·综述·

非编码RNA调控细胞程序性死亡影响慢性肾脏病的研究进展

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摘 要：慢性肾脏病(CKD)是一种发病率和死亡率较高的常见疾病。越来越多的研究表明，程序性死亡(PCD)在CKD的发生发展中具有重要作用。非编码RNA(ncRNA)是指不具有编码功能的RNA，已被确定为调控基因表达的关键因子，可影响包含PCD在内的多种生物过程。本文综述了ncRNA参与调控CKD后细胞凋亡、自噬、焦亡、铁死亡、坏死性凋亡和泛凋亡的最新研究进展，探究了不同途径之间的串扰，并从外泌体疗法、中药活性成分、新型药物3方面归纳了ncRNA调控PCD相关的治疗策略，以期为临床提供新的治疗靶点和思路。

关键词：慢性肾脏病；非编码RNA；凋亡；自噬；焦亡；铁死亡
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Advances on the Regulation of Programmed Cell Death by Non-coding RNAs in Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) is a common disease with high morbidity and mortality. Increasing evidence has indicated that programmed cell death (PCD) plays a significant role in the pathogenesis and progression of CKD. Non-coding RNA (ncRNA), defined as a category of RNA that lacks coding potential, has emerged as a pivotal regulator of gene expression. This regulatory function of ncRNA extends to various biological processes, including PCD. This paper reviews the recent advances on the involvement of ncRNAs in the regulation of apoptosis, autophagy, pyroptosis, ferroptosis, necroptosis, and PANoptosis in CKD. It explores the crosstalk between different pathways and categorizes therapeutic strategies targeting ncRNA regulation of PCD into three main areas: the active ingredients of traditional Chinese medicine, tissue engineering technologies, and drugs. The objective of this study is to identify novel therapeutic targets and strategies for clinical treatment.

Key words: chronic kidney disease; non-coding RNA; apoptosis; autophagy; pyroptosis; ferroptosis
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慢性肾脏病(chronic kidney disease, CKD)是指患者存在肾脏结构或功能异常持续超过3个月，并影响其健康的非传染性疾病。作为重要的全球公共卫生问题之一，CKD与加速心血管疾病发展、

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诱发终末期肾病以及过早死亡密切相关，流行病学数据显示2022年全球高达8.5亿人患CKD，给患者及家庭乃至社会医疗系统带来了巨大的压力[1]。然而，由于CKD病理机制的复杂性，目前仍缺乏特定的治疗手段以延缓肾功能的恶化。

细胞程序性死亡（programmed cell death，PCD）包含一系列由基因表达调控的细胞主动死亡过程，如凋亡、自噬、焦亡、铁死亡、坏死性凋亡、泛凋亡、铜死亡和双硫死亡[2]。在生理条件下，PCD可促进细胞群更新，并作为一种保护机制以清除受损的细胞，如足细胞或肾小管上皮细胞，从而维持机体稳态。然而，在病理条件下，PCD失衡会促进细胞过度裂解或有害物质的积累，破坏相关肾细胞活性，最终导致多种疾病[3]。PCD受诸多因素调控，包括葡萄糖水平、蛋白质水平、线粒体功能障碍、氧化应激以及非编码RNA（non-coding RNA，ncRNA）等[4]。

ncRNA是指不具有编码功能的RNA，主要包括微小RNA（microRNA，miRNA）、长链非编码RNA（long non-coding RNA，lncRNA）、环状RNA（circular RNA，circRNA）以及最新发现的tRNA衍生的小RNA（transfer RNA-derived small RNA，tsRNA）[5-6]。ncRNA是基因表达的关键调节因子，其在表观遗传、转录以及转录后水平均发挥着重要作用。miRNA通过与信使RNA（messenger RNA，mRNA）特异性结合来抑制基因表达，从而阻止其翻译。而lncRNA和circRNA可充当miRNA的“分子海绵”，通过隔离miRNA并作为竞争性内源性RNA（competitive endogenous RNA，ceRNA）起作用，上述过程可以调节目标mRNA中miRNA可用性，最终影响疾病进展[7]。最新研究表明，某些ncRNA的作用机制并不局限于“分子海绵”，它们可通过形成特定的空间结构（如G-四链体、茎环结构），像“适配体”一样直接与功能蛋白结合，从而行使调控功能[8]。通过充当分子调节剂，ncRNA可以调控与PCD相关的基因表达和细胞过程，从而影响CKD后细胞命运，这有助于深入理解CKD的病理机制并基于此开发新的治疗策略。近年来有较多ncRNA参与PCD调控治疗CKD的相关报道，但该领域缺乏系统的梳理，本文就相关内容作一综述，以期为PCD的调控、ncRNA的分子机制以及CKD的治疗策略提供新的思路。

1　细胞凋亡

1.1　细胞凋亡与慢性肾脏病

作为维持组织稳态的重要过程之一，细胞凋亡在胚胎形成、维持免疫系统功能、细胞更替中起关键作用，其主要由内源性途径（即线粒体途径）、外源性途径（即死亡受体途径）和内质网应激（endoplasmic reticulum stress，ERS）途径介导[9]。细胞凋亡始于细胞核收缩和染色质固缩，随后细胞核进一步凝聚、碎裂，细胞分离并发展出褶皱延伸，随着质膜封闭而出芽，形成凋亡小体。这些含有核碎片和细胞器的凋亡小体可以被邻近细胞快速吞噬，而不继发炎症反应[10]。目前在CKD中，研究较多的细胞凋亡主要发生于足细胞、肾小管上皮细胞、肾小球系膜细胞和内皮细胞中，其与肾小管萎缩、肾小球硬化、肾纤维化以及肾功能下降相关。

1.2　非编码RNA在慢性肾脏病中细胞凋亡的调控机制

miRNA与lncRNA通常在CKD后细胞凋亡的调控中发挥作用（表1）。过表达miR-181a通过与CRY1结合，可下调toll样受体（toll-like receptor，TLR）/核因子-κB（nuclear factor-kappa B，NF-κB）信号通路，从而减轻CKD大鼠肾小管上皮细胞凋亡和肾小球硬化[11]。同样，过表达miR-27b-3p可靶向抑制信号传导与转录激活因子1（signal transducers and activators of transcription1，STAT1）表达，减轻细胞凋亡并缓解肾纤维化[12]。同型半胱氨酸（homocysteine，Hcy）水平升高会导致CKD患者足细胞凋亡和肾小球损伤，具体来说，c-Myc通过募集zeste同源物增强子2（enhancer of zeste homolog 2，EZH2）和DNA甲基转移酶1（DNA methyltransferase 1，DNMT1），在Hcy诱导足细胞凋亡过程中，借助组蛋白和DNA甲基化对miR-1929-5p进行表观遗传学沉默[13]。此外，lncRNA MALAT1通过与Lin28A（Lin-28 homolog A）相互作用，激活NADPH氧化酶4（NADPH oxidase4，Nox4）/腺苷酸活化蛋白激酶（AMP-actived protein kinase，AMPK）/雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号通路，进而加重糖尿病肾病（diabetic nephropathy，DN）诱导的肾小管上皮细胞凋亡[14]。

在部分研究中，lncRNA与miRNA结合位点竞

争性结合,构成lncRNA-miRNA- mRNA调控网络起作用。与健康人相比,CKD患者血清中lncRNA NOP14-AS1表达降低,miR-326表达升高,进一步研究表明,lncRNA NOP14-AS1减少可增加miR-326表达,导致细胞增殖能力下降、凋亡率升高以及炎细胞浸润,最终加速肾纤维化的发展[15]。Chen等[16]研究表明降低lncRNA LINC00667可通过miR-19b-3p/lncRNA LINC00667/结缔组织生长因子(connective tissue growth factor, CTGF)信号通路,抑制慢性肾功能衰竭(chronic renal failure, CRF)大鼠肾小管上皮细胞凋亡,促进其增殖与迁移并改善肾纤维化。Xia等[17]发现敲低lncRNA XIST通过上调miR-19b,从而减少SRY-box转录因子6(SRY-box transcription factor 6, SOX6)表达,进而抑制肾纤维化小鼠中肾脏细胞的凋亡与炎症。除此之外,circRNA也可充当miRNA的"分子海绵"来介导基因表达。在DN小鼠中,circ MRP4过表达通过调节miR-499-5p/RRAGB/ mTORC1/ 70 ku核糖体S6激酶(ribosome S6 protein kinase, P70S6K)轴,诱发足细胞凋亡和炎症[18]。同样,has_circ 0037128通过介导miR-31-5p/ Krüppel样转录因子9(Kruppel-like factor 9, KLF9)加重高葡萄糖诱导的足细胞凋亡[19]。

2 细胞自噬

2.1 细胞自噬与慢性肾脏病

细胞自噬是一种高度保守的细胞过程,依赖于溶酶体,通过降解细胞成分、回收异常蛋白质和受损的细胞器以获取能量,在维持细胞稳态方面起着至关重要的作用[20]。尽管适度的自噬有助于细胞进行正常的生理活动,但过度的自噬会转化为细胞凋亡,不利于细胞存活。研究表明,在病理条件下,持续异常的自噬激活可能会导致一系列复杂分子机制的相互作用,包括细胞凋亡、氧化应激、炎症、促纤维化因子分泌、细胞衰老、细胞周期停滞和组织损伤等,最终导致肾纤维化,而肾纤维化是CKD进展的关键病理特征和驱动因素,在由CKD发展为终末期肾病的患者中经常观察到严重的肾纤维化[21]。足细胞数量的减少会加速CKD的进展,研究表明,足细胞在内源性肾细胞中表现出最高的基底自噬水平,自噬相关蛋白5(autophagy-related 5, ATG5)的缺失会导致氧化和泛素化蛋白的积累以及内质网应激,最终引发小鼠足细胞丢失和迟发性肾小球硬化,提示诱导自噬是维持足细胞完整性和稳态的关键机制[22]。此外,在人体中,肾脏的线粒体含量位于第二位,线粒体自噬可以消除受损的线粒体,促进能量代谢的调节,调节炎症反应和细胞死亡,减少氧化应激,从而延缓或改善CKD的进展,减轻肾损伤[23]。

2.2 非编码RNA在慢性肾脏病中细胞自噬的调控机制

肾脏作为一个高代谢需求的器官,其更容易受到自噬失调的影响。近年来,ncRNA在细胞自噬调控中的作用逐渐成为研究热点,通过表观遗传、转录及转录后等多层次调控机制,有助于克服CKD后传统自噬靶向疗法的局限性(表2)。一项最新的临床证据显示,DN患者尿液中葡萄糖-6-磷酸脱氢酶(glucose-6-phosphate dehydrogenase, G6PD)的活性降低,这与早期肾损伤呈正相关。进一步动物研究表明抑制miR-7977水平可能导致G6PD表达显著增加,从而逆转高葡萄糖对白蛋白诱导的自噬的影响[24]。足细胞是ncRNA调控细胞自噬的主要靶标。临床中DN患者的血清和尿液中均检测到高水平的miR-150-5p,而在DN小鼠模型中,沉默miR-150-5p通过与Sirt1的3'-UTR结合,靶向下游的p53乙酰化和AMPK依赖性足细胞自噬来发挥肾保护作用[25]。Su等[26]研究发现抑制lncRNA AK044604可通过调节Sirt1/糖原合酶激酶-3β轴促进足细胞自噬,从而缓解DN诱导的足细胞损伤。一项研究使用了自发性Ⅱ型DN(T2DN)小鼠模型,发现lncRNA AA465934可以与tristetraprolin(TTP)结合,阻断TTP-PIM2的结合从而抑制其降解,下调高迁移率族蛋白B1(high mobility group box, 1 HMGB1),从而逆转自噬下调并改善足细胞损伤[27]。

通过调控细胞自噬,ncRNA在改善肾纤维化方面表现出较优的效果。Yang等[28]研究表明,下调miR-376b的表达可以通过上调CKD小鼠中ATG5所诱导的巨噬细胞自噬来缓解肾间质纤维化。同样,下调miR-32-5p的表达通过靶向母对抗磷酸化蛋白同源物7(mothers against decapentaplegic homolog 7, SMAD7),从而减轻DN大鼠的自噬抑制、上皮间充质转化和肾纤维化[29]。此外,circ Inpp5b通过与DEAD-box解旋酶1(The DEAD-box RNA1, DDX1)结合并促进其溶酶体降解来改善

表1　ncRNA调控细胞凋亡影响CKD的相关靶点和机制

Table 1　The pertinent targets and mechanisms through which ncRNAs regulate apoptosis in CKD

Item	ncRNA	Mechanism of action	Role in apoptosis	Impact on CKD	Reference
miRNA	miR-181a	Targets CRY1 to inhibit the TLR/NF-κB pathway	Inhibition	Reduces the levels of urinary albumin, urinary uric acid, urinary urea, serum urea nitrogen, and serum creatinine	[11]
	miR-27b-3p	Binds to the 3′-UTR of STAT1 to downregulate its expression	Inhibition	Alleviates renal fibrosis	[12]
	miR-1929-5p	Hcy-mediated upregulation of DNMT1 and EZH2 leads to epigenetic silencing of miR-1929-5p, following c-Myc-dependent recruitment of DNMT1 and EZH2 to the miR-1929-5p promoter	Inhibition	Alleviates podocyte injury	[13]
	miR-19b-3p	Inhibits the lncRNA LINC00667/CTGF pathway	Inhibition	Alleviates renal fibrosis	[16]
lncRNA	lncRNA MALAT1	Activates the Nox4/AMPK/mTOR pathway through interaction with Lin28A	Activation	Aggravates renal tubular epithelial injury	[14]
	lncRNA NOP14-AS1	Inhibits miR-326 and its downstream PI3K/AKT pathway	Inhibition	Alleviates renal fibrosis	[15]
	lncRNA XIST	Binds to miR-19b to upregulate SOX6 expression	Activation	Aggravates renal fibrosis	[17]
circRNA	circ MRP4	Acts as a sponge for miR-499-5p, leading to the upregulation of its target RRAGB and subsequent activation of the mTORC1/P70S6K pathway	Activation	Aggravates podocyte injury	[18]
	has_circ 0037128	Acts as a sponge for miR-31-5p to upregulate KLF9 expression	Activation	Aggravates podocyte injury	[19]

CRY1: cryptochrome circadian regulator 1; TLR: Toll-like receptor; NF-κB: nuclear factor-kappa B; 3′-UTR: 3′-untranslated region; STAT1: signal transducers and activators of transcription1; Hcy: homocysteine; DNMT1: DNA methyltransferase 1; EZH2: enhancer of zeste homolog 2; c-Myc: cellular myelocytomatosis oncogene; CTGF: connective tissue growth factor; Nox4: NADPH oxidase 4; AMPK: Adenosine 5‘-monophosphate-activated protein kinase; mTOR: mechanistic target of rapamycin; Lin28A: Lin-28 homolog A; AKT: Protein Kinase B; PI3K: Phosphoinositide 3-Kinase; SOX6: SRY-box transcription factor 6; RRAGB: Homo sapiens Ras-related GTP binding B; mTORC1: mechanistic target of rapamycin complex1; KLF9: Kruppel-like factor 9; P70S6K: ribosome S6 protein kinase.

CKD小鼠的肾间质纤维化[30]。最新研究表明，在单侧输尿管梗阻（unilateral ureteral obstruction，UUO）小鼠模型，低氧诱导产生的tRNA-Asp-GTC-3′tDR能通过形成G-四链体结构捕获假尿苷合成酶7蛋白（pseudouridine synthase 7，PUS7），从而调节自噬通量来维持肾内细胞动态平衡，保护细胞免受损伤、炎症和纤维化的影响[8]。血管钙化也是CKD的重要并发症之一，有证据表明特定的miRNA通过表观遗传调控参与异位钙化的过程，例如下调miR-30b的表达可通过mTOR信号通路降低线粒体膜电位和自噬，加速血管钙化，而上调miR-30b的表达则减弱了体内血管钙化[31]。

表2 ncRNA调控细胞自噬影响CKD的相关靶点和机制

Table 2 The pertinent targets and mechanisms through which ncRNAs regulate autophagy in CKD

Item	ncRNA	Mechanism of action	Role in autophagy	Impact on CKD	Reference
miRNA	miR-7977	Binds to the 3′-UTR of G6PD to downregulate its expression	Activation	Impairs the endocytosis of renal tubular epithelial cells	[24]
	miR-150-5p	Binds to the 3′-UTR of Sirt1, thereby activating downstream p53 acetylation and AMPK signaling	Inhibition	Aggravates podocyte injury	[25]
	miR-376b	Binds to the 3′-UTR of ATG5 to downregulate its expression	Inhibition	Aggravates renal interstitial fibrosis	[28]
	miR-32-5p	Upregulates SMAD7 expression	Inhibition	Aggravates renal fibrosis	[29]
	miR-30b	Downregulates SOX9 expression and inhibits activation of the mTOR pathway	Activation	Alleviates CKD-induced vascular calcification	[31]
lncRNA	lncRNA AK044604	Inhibits the Sirt1/GSK3β pathway	Inhibition	Aggravates podocyte injury	[26]
	lncRNA AA465934	Binds to TTP, inhibiting TTP-PIM2 binding and thereby preventing TTP degradation, resulting in downregulation of HMGB1 expression	Activation	Alleviates podocyte injury	[27]
circRNA	circ Inpp5b	Binds to DDX1 and promotes its lysosomal degradation	Activation	Alleviates renal interstitial fibrosis	[30]
tsRNA	tRNA-Asp-GTC-3′tDR	Forms a G-quadruplex structure that binds to and sequesters PUS7, thereby inhibiting pseudouridylation of histone mRNA	Activation	Alleviates renal fibrosis	[8]

3′-UTR: 3′-untranslated region; G6PD: glucose-6-phosphate dehydrogenase; AMPK: Adenosine 5‘-monophosphate-activated protein kinase; ATG5: Autophagy-related gene 5; SMAD7: 7mothers against decapentaplegic homolog 7; SOX9: SRY-box transcription factor 9; mTOR: mammalian target of rapamycin; Sirt1: Silent Information Regulator 1; GSK3β: Glycogen synthase kinase 3β; TTP: tristetraprolin; PIM2: proviral insertion in murine lymphomas 2; HMGB1: high mobility group box1; DDX1: DEAD-box RNA1; PUS7: pseudouridine synthase 7.

3 细胞焦亡

3.1 细胞焦亡与慢性肾脏病

焦亡,PCD中一种典型的炎症模式,由病原体或组织损伤驱动炎性小体的组装,激活caspase,从而裂解焦亡的效应蛋白Gasdermin家族,这些裂解的Gasdermin与细胞膜的脂质结合形成膜孔并引起细胞焦亡[32]。在生理水平下,焦亡介导的炎症反应和肾脏常驻细胞死亡通过清除病原体、抑制氧化应激或其他危险信号来发挥保护功能。然而,炎症小体的过度激活和持续性焦亡会引发严重的炎症反应,促进成纤维细胞向肌成纤维细胞分化,最终导致肾纤维化的发生发展[33]。NLRP3/caspase-1/GSDMD信号通路所介导的经典焦亡途径是CKD炎症性肾损伤的主要机制。研究表明,NLRP3主要在肾固有细胞和免疫细胞中表达,例如在肾巨噬细胞、足细胞、内皮细胞中,NLRP3炎性小体其下游效应子可以被激活以促进炎症反应并加速CKD的发生与发展[34]。此外,caspase-3/4/5/11依赖性的非经典焦亡途径也参与了CKD的发生发展。研究发

现，GSDME的表达在UUO小鼠模型中显著升高，而caspase-3抑制剂能够抑制caspase-3介导的GSDME裂解，减轻肾纤维化和肾功能障碍[35]。过度激活的内质网应激会触发C/EBP同源蛋白/caspase-11通路，诱导肾小管上皮细胞的焦亡，加重肾脏结构和功能的损伤[36]。

3.2　非编码RNA在慢性肾脏病中细胞焦亡的调控机制

ncRNA是CKD后肾小管上皮细胞焦亡的关键调节因子（表3）。与健康人相比，IgA肾病患者血清中lncRNA CRNDE和NLRP3表达升高，进一步研究表明，lncRNA CRNDE通过抑制三基序蛋白31（TRIM family member 31，TRIM31）介导的NLRP3泛素化和降解并促进巨噬细胞中NLRP3的激活，从而加剧IgA肾病的进展[37]。一些研究报道了lncRNA和circRNA作为miRNA的“分子海绵”起作用。在DN大鼠中，lncRNA MALAT1的表达显著增加，而miR-23c的表达显著降低，抑制lncRNA MALAT1可以上调miR-23c，继而靶向下调ELAVL1，从而抑制下游蛋白NLRP3、caspase-1和白细胞介素-1β（interleukin-1 β，IL-1β）的表达，减轻肾小管上皮细胞焦亡[38]。而在高葡萄糖诱导的DN细胞模型中，lncRNA MALAT1通过靶向NLRP3的miR-30c促进肾小管上皮细胞焦亡[39]。LncRNA NEAT1通过介导miR-34c/NLRP3轴调节DN大鼠和体外肾小球系膜细胞的焦亡[40]。LncRNA GAS5过表达通过下调miR-452-5p，从而抑制DN中肾小管细胞的焦亡、炎症和氧化应激[41]。肌肉萎缩是CKD常见的并发症，lncRNA GAS5还可以与线粒体翻译延伸因子（mitochondrial translation elongation factor，TUFM）相互作用，引起NLRP3活性增加，促进细胞焦亡的激活，从而导致CKD患者肌肉萎缩[42]。先前研究使用circRNA微阵列分析探讨了高葡萄糖处理的近端肾小管上皮细胞中circRNA的差异表达，发现circ ACTR2能够调节肾小管细胞焦亡、炎症和纤维化[43]。进一步研究表明，circ ACTR2通过充当miR-561的“分子海绵”，激活NLRP3并诱导IL-1β的分泌，从而调节巨噬细胞炎症、肾小管上皮细胞的上皮-间质转化，促进肾纤维化的发展[44]。此外，在DN患者的肾活检组织中，circ 0004951表达显著上调，细胞实验表明其能够吸附并结合miR-93-5p位点，受到分子海绵吸附作用的负向调控，从而上调NLRP3表达，促进肾小管上皮细胞焦亡[45]。

表3　ncRNA调控细胞焦亡影响CKD的相关靶点和机制

Table3　The pertinent targets and mechanisms through which ncRNAs regulate pyroptosis in CKD

Item	ncRNA	Mechanism of action	Role in pyroptosis	Impact on CKD	Reference
lncRNA	lncRNA MALAT1	Targets miR-23c to downregulate ELAVL1 expression, thereby downregulating NLRP3 expression	Inhibition	Exerts a renoprotective effect	[38]
	lncRNA MALAT1	Sponges miR-30c to upregulate NLRP3 expression	Activation	/	[39]
	lncRNA NEAT1	Inhibits miR-34c to upregulate NLRP3 expression	Activation	Aggravates renal injury	[40]
	lncRNA GAS5	Downregulates miR-452-5p expression	Inhibition	/	[41]
	lncRNA GAS5	Interacts with TUFM to enhance NLRP3 activity	Activation	Aggravates CKD-induced muscle atrophy	[42]
circRNA	circ ACTR2	Sponges miR-561 to upregulate NLRP3 expression	Activation	Aggravates renal fibrosis	[44]
	circ 0004951	Binds to miR-93-5p to upregulate NLRP3 expression	Activation	/	[45]

CKD: chronic kidney disease; ELAVL1: ELAV-like protein 1; NLRP3: NOD-like receptor family pyrin domain containing 3; TUFM: mitochondrial translation elongation factor.

4 铁死亡

4.1 铁死亡与慢性肾脏病

铁死亡是一种由铁依赖性磷脂过氧化和活性氧过度积累所驱动的独特的细胞死亡模式,与自噬中自噬体的形成或细胞凋亡中的核碎裂不同,铁死亡的主要特征是线粒体减小、线粒体嵴减少、线粒体膜密度上升和线粒体膜破裂增加[46]。铁死亡受多种细胞代谢信号通路和分子机制直接或间接的调控。在正常肾脏中,近端肾小管中的铁调节蛋白能够调节铁代谢[47]。但铁失衡在肾脏疾病中也较为常见,缺铁会增加CKD患者的死亡率[48],而过度的铁沉积可通过芬顿反应引起氧化损伤,启动铁死亡,加速CKD患者的肾损伤[49]。因此,调节参与铁代谢的蛋白质以恢复肾铁代谢并减少铁死亡的发生对CKD患者来说至关重要。

4.2 非编码RNA在慢性肾脏病中铁死亡的调控机制

ncRNA作为表观遗传调控的关键介质,可通过靶向铁死亡相关分子通路参与CKD的调控,为该疾病的治疗提供了新视角(表4)。研究表明,DN患者表现出血清中铁离子、钙离子和脂质过氧化水平升高,而过表达miR-223-3p通过靶向肌醇1,4,5-三磷酸受体3型(inositol 1, 4, 5-trisphosