mRNA通过反向剪接机制产生的内源性转录物。CircRNA可以通过调节心肌细胞的增殖、迁移、分化、衰老以及凋亡等多种病理生理过程来参与心房颤动、动脉粥样硬化、心肌梗死、心力衰竭、扩张性心肌病和肥厚性心肌病等多种心血管疾病。阿霉素是一种用于抗癌治疗的常用药物, 但其心脏毒性极大地限制了其临床应用。多项研究发现, circRNA与阿霉素心脏毒性之间存在密切联系, 不仅能通过作为竞争性内源RNA及与蛋白质相互作用等分子机制参与阿霉素心脏毒性, 还可能通过参与氧化应激、细胞凋亡、细胞焦亡、细胞自噬和铁死亡等多种细胞生物学过程来影响阿霉素心脏毒性。该文通过描述circRNA的形成过程及生物学功能, 总结其在阿霉素心脏毒性中的生物学作用, 旨在为阿霉素心脏毒性的治疗提供新的研究基础和理论支持。

关键词 环状RNA; 微小RNA; RNA结合蛋白; 阿霉素心脏毒性

The Biological Role of Circular RNA in Doxorubicin-Induced Cardiotoxicity

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Abstract circRNAs (circular RNAs) are a class of non-coding RNA molecules characterized by their covalent circular structure, arising from linear precursor mRNAs via a back-splicing mechanism. These endogenous transcripts have been implicated in the regulation of various pathophysiological processes in cardiomyocytes, such as proliferation, migration, differentiation, senescence, and apoptosis, playing significant roles in cardiovascular diseases including atrial fibrillation, atherosclerosis, myocardial infarction, heart failure, hypertrophic cardiomyopathy, and dilated cardiomyopathy. Doxorubicin, a chemotherapy agent widely used in cancer treatment, is notably limited in clinical application due to its cardiotoxicity. Numerous studies suggest a profound association between circRNAs and doxorubicin-induced cardiotoxicity. They participate not only through molecular mechanisms like acting as competitive endogenous RNAs and interacting with proteins but also by engaging in cellular biological processes

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including oxidative stress, apoptosis, pyroptosis, autophagy, and ferroptosis. This paper provides a detailed account of the formation and biological functions of circRNAs, summarizing their biological roles in doxorubicin-induced cardiotoxicity, thereby offering a novel research foundation and theoretical support for the treatment of doxorubicin-induced cardiotoxicity.

Keywords circular RNA; microRNA; RNA binding-proteins; doxorubicin-induced cardiotoxicity

环状RNA(cicular RNA, circRNA)是一类新型非编码RNA, 是真核细胞中线性前体mRNA反向剪接产生的单链共价闭合环状RNA[1-2]。CircRNA缺乏自由端、5′帽和3′聚A结构, 独特的结构特征使其不易受到核酸酶的降解攻击, 从而在细胞中更稳定地存在[3]。多项研究证明, circRNA在心血管组织中广泛表达, 并与动脉粥样硬化、心肌梗死、心力衰竭、扩张性心肌病和肥厚性心肌病等心血管疾病的发生发展密切相关[4-11]。阿霉素是一种蒽环类的抗肿瘤药物, 广泛应用于乳腺癌、非霍奇金淋巴瘤、软组织肉瘤和急性白血病等肿瘤性疾病, 但可导致心律失常、心肌炎、心肌病、充血性心力衰竭等心血管疾病。因此, 其临床应用受到极大限制[12]。研究发现, circRNA可以通过作为竞争性内源RNA及与蛋白质相互作用的分子机制直接调控阿霉素心脏毒性。此外, circRNA还可能通过参与氧化应激、细胞凋亡、细胞焦亡、细胞自噬和铁死亡等细胞生物学过程调控阿霉素心脏毒性。本文通过介绍circRNA的形成过程和生物学功能, 阐述circRNA与阿霉素心脏毒性的紧密联系, 来总结circRNA参与阿霉素心脏毒性的分子机制和细胞生物学功能, 旨在为circRNA作为阿霉素心脏毒性的诊断及治疗靶点提供理论依据。

1 CircRNA的概述

1.1 CircRNA的形成

CircRNA是一种特殊的非编码RNA, 与线性RNA(通常包括信使RNA和大多数转录产物)不同, circRNA是环状结构而非线性链, 其形成通常涉及反向转录和剪接过程, 分为三种主要结构类型: (1) ecircRNA(exonic circRNA), ecircRNA是通过背剪接而非常规线性剪接将mRNA前体一个外显子上的5′端与另一个外显子上的3′端连接在一起形成的封闭的环; (2) ciRNA(intronic circRNA), ciRNA是由一个或多个内含子通过剪接形成的环状结构, 可能在调控基因表达方面发挥作用; (3) EIciRNA(exon-intron circRNA), EIciRNA是一种同时包含外显子和内含子序列的混合型circRNA, 具有部分ecircRNA和ciRNA的特点。CircRNA的环状结构使它们相对于线性RNA更加稳定, 不容易受到核酸酶的降解, 因此在细胞中拥有更长的半衰期和更好的稳定性。不同类型的circRNA在不同的病理生理过程中扮演不同的角色[13-15]。

1.2 CircRNA的功能

1.2.1 *作为竞争性内源RNA* miRNA是一种非编码的短小RNA, 在细胞周期、发育、免疫等过程中起着重要的调控作用。CircRNA可以作为miRNA的“海绵”(也可以称作“吸附剂”), 结合并抑制miRNA的功能[16]。CircRNA可以通过与miRNA相互作用调节miRNA对其靶基因的调控, 被称为竞争性内源RNA机制[17]。LIU等[18]发现circRNA75和circRNA72通过吸附于miRNA-200抑制其靶标Toll样蛋白的表达, 最终抑制细胞凋亡。

1.2.2 *调控基因表达* CircRNA通过多种方式调控基因表达, 最新研究发现circRNA可以与RNA结合蛋白(RNA binding proteins, RBPs)相互作用, 调节转录过程, 从而实现对基因表达的精确调控[19]。ABDELMOHSEN等[20]研究发现, circPABPN1可以与RBPs中的人抗原R结合抑制*Pabpn1*的转录, 最终抑制细胞增殖。CHEN等[21]发现环状RNA辅肌动蛋白A4可以吸附于miR-424-5p, 并与Y-box结合蛋白1相互作用激活卷曲蛋白受体7的转录, 从而促进癌细胞的增殖和转移。

1.2.3 *与蛋白质相互作用* 部分circRNA已被发现可以作为蛋白质的分子“诱饵”在细胞中执行特定的功能, 从而影响蛋白质功能。研究发现circ-FOXO3上同时存在双微体2(mouse double-minute 2, MDM2)和P53蛋白的结合位点, 能促使MDM2诱导P53泛素化, 导致P53蛋白的整体降解[22]。此外, 部分circRNA具有开放阅读框, 可以被核糖体翻译成蛋白质[23]。LEGNINI等[24]证明环状RNA锌指蛋白609(circular RNA zinc finger protein 609, circ-ZNF609)包含一个开放的阅读框, 因此, 其可进行翻译从而生成相应的

蛋白。因此, circRNA可通过与相关蛋白相互作用以及翻译为相应蛋白来改变其对应的细胞功能。

2 CircRNA和阿霉素心脏毒性

最新研究发现, circRNA在阿霉素心脏毒性的发生和发展中扮演着重要的角色[25-27]。阿霉素心脏毒性可表现为急性心脏毒性和慢性心脏毒性: 前者表现为短暂性心律失常、心包炎/心肌炎综合征等; 后者表现为心肌病、充血性心力衰竭等, 常发生在治疗第1年内, 属于不可逆性改变[12]。CircRNA通过上述分子功能直接影响阿霉素心脏毒性, 以及可能通过上述分子功能参与氧化应激、细胞凋亡、细胞焦亡、细胞自噬、铁死亡等各种细胞生物学功能, 从而影响阿霉素心脏毒性(表1和图1)[28-38]。

2.1 CircRNA作为内源性RNA影响阿霉素心脏毒性

CircRNA通过作为miRNA的海绵分子通常抑制阿霉素心脏毒性。HAN等[39]研究发现, circITCH作为miR-330-5p的海绵分子, 抑制miR-330-5p对沉默调节性蛋白6、含杆状病毒IAP重复序列蛋白5、肌浆网钙泵2a等抗细胞凋亡蛋白的下调作用, 从而缓解阿霉素诱导的心肌损伤和功能障碍。WANG等[40]研究指出, circArhgap12通过作为miR-135a-5p的海绵分子来抑制其功能, 从而增加具有调节心肌细胞收缩和舒张功能的腺苷酸环化酶1(adenylate cyclase 1, ADCY1)的表达水平, 最终减轻阿霉素诱导的心脏毒性。LI等[41]的研究同样发现, 环状RNA潜在转化生长因子β结合蛋白1通过作为miR-107的海绵分子, 从而提升其靶标ADCY1在心肌细胞中的表达水平, 最终缓解阿霉素诱导的炎症、凋亡和氧化应激。Circ_0001312通过作为miR-409-3p的海绵分子从而促进其靶标高迁移率族蛋白B1的表达, 最终抑制阿霉素诱导的细胞凋亡[42]。然而, SHAO等[43]的研究发现, 环状RNA纺锤体和着丝粒相关蛋白3通过作为miR-1303的海绵分子, 可以提升其靶标Toll样受体4的表达水平, 最终加剧阿霉素心脏毒性。

2.2 CircRNA与蛋白质相互作用影响阿霉素心脏毒性

2.2.1 RBPs CircRNA与RBPs相互作用调节阿霉素诱导的心脏毒性的研究目前主要集中在颤抖蛋白(quaking, QKI)。GUPTA等[8]研究证明下调QKI会使心肌细胞中来自肌联蛋白、*Fhod3*和纹蛋白3等基因的特定circRNA降低, 从而加剧阿霉素诱导的细胞萎缩和凋亡。然而, 这些circRNA和QKI之间的功能关系目前尚未确定。此外, 环状RNA肌联蛋白抑制心肌细胞凋亡潜在机制还有待研究。WANG研究团队[44]发现, 阿霉素通过诱导miR-31-5p表达量的增加来抑制QKI的表达, 从而使抑制心肌细胞凋亡的circPan3形成减少, 最终加剧心脏毒性。CircRNA与RBPs相互作用参与阿霉素心脏毒性有待进一步研究。

2.2.2 细胞凋亡相关蛋白 CircRNA可通过与细胞凋亡相关蛋白结合并改变其活性来调节阿霉素引起的心脏毒性。研究显示, 在阿霉素诱导的心脏毒性条件下, 胰岛素受体(insulin receptor, INSR)信号被阻断, 而circ-INSR通过增加单链DNA结合蛋白1的表达量来稳定线粒体DNA从而调节心肌细胞的凋亡和代谢, 发挥心脏保护作用, 此外, 体外转录的circ-INSR模拟物还可以预防阿霉素诱导心肌细胞凋亡[45-46]。同样, ZENG等[47]表明circ-Amotl1通过与磷酸肌醇依赖性蛋白激酶-1和AKT丝氨酸/苏氨酸激酶1结合从而激活AKT丝氨酸/苏氨酸激酶的磷酸化和核易位, 减少阿霉素诱导的细胞凋亡。然而, 有研究表明阿霉素可增加心肌细胞circ-Foxo3水平, circFoxo3与DNA结合抑制蛋白-1和转录因子E2F1等衰老相关蛋白以及局部黏着斑激酶和缺氧诱导因子-1α等应激相关蛋白相互作用, 并将上述蛋白保留在细胞质中, 阻止其发挥抗衰老和抗应激作用, 最终加剧心肌细胞凋亡[7]。因此, circRNA调节细胞凋亡相关蛋白活性在阿霉素心脏毒性中具有双面性。

2.2.3 CircRNA翻译产物 CircNlgn通过其翻译蛋白Nlgn173参与心脏超负荷诱导的心肌重构[48], 并且XU等[49]通过建立过表达circNlgn的小鼠系发现circNlgn是阿霉素诱导心肌纤维化的介质, circNlgn表达量增加可上调Gadd45b、Sema4C和RAD50的表达, 从而激活P38和c-Jun氨基末端激酶, 最终诱导心肌纤维化, 抑制心功能。此外, circNlgn的翻译蛋白Nlgn173可以结合并激活组蛋白H2AX产生磷酸化组蛋白H2AX, 导致该信号通路中的白介素-1β、白介素-6、白介素-2Rβ、人早期生长反应蛋白1以及人早期生长反应蛋白3的上调, 从而使阿霉素诱导的心肌细胞凋亡水平增加, 并促进阿霉素作用下心脏成纤维细胞的增殖, 促使胶原产生。因此, circNlgn及其自身翻译的蛋白均参与调节阿霉素心脏毒性, 未来有望成为阿霉素心脏毒性的生物学标志物。

表1 环状RNA在阿霉素心脏毒性中的生物学作用

Table 1 Biological roles of circRNA in doxorubicin cardiotoxicity

功能 Function		环状RNA Circular RNA	机制 Mechanisms	参献文献 References
As competing endogenous RNAs		CircITCH	As a sponge for miR-330-5p to upregulate SIRT6, BIRC5 and SERCA2a	[39]
		CircArhgap12	As a sponge for miR-135a-5p to upregulate ADCY1	[40]
		CircSKA3 (circular RNA spindle and kinetochore associated protein 3)	As a sponge for miR-107 to upregulate ADCY1	[41]
		Circ_0001312	As a sponge for miR-409-3p to upregulate HMGB1	[42]
		CircSKA3 (circular RNA spindle and kinetochore associated protein 3)	As a sponge for miR1303 to upregulate TLR4	[43]
Interaction with proteins	RNA binding proteins	CircTTNcircFHOD3circSTRN3 (circular RNA of titin formin homology 2 domain containing 3 and Striatin 3)	Doxorubicin regulates cardiotoxicity by downregulating QKI and thereby negatively regulating the expression of circular RNA of TTN, FHOD3, and STRN3	[8]
		CircPan3	Doxorubicin-induced miR-31-5p up-regulation inhibits circPan3 formation by negatively regulating QKI expression, leading to cardiotoxicity	[44]
	Apoptosis-related proteins	CircINSR (circular RNA insulin receptor)	Interacted with SSBP1 to rescue mitochondrial impairment	[46]
		CircAmotl1	Interacted with PDK1 and AKT1 to facilitate AKT activation and nucleartranslocation	[47]
		Circ-FOXO3	Interacted with the ID-1 and E2F1, as well as FAK and HIF1α, and retaining these proteins in the cytoplasm	[7]
	Translation products of circular RNAs	CircNlgn	CircNlgn translation protein Nlgn173 binds to and activates histone H2AX to produce phosphorylated histone H2AX, resulting in upregulation of IL-1β, IL-6, IL-2Rβ, EGR1 and EGR3	[49]
	RNA N6-adenosine methylation-related proteins	Circ-ZNF609 (circular RNA zinc finger protein 609)	METTL14 positively regulates circ-ZNF609 expression, and circ-ZNF609 negatively regulates FTO expression, thus exacerbating doxorubicin-induced cardiotoxicity	[50]
Oxidative Stress		CircRNF111	(1) As a sponge for miR-140-5p (2) miR-140-5p directly targeted Nrf2 and Sirt2, as a result of Inhibiting the expression levels of HO-1, NQO1 and Gst,	[54-55]
		CircSamd4	CircSamd4 reduced oxidative stress generation by inducing the transportion of the Vcp protein, which downregulated Vdac1 expression and prevented the mPTP from opening	[28]
Apoptosis		Circ_0129657	(1) As a sponge for miR-194-5p (2) miR-194-5p can aggravate doxorubicin induced cardiomyocyte apoptosis	[60-61]
		CircRSF1	As a sponge for miR-135b-5p to upregulate HDAC1	[62]
Pyroptosis		CircUSP9X (circular RNA ubiquitin specific peptidase 9 X-linked gene)	Interacted with EIF4A3 to enhance the GSDMD stability	[32]
		Circ_0090231	As a sponge for miR-635 to upregulate NLRP3	[66]
		CircHMGA2 (circular RNA high mobility group A2)	Promoted NLRP3 expression directly	[67]
		CircHelz	As a sponge for miR-133a-3p to upregulate NLRP3	[68]
		Hsa_Circ_0076631	As a sponge for miR-214-3p to upregulate caspase-1	[69]
		Circ_0071269	As a sponge for miR-145 to upregulate GSDMA	[70]

续表1

功能 Function	环状RNA Circular RNA	机制 Mechanisms	参献文献 References
Autophagy	Circ_101237	As a sponge for Let-7a-5p to upregulate IGF2BP3, thereby increasing IGF-2 expression , finally increase the expression of LC3-II	[76]
	CircPan3	(1) As a sponge for miRNA221 to upregulate FOXO3 and thus promotes the expression of ATG7	[33]
		(2) As a sponge for miRNA421 to upregulate PINK1	[79]
	ACR (autophagy-related circular RNA)	Interacted with DNMT3B and inhibits DNA methylation of *Pink1* promoter, thereby promoting PINK1 expression	[4]
Ferroptosis	Mmu_circ_0000309	As a sponge for miR-188-3p to upregulate GPX4	[35]
	CircIL-4R (circular RNA IL-4 receptor)	As a sponge for miR-541-3p to upregulate GPX4	[85]
	CircRNARHBG	As a sponge for miR-515-5p to upregulate SLC7A11	[86]
	Mmu_circ_0000130	As a sponge for miR-351-5p to upregulate 5-LOX	[87]

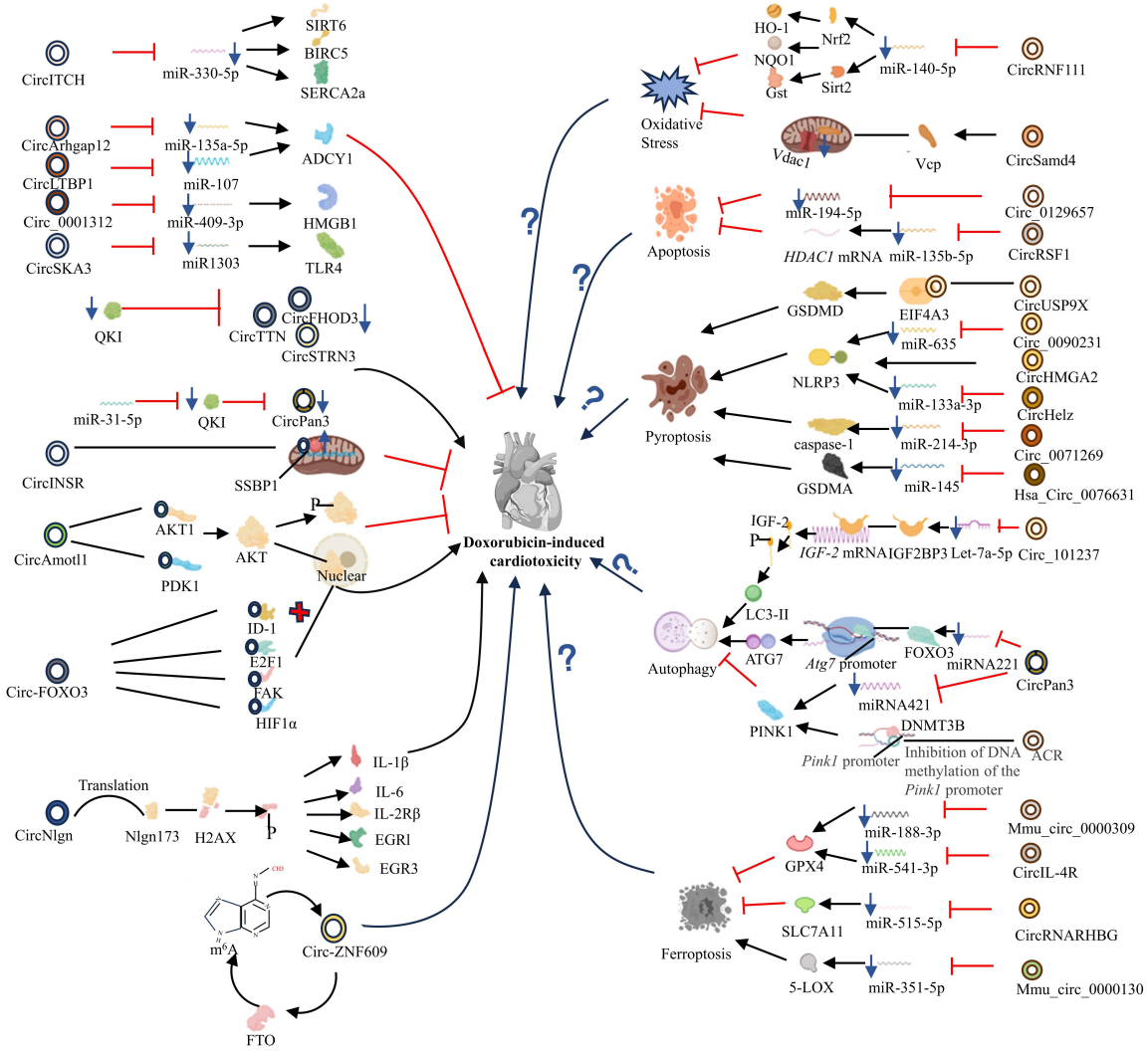
2.2.4 RNA N6-腺苷酸甲基化相关蛋白 CircRNA可以通过作用于RNA N6-腺苷酸甲基化(N6-adenosine methylation, m^{6}A)相关蛋白影响阿霉素心脏毒性。YU等[50]的研究发现, circ-ZNF609通过负调节去甲基化酶肥胖相关蛋白质的表达, 提高阿霉素处理心肌细胞的RNA m^{6}A水平, 进而加剧心肌细胞凋亡。同时, circ-ZNF609受甲基转移酶蛋白14的正向调控, 形成一个前馈机制, 进一步放大RNA m^{6}A水平的变化, 加剧阿霉素诱导的心脏毒性。这一发现揭示了circ-ZNF609在阿霉素心脏毒性中的作用机制, 为开发针对性治疗提供了依据。

2.3 CircRNA调节氧化应激影响阿霉素心脏毒性

氧化应激在阿霉素心脏毒性的发生发展中起着重要作用, 主要表现为心肌细胞氧化和抗氧化体系的失衡[51]。CircRNA可能通过充当氧化还原相关miRNA的海绵分子或者直接调节活性氧的生成来影响阿霉素心脏毒性[28,52-53]。ZANG等[54]的研究证明circ-RNF111通过作为miR-140-5p的海绵分子来抑制miR-140-5p的表达, ZHAO等[55]的研究表明, miR-140-5p通过降低其靶标核因子E2相关因子2和沉默调节性蛋白2的表达水平来抑制血红素氧合酶1、NAD(P)H醌脱氢酶1和谷胱甘肽*S*-转移酶等还原相关酶的表达, 最终促进阿霉素对心肌的氧化损伤, 由此circ-RNF111可能通过充当miR-140-5p的海绵分子, 从而使被miR-140-5p抑制的还原相关酶表达量增多, 最终缓解阿霉素心脏毒性。ZHENG等[28]的研究指出, circSamd4可以促进含缬酪肽蛋白向线粒体转运, 从而下调电压依赖性阴离子通道蛋白1的表达, 阻止线粒体通透性转换孔开放, 从而抑制线粒体来源的活性氧的产生, 减轻线粒体氧化应激和随后的DNA氧化损伤。由此, circSamd4可能通过直接降低氧化应激中的活性氧水平来抑制阿霉素心脏毒性。因此, circRNA可能通过参与氧化应激来调节阿霉素心脏毒性, 但仍需研究人员深入了解circRNA与氧化应激之间的相互作用, 以及它们对阿霉素心脏毒性的调节机制。

2.4 CircRNA调节细胞凋亡影响阿霉素心脏毒性

阿霉素可导致心肌细胞以及与心肌修复相关的心脏祖细胞(cardiac progenitor cells, CPCs)凋亡, 从而诱导心脏毒性[56]。研究指出, 阿霉素直接作用于心肌细胞中的拓扑异构酶IIβ, 并形成阿霉素–拓扑异构酶IIβ-DNA复合物, 随后, 这些复合物通过促进p53的磷酸化而引起DNA损伤最终导致心肌细胞凋亡[57]。此外, 阿霉素可通过激活聚ADP-核糖聚合酶所裂解产物的释放导致细胞凋亡[58-59]。CircRNA作为部分细胞凋亡相关miRNA的海绵分子, 通过调控细胞凋亡最终影响阿霉素心脏毒性[30-31]。YUN等[60]发现, circ_0129657可作为miR-194-5p的海绵分子, 在FA等[61]的研究中发现, miR-194-5p可加剧阿霉素诱导的心肌细胞凋亡。由此, circ_0129657可能通过作为miR-194-5p的海绵分子来减少心肌细胞凋亡最终缓解阿霉素心脏毒性。此外, circRNA可通过凋亡影响缺血性心脏病, 在ZHANG等[62]的研究中指出, 在动脉粥样硬化(atherosclerosis, AS)中,



→: 表示促进; ⊣: 表示抑制; ？: 表示可能的机制; ⬇: 表示下降。SIRT6: 沉默调节蛋白6; BIRC5: 含杆状病毒IAP重复序列蛋白5; SERCA2a: 肌浆网钙泵 2a; ADCY 1: 腺苷酸环化酶1; circLTBP1: 环状RNA潜在转化生长因子β结合蛋白1; HMGB1: 高迁移率族蛋白B1; TLR4: toll样受体4; QKI: 震颤蛋白; circTTN: 环状RNA肌联蛋白; circSTRN3: 环状RNA纹蛋白3; circ-INSR: 环状RNA胰岛素受体; SSBP1: 单链DNA结合蛋白 1; AKT1: AKT丝氨酸/苏氨酸激酶1; PDK1: 磷酸肌醇依赖性蛋白激酶-1; ID-1: DNA结合抑制蛋白-1; FAK: 局部黏着斑激酶; HIF-1α: 缺氧诱导因子-1α; IL-1β: 白介素-1β; IL-6: 白介素-6; IL-2Rβ: 白介素-2Rβ; EGR1:人早期生长反应蛋白1; EGR3: 人早期生长反应蛋白3; FTO: 肥胖相关蛋白质; m^{6}A: N6-腺苷酸甲基化; Nrf2: 核因子E2相关因子2; Sirt2: 沉默调节性蛋白2; HO-1: 血红素氧合酶1; NQO1: NAD(P)H醌脱氢酶1; Gst: 谷胱甘肽*s*-转移酶; Vcp: 含缬酪肽蛋白; Vdac1: 电压依赖性阴离子通道蛋白1; HDAC1: 组蛋白脱乙酰酶1; CircUSP9X: 环状RNA泛素特异性肽酶 9 X-连锁; EIF4A3: 真核翻译起始因子4A3; GSDMD: 消皮素D; CircHMGA2: 环状RNA高迁移率族蛋白A2; NLRP3: NOD样受体热蛋白结构域相关蛋白3; GSDMA: 消皮素A; IGF2BP3: *IGF-2* mRNA结合蛋白3; LC3-II: 微管相关蛋白1-轻链3-II; ATG7: 自噬相关蛋白7; PINK1: PTEN诱导激酶1; DNMT3B: DNA甲基转移酶3B; Circ-IL-4R: 环状RNA白介素-4受体; GPX4: 谷胱甘肽过氧化酶4; SLC7A11: 溶质载体家族7成员11; 5-LOX: 5-脂氧合酶。

→: promotion, ⊣: inhibition; ？: possible mechanisms; ⬇: decrease. SIRT6: sirtuin6; BIRC5: baculoviral IAP repeat containing 5; SERCA2a: sarco-endoplasmic reticulum ATPase 2a; circLTBP1: circular RNA latent transforming growth factor beta binding protein 1; ADCY 1: adenylate cyclase 1; HMGB1: high mobility group box-1 protein; TLR4: toll-like receptor 4; QKI: quaking; circTTN: circular RNA titin; circSTRN3: circular RNA striatin 3; circ-INSR: circular RNA insulin receptor; SSBP1: single strand DNA-binding protein1; AKT1: AKT serine/threonine kinase1; PDK1: phosphoinositide-dependent protein kinase 1; ID-1: inhibitor of DNA binding protein 1; FAK: focal adhesion kinase; HIF-1α: hypoxia inducible factor-1; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-2Rβ: interleukin-2Rβ; EGR1: early growth response factor 1; EGR3: early growth response factor 3; FTO: fat mass and obesity-associated protein; m^{6}A: N6-adenosine methylation; Nrf2: nuclear factor erythroid2-related factor 2 ; Sirt2: sirtuin2; HO-1: heme Oxygenase-1; NQO1: NAD(P)H dehydrogenase quinone 1; Gst: glutathione *s*-transferase; Vcp: valosin containing protein; Vdac1: voltage dependent anion channel 1; HDAC1: histone deacetylase 1; CircUSP9X: circular RNA ubiquitin specific peptidase 9 X-linked Gene; EIF4A3: eukaryotic translation initiation factor; GSDMD: gasdermin D; CircHMGA2: circular RNA high mobility group A2; NLRP3: nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3; GSDMA: gasdermin A; IGF2BP3: *IGF2* mRNA binding protein 3; LC3- Ⅱ : microtubule-associated-proteinlight-chain-3-II; ATG7: autophagy related protein 7; PINK1: PTEN induced putative kinase 1; DNMT3B: DNA methyltransferase 3B; Circ-IL-4R: circular RNA interleukin-4R; GPX4: glutathione peroxidase 4; SLC7A11: recombinant Ssolute carrier family 7 member 11; 5-LOX: 5-lipoxygenase.

图1 环状RNA在阿霉素心脏毒性中生物学作用

Fig.1 The biological role of circular RNA in Doxorubicin-induced cardiotoxicity

circRSF1可作为miR-135b-5p海绵分子, 从而促进组蛋白脱乙酰酶1的mRNA的生成, 最终抑制氧化修饰低密度脂蛋白引起的血管内皮细胞凋亡。然而, 目前缺乏直接的研究证明circRNA通过细胞凋亡影响阿霉素心脏毒性, 需要研究者进一步探索这一潜在机制。

2.5 CircRNA调节细胞焦亡影响阿霉素心脏毒性

阿霉素可以诱发心肌细胞焦亡从而导致心脏毒性。有研究证明阿霉素可激活caspase和消皮素从而引起细胞焦亡[63-64]。此外, 阿霉素也可诱导NADPH氧化酶1和NADPH氧化酶4过表达, 引起线粒体裂变, 促进活性氧的积累, 激活NOD样受体热蛋白结构域相关蛋白3(nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3, NLRP3)炎症小体, 最终导致细胞焦亡[65]。有研究指出, circRNA通过影响这些焦亡相关蛋白的表达和活性, 参与焦亡过程, 从而影响动脉粥样硬化、心肌梗死和糖尿病心肌病等心血管疾病的发展。AS中, 环状RNA泛素特异性肽酶9 X-连锁与真核翻译起始因子4 A3相互作用, 增强消皮素D的稳定性, 促进氧化低密度脂蛋白诱导的内皮细胞焦亡, 加剧AS[32]。也有研究证明, circ_0090231通过作为miR-635的海绵分子增加NLRP3表达量, 促进内皮细胞焦亡, 从而加快AS的发展[66]; 在心肌梗死中, 敲低环状RNA高迁移率族蛋白A2直接抑制NLRP3的表达, 抑制细胞焦亡, 缓解心肌梗死中的心肌损伤[67]。此外, 有文献指出, circHelz通过作为miR-133a-3p的海绵分子来增加NLRP3表达量, 促进细胞焦亡, 加剧心肌损伤[68]; 在糖尿病心肌病中, hsa_circ_0076631表达量增加, 其可以作为miR-214-3p的海绵分子从而加剧caspase-1诱导的细胞焦亡[69]。也有研究表明, 高糖处理后的心肌细胞中circ_0071269表达量增加, 其通过作为miR-145的海绵分子从而促进消皮素A的表达, 加剧细胞焦亡[70]。综上, circRNA可能通过调节焦亡相关蛋白的表达和活性来调节阿霉素心脏毒性。然而, 以上机制只是假设, 需要更多的研究来深入探究circRNA通过焦亡影响阿霉素心脏毒性中的具体作用机制。

2.6 CircRNA调节细胞自噬影响阿霉素心脏毒性

细胞自噬是一把双刃剑, 研究认为激活自噬可抑制阿霉素心脏毒性, 但过度自噬可加剧阿霉素心脏毒性。研究发现, 灯盏花乙素可通过PTEN诱导激酶1(PTEN induced putative kinase 1, PINK1)/Parkin通路的激活, 增强线粒体自噬来清除阿霉素引起的积累的受损线粒体[71-72]。但过度自噬是发生阿霉素心脏毒性的重要原因, 有研究表明, 在阿霉素作用的小鼠心肌细胞中, 微管相关蛋白1-轻链3-II过度积累, 从而导致细胞自噬, 进一步加剧心脏毒性[73]。此外, 自噬相关蛋白7(autophagy related protein 7, ATG7)过表达促进阿霉素作用下心肌细胞中的自噬导致阿霉素心脏毒性[74-75]。另有相关研究指出, circRNA可以通过调控自噬参与缺血性心脏病发生, 既往文献指出, 心肌缺氧复氧过程中, circ_101237的表达量随时间推移逐渐增加, 同时促进自噬, 其分子机制为circ_101237作为Let-7a-5p的海绵分子, 从而促进*IGF-2* mRNA结合蛋白3的表达, *IGF-2* mRNA结合蛋白3与*IGF-2* mRNA的5′UTR结合并促进IGF-2的表达, IGF-2的磷酸化可激活丝裂原活化蛋白激酶激酶信号通路, 这促进了微管相关蛋白1-轻链3-II的表达, 从而促进了心肌细胞中的自噬[76-78]。小鼠心肌梗死模型中, circPan 3表达上调并通过作为miRNA221的海绵分子促进FOXO3表达, FOXO3作为转录因子, 与*Atg7*启动子区结合, 以促进其表达, 最终促进自噬[33]。在缺血性心脏病中, circRNA还可以抑制细胞自噬。研究指出自噬相关circRNA可直接与DNA甲基转移酶3B结合, 抑制*Pink1*启动子的DNA甲基化, 从而促进PINK1的表达, 抑制心肌细胞自噬, circPan3也可通过作为miRNA421的海绵分子促进PINK1表达, 抑制自噬, 因此上述两种circRNA均可降低细胞凋亡率, 减少心梗面积, 从而产生心脏保护作用[4,79]。综上, circRNA可能通过调节细胞自噬来影响阿霉素心脏毒性, 但自噬作为一个复杂的调控网络, 受到多种因素的影响, 因此, 该调控机制还需研究人员的深入研究。

2.7 CircRNA调节铁死亡影响阿霉素心脏毒性

铁死亡作为一种新型的细胞死亡形式, 与阿霉素心脏毒性的发生发展密切相关[80-82]。TADOKORO等[83]证实, 阿霉素通过下调谷胱甘肽过氧化酶4(glutathione peroxidase 4, GPX4)表达诱导过度脂质过氧化导致铁死亡。此外, 有文献报道阿霉素抑制溶质载体家族7成员11(recombinant Ssolute carrier family 7 member 11, SLC7A11)的表达, 导致谷胱甘肽合成减少, 从而使GPX4清除由5-脂氧合酶介导形成的脂质过氧化物这一过程受阻, 最终导致铁死亡[84]。

此外, 也有研究指出circRNA可以调节铁死亡相关酶的表达。有文献指出, mmu_circ_0000309作为miR-188-3p的海绵分子, 促进靶蛋白GPX4表达, 从而抑制铁死亡[35]。肝细胞癌中, 环状RNA白介素-4受体通过作为miR-541-3p的海绵分子促进GPX4的表达, 促进肿瘤发生并抑制铁死亡过程[85]。ZHANG等[86]发现circRNARHBG在多囊卵巢综合征患者的颗粒细胞中显著上调, 其通过作为miR-515-5p的海绵分子促进SLC7A11表达, 从而抑制卵巢细胞中的铁死亡。WU等[87]在褪黑激素治疗的创伤性脑损伤后小鼠中发现, mmu_circ_0000130通过作为miR-351-5p的海绵分子来增加5-脂氧合酶水平, 导致脂质过氧化作用增强从而引起铁死亡发生。因此, circRNA可能通过调节铁死亡过程参与阿霉素心脏毒性过程。但研究者仍需进一步探索circRNA调控铁死亡参与阿霉素心脏毒性的潜在机制。

3 总结与展望

本文首先总结circRNA的形成及生物学功能, 接着总结circRNA通过作为竞争性内源RNA和与蛋白质相互作用的分子机制, 以及可能通过参与氧化应激、细胞凋亡、细胞焦亡、细胞自噬和铁死亡等多种细胞生物学过程来影响阿霉素心脏毒性, 并揭示circRNA诊断和治疗阿霉素心脏毒性的潜力。CircRNA在阿霉素心脏毒性中的生物学作用机制目前尚未得到完整阐述, 未来研究者可以向此方向研究: 继续探索circRNA在阿霉素诱导心脏毒性中的潜在生物学机制, 在此基础上开发circRNA作为预测和治疗靶标, 为阿霉素心脏毒性的诊断和治疗提供更多的理论与技术支持, 最终实现circRNA在阿霉素心脏毒性中的临床应用。

参考文献 (References)

[1] HAN B, CHAO J, YAO H. Circular RNA and its mechanisms in disease: from the bench to the clinic [J]. Pharmacol Ther, 2018, 187: 31-44.

[2] FISCHER J W, LEUNG A K. CircRNAs: a regulator of cellular stress [J]. Crit Rev Biochem Mol Biol, 2017, 52(2): 220-33.

[3] JECK W R, SHARPLESS N E. Detecting and characterizing circular RNAs [J]. Nat Biotechnol, 2014, 32(5): 453-61.

[4] ZHOU L Y, ZHAI M, HUANG Y, et al. The circular RNA ACR attenuates myocardial ischemia/reperfusion injury by suppressing autophagy via modulation of the Pink1/FAM65B pathway [J]. Cell Death Differ, 2019, 26(7): 1299-315.

[5] LIM T B, ALIWARGA E, LUU T D A, et al. Targeting the highly abundant circular RNA circSlc8a1 in cardiomyocytes attenuates pressure overload induced hypertrophy [J]. Cardiovasc Res, 2019, 115(14): 1998-2007.

[6] ZHU Y, PAN W, YANG T, et al. Upregulation of circular RNA circNFIB attenuates cardiac fibrosis by sponging miR-433 [J]. Front Genet, 2019, 10: 564.

[7] DU W W, YANG W, CHEN Y, et al. Foxo3 circular RNA promotes cardiac senescence by modulating multiple factors associated with stress and senescence responses [J]. Eur Heart J, 2017, 38(18): 1402-12.

[8] GUPTA S K, GARG A, BAR C, et al. Quaking inhibits doxorubicin-mediated cardiotoxicity through regulation of cardiac circular rna expression [J]. Circ Res, 2018, 122(2): 246-54.

[9] HALL I F, CLIMENT M, QUINTAVALLE M, et al. Circ_Lrp6, a circular RNA enriched in vascular smooth muscle cells, acts as a sponge regulating miRNA-145 function [J]. Circ Res, 2019, 124(4): 498-510.

[10] YANG L, YANG F, ZHAO H, et al. Circular RNA circCHFR facilitates the proliferation and migration of vascular smooth muscle via miR-370/FOXO1/Cyclin D1 pathway [J]. Mol Ther Nucleic Acids, 2019, 16: 434-41.

[11] LI B, LI Y, HU L, et al. Role of circular RNAs in the pathogenesis of cardiovascular disease [J]. J Cardiovasc Transl Res, 2020, 13(4): 572-83.

[12] CAPPETTA D, ROSSI F, PIEGARI E, et al. Doxorubicin targets multiple players: a new view of an old problem [J]. Pharmacol Res, 2018, 127: 4-14.

[13] TALHOUARNE G J S, GALL J G. Lariat intronic RNAs in the cytoplasm of vertebrate cells [J]. Proc Natl Acad Sci USA, 2018, 115(34): E7970-E7.

[14] CHEN L L. The expanding regulatory mechanisms and cellular functions of circular RNAs [J]. Nat Rev Mol Cell Biol, 2020, 21(8): 475-90.

[15] ZHANG Y, ZHANG X O, CHEN T, et al. Circular intronic long noncoding RNAs [J]. Mol Cell, 2013, 51(6): 792-806.

[16] JARLSTAD OLESEN M T, L S K. Circular RNAs as microRNA sponges: evidence and controversies [J]. Essays Biochem, 2021, 65(4): 685-96.

[17] HANSEN T B, JENSEN T I, CLAUSEN B H, et al. Natural RNA circles function as efficient microRNA sponges [J]. Nature, 2013, 495(7441): 384-8.

[18] LIU J, ZHAO X, DUAN X, et al. CircRNA75 and circRNA72 function as the sponge of microRNA-200 to suppress coelomocyte apoptosis via targeting tollip in apostichopus japonicus [J]. Front Immunol, 2021, 12: 770055.

[19] ZANG J, LU D, XU A. The interaction of circRNAs and RNA binding proteins: an important part of circRNA maintenance and function [J]. J Neurosci Res, 2020, 98(1): 87-97.

[20] ABDELMOHSEN K, PANDA A C, MUNK R, et al. Identification of HuR target circular RNAs uncovers suppression of PABPN1 translation by CircPABPN1 [J]. RNA Biol, 2017, 14(3): 361-9.

[21] CHEN Q, WANG H, LI Z, et al. Circular RNA ACTN4 promotes intrahepatic cholangiocarcinoma progression by recruiting YBX1 to initiate FZD7 transcription [J]. J Hepatol, 2022, 76(1): 135-47.

[22] DU W W, FANG L, YANG W, et al. Induction of tumor apoptosis through a circular RNA enhancing Foxo3 activity [J]. Cell Death Differ, 2017, 24(2): 357-70.

[23] WEN S Y, QADIR J, YANG B B. Circular RNA translation: novel protein isoforms and clinical significance [J]. Trends Mol Med, 2022, 28(5): 405-20.
[24] LEGNINI I, DI TIMOTEO G, ROSSI F, et al. Circ-ZNF609 is a circular RNA that can be translated and functions in myogenesis [J]. Mol Cell, 2017, 66(1): 22-37,e9.
[25] GAO C, WANG Y. The emerging role of circular RNAs in cardio-oncology [J]. JACC Basic Transl Sci, 2023, 8(6): 699-701.
[26] LIM G B. Circular RNA prevents doxorubicin-induced cardiotoxicity [J]. Nat Rev Cardiol, 2022, 19(9): 574.
[27] CHENG Z, QIN W, LI S, et al. Emerging roles of circular RNAs in cancer therapy-induced cardiotoxicity [J]. Front Cardiovasc Med, 2023, 10: 1152436.
[28] ZHENG H, HUANG S, WEI G, et al. CircRNA Samd4 induces cardiac repair after myocardial infarction by blocking mitochondria-derived ROS output [J]. Mol Ther, 2022, 30(11): 3477-98.
[29] WANG L, YI J, LU L Y, et al. Estrogen-induced circRNA, circPGR, functions as a ceRNA to promote estrogen receptor-positive breast cancer cell growth by regulating cell cycle-related genes [J]. Theranostics, 2021, 11(4): 1732-52.
[30] GENG H H, LI R, SU Y M, et al. The circular RNA Cdr1as promotes myocardial infarction by mediating the regulation of miR-7a on its target genes expression [J]. PLoS One, 2016, 11(3): e0151753.
[31] LI M, DING W, TARIQ M A, et al. A circular transcript of ncx1 gene mediates ischemic myocardial injury by targeting miR-133a-3p [J]. Theranostics, 2018, 8(21): 5855-69.
[32] XU S, GE Y, WANG X, et al. Circ-USP9X interacts with EIF4A3 to promote endothelial cell pyroptosis by regulating GSDMD stability in atherosclerosis [J]. Clin Exp Hypertens, 2023, 45(1): 2186319.
[33] LI F, LONG T Y, BI S S, et al. circPAN3 exerts a profibrotic role via sponging miR-221 through FoxO3/ATG7-activated autophagy in a rat model of myocardial infarction [J]. Life Sci, 2020, 257: 118015.
[34] DU W W, YANG W, LIU E, et al. Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2 [J]. Nucleic Acids Res, 2016, 44(6): 2846-58.
[35] JIN J, WANG Y, ZHENG D, et al. A novel identified circular RNA, mmu_mmu_circRNA_0000309, involves in germacrone-mediated improvement of diabetic nephropathy through regulating ferroptosis by targeting miR-188-3p/GPX4 signaling axis [J]. Antioxid Redox Signal, 2022, 36(10/11/12): 740-59.
[36] HUANG G, LIANG M, LIU H, et al. CircRNA hsa_circRNA_104348 promotes hepatocellular carcinoma progression through modulating miR-187-3p/RTKN2 axis and activating Wnt/beta-catenin pathway [J]. Cell Death Dis, 2020, 11(12): 1065.
[37] CHEN Z, CHENG H, ZHANG J, et al. Hsa_circRNA_102051 regulates colorectal cancer proliferation and metastasis by mediating Notch pathway [J]. Cancer Cell Int, 2023, 23(1): 230.
[38] WANG Y, YIN L, SUN X. CircRNA hsa_circ_0002577 accelerates endometrial cancer progression through activating IGF1R/PI3K/Akt pathway [J]. J Exp Clin Cancer Res, 2020, 39(1): 169.
[39] HAN D, WANG Y, WANG Y, et al. The tumor-suppressive human circular RNA circITCH sponges miR-330-5p to ameliorate doxorubicin-induced cardiotoxicity through upregulating SIRT6, Survivin, and SERCA2a [J]. Circ Res, 2020, 127(4): e108-e25.
[40] WANG X, CHENG Z, XU J, et al. Circular RNA Arhgap12 modulates doxorubicin-induced cardiotoxicity by sponging miR-135a-5p [J]. Life Sci, 2021, 265: 118788.
[41] LI C, ZHANG L, BU X, et al. Circ-LTBP1 is involved in doxorubicin-induced intracellular toxicity in cardiomyocytes via miR-107/ADCY1 signal [J]. Mol Cell Biochem, 2022, 477(4): 1127-38.
[42] HU X, LIAO W, TENG L, et al. Circ_0001312 silencing suppresses doxorubicin-induced cardiotoxicity via miR-409-3p/HMGB1 axis [J]. Int Heart J, 2023, 64(1): 71-80.
[43] LI B, CAI X, WANG Y, et al. Circ-SKA3 enhances doxorubicin toxicity in AC16 cells through miR-1303/TLR4 axis [J]. Int Heart J, 2021, 62(5): 1112-23.
[44] JI X, DING W, XU T, et al. MicroRNA-31-5p attenuates doxorubicin-induced cardiotoxicity via quaking and circular RNA Pan3 [J]. J Mol Cell Cardiol, 2020, 140: 56-67.
[45] GUO C A, GUO S. Insulin receptor substrate signaling controls cardiac energy metabolism and heart failure [J]. J Endocrinol, 2017, 233(3): R131-R43.
[46] LU D, CHATTERJEE S, XIAO K, et al. A circular RNA derived from the insulin receptor locus protects against doxorubicin-induced cardiotoxicity [J]. Eur Heart J, 2022, 43(42): 4496-511.
[47] ZENG Y, DU W W, WU Y, et al. A circular RNA binds to and activates AKT phosphorylation and nuclear localization reducing apoptosis and enhancing cardiac repair [J]. Theranostics, 2017, 7(16): 3842-55.
[48] DU W W, XU J, YANG W, et al. A neuroligin isoform translated by circNlgn contributes to cardiac remodeling [J]. Circ Res, 2021, 129(5): 568-82.
[49] XU J, DU W W, WU N, et al. The circular RNA circNlgnmediates doxorubicin-inducedcardiac remodeling and fibrosis [J]. Mol Ther Nucleic Acids, 2022, 28: 175-89.
[50] YU P, WANG J, XU G E, et al. RNA m^6A-Regulated circ-ZNF609 suppression ameliorates doxorubicin-induced cardiotoxicity by upregulating FTO [J]. JACC Basic Transl Sci, 2023, 8(6): 677-98.
[51] SANGWENI N F, GABUZA K, HUISAMEN B, et al. Molecular insights into the pathophysiology of doxorubicin-induced cardiotoxicity: a graphical representation [J]. Arch Toxicol, 2022, 96(6): 1541-50.
[52] SANG Y, CHEN B, SONG X, et al. circRNA_0025202 regulates tamoxifen sensitivity and tumor progression via regulating the miR-182-5p/FOXO3a axis in breast cancer [J]. Mol Ther, 2021, 29(12): 3525-7.
[53] DU M, WU C, YU R, et al. A novel circular RNA, circIgfbp2, links neural plasticity and anxiety through targeting mitochondrial dysfunction and oxidative stress-induced synapse dysfunction after traumatic brain injury [J]. Mol Psychiatry, 2022, 27(11): 4575-89.
[54] ZANG H, LI Y, ZHANG X, et al. Circ-RNF111 contributes to paclitaxel resistance in breast cancer by elevating E2F3 expression via miR-140-5p [J]. Thorac Cancer, 2020, 11(7): 1891-903.
[55] ZHAO L, QI Y, XU L, et al. MicroRNA-140-5p aggravates doxorubicin-induced cardiotoxicity by promoting myocardial oxidative stress via targeting Nrf2 and Sirt2 [J]. Redox Biol, 2018, 15: 284-96.
[56] LEE E J, JANG W B, CHOI J, et al. The protective role of glutathione against doxorubicin-induced cardiotoxicity in human cardiac progenitor cells [J]. Int J Mol Sci, 2023, 24(15): 12070.
[57] ZHANG S, LIU X, BAWA-KHALFE T, et al. Identification of

the molecular basis of doxorubicin-induced cardiotoxicity [J]. Nat Med, 2012, 18(11): 1639-42.

[58] SAHU B D, KUMAR J M, KUNCHA M, et al. Baicalein alleviates doxorubicin-induced cardiotoxicity via suppression of myocardial oxidative stress and apoptosis in mice [J]. Life Sci, 2016, 144: 8-18.

[59] ALI M, KAMJOO M, THOMAS H D, et al. The clinically active PARP inhibitor AG014699 ameliorates cardiotoxicity but does not enhance the efficacy of doxorubicin, despite improving tumor perfusion and radiation response in mice [J]. Mol Cancer Ther, 2011, 10(12): 2320-9.

[60] QIAN Y, TANG B, ZHANG H, et al. Highly-expressed circ_0129657 inhibits proliferation as well as promotes apoptosis and inflammation in HBMECs after oxygen-glucose deprivation via miR-194-5p/GMFB axis [J]. Autoimmunity, 2023, 56(1): 2201405.

[61] FA H, XIAO D, CHANG W, et al. microRNA-194-5p attenuates doxorubicin-induced cardiomyocyte apoptosis and endoplasmic reticulum stress by targeting P21-activated kinase 2 [J]. Front Cardiovasc Med, 2022, 9: 815916.

[62] ZHANG X, LU J, ZHANG Q, et al. CircRNA RSF1 regulated ox-LDL induced vascular endothelial cells proliferation, apoptosis and inflammation through modulating miR-135b-5p/HDAC1 axis in atherosclerosis [J]. Biol Res, 2021, 54(1): 11.

[63] TAVAKOLI DARGANI Z, SINGLA D K. Embryonic stem cell-derived exosomes inhibit doxorubicin-induced TLR4-NLRP3-mediated cell death-pyroptosis [J]. Am J Physiol Heart Circ Physiol, 2019, 317(2): H460-H71.

[64] SINGLA D K, JOHNSON T A, TAVAKOLI DARGANI Z. Exosome treatment enhances anti-inflammatory M2 macrophages and reduces inflammation-induced pyroptosis in doxorubicin-induced cardiomyopathy [J]. Cells, 2019, 8(10): 1224.

[65] ZENG C, DUAN F, HU J, et al. NLRP3 inflammasome-mediated pyroptosis contributes to the pathogenesis of non-ischemic dilated cardiomyopathy [J]. Redox Biol, 2020, 34: 101523.

[66] GE Y, LIU W, YIN W, et al. Circular RNA circ_0090231 promotes atherosclerosis *in vitro* by enhancing NLR family pyrin domain containing 3-mediated pyroptosis of endothelial cells [J]. Bioengineered, 2021, 12(2): 10837-48.

[67] FENG P, CHU Y, LI J, et al. Effect and mechanism of circHMGA2 on ferroptosis and pyroptosis in myocardial ischemia-reperfusion model CircHMGA2 exacerbates MI/R injury [J]. Heliyon, 2023, 9(7): e17849.

[68] BIAN Y, PANG P, LI X, et al. CircHelz activates NLRP3 inflammasome to promote myocardial injury by sponging miR-133a-3p in mouse ischemic heart [J]. J Mol Cell Cardiol, 2021, 158: 128-39.

[69] YANG F, LI A, QIN Y, et al. A novel circular RNA mediates pyroptosis of diabetic cardiomyopathy by functioning as a competing endogenous RNA [J]. Mol Ther Nucleic Acids, 2019, 17: 636-43.

[70] FU L, ZHANG J, LIN Z, et al. CircularRNA circ_0071269 knockdown protects against from diabetic cardiomyopathy injury by microRNA-145/gasdermin A axis [J]. Bioengineered, 2022, 13(2): 2398-411.

[71] BARTLETT J J, TRIVEDI P C, PULINILKUNNIL T. Autophagic dysregulation in doxorubicin cardiomyopathy [J]. J Mol Cell Cardiol, 2017, 104: 1-8.

[72] LI M J, SUN W S, YUAN Y, et al. Breviscapine remodels myocardial glucose and lipid metabolism by regulating serotonin to alleviate doxorubicin-induced cardiotoxicity [J]. Front Pharmacol, 2022, 13: 930835.

[73] ABDULLAH C S, ALAM S, AISHWARYA R, et al. Doxorubicin-induced cardiomyopathy associated with inhibition of autophagic degradation process and defects in mitochondrial respiration [J]. Sci Rep, 2019, 9(1): 2002.

[74] WANG Y, LU X, WANG X, et al. Atg7-based autophagy activation reverses doxorubicin-induced cardiotoxicity [J]. Circ Res, 2021, 129(8): e166-e82.

[75] SUN X, MENG H, XIAO J, et al. Pretreatment of 3-MA prevents doxorubicin-induced cardiotoxicity through inhibition of autophagy initiation [J]. Toxicology, 2023, 490: 153512.

[76] GAN J, YUAN J, LIU Y, et al. Circular RNA_101237 mediates anoxia/reoxygenation injury by targeting let-7a-5p/IGF2BP3 in cardiomyocytes [J]. Int J Mol Med, 2020, 45(2): 451-60.

[77] LEDERER M, BLEY N, SCHLEIFER C, et al. The role of the oncofetal IGF2 mRNA-binding protein 3 (IGF2BP3) in cancer [J]. Semin Cancer Biol, 2014, 29: 3-12.

[78] PANEBIANCO F, KELLY L M, LIU P, et al. THADA fusion is a mechanism of IGF2BP3 activation and IGF1R signaling in thyroid cancer [J]. Proc Natl Acad Sci USA, 2017, 114(9): 2307-12.

[79] ZHANG C L, LONG T Y, BI S S, et al. CircPAN3 ameliorates myocardial ischaemia/reperfusion injury by targeting miR-421/Pink1 axis-mediated autophagy suppression [J]. Lab Invest, 2021, 101(1): 89-103.

[80] XU M, TAO J, YANG Y, et al. Ferroptosis involves in intestinal epithelial cell death in ulcerative colitis [J]. Cell Death Dis, 2020, 11(2): 86.

[81] XIE L H, FEFELOVA N, PAMARTHI S H, et al. Molecular mechanisms of ferroptosis and relevance to cardiovascular disease [J]. Cells, 2022, 11(17): 2726.

[82] KITAKATA H, ENDO J, MATSUSHIMA H, et al. MITOL/MARCH5 determines the susceptibility of cardiomyocytes to doxorubicin-induced ferroptosis by regulating GSH homeostasis [J]. J Mol Cell Cardiol, 2021, 161: 116-29.

[83] TADOKORO T, IKEDA M, IDE T, et al. Mitochondria-dependent ferroptosis plays a pivotal role in doxorubicin cardiotoxicity [J]. JCI Insight, 2023, 8(6): e169756.

[84] LI X, LIANG J, QU L, et al. Exploring the role of ferroptosis in the doxorubicin-induced chronic cardiotoxicity using a murine model [J]. Chem Biol Interact, 2022, 363: 110008.

[85] XU Q, ZHOU L, YANG G, et al. CircIL4R facilitates the tumorigenesis and inhibits ferroptosis in hepatocellular carcinoma by regulating the miR-541-3p/GPX4 axis [J]. Cell Biol Int, 2020, 44(11): 2344-56.

[86] ZHANG D, YI S, CAI B, et al. Involvement of ferroptosis in the granulosa cells proliferation of PCOS through the circRHBG/miR-515/SLC7A11 axis [J]. Ann Transl Med, 2021, 9(16): 1348.

[87] WU C, DU M, YU R, et al. A novel mechanism linking ferroptosis and endoplasmic reticulum stress via the circPtpn14/miR-351-5p/5-LOX signaling in melatonin-mediated treatment of traumatic brain injury [J]. Free Radic Biol Med, 2022, 178: 271-94.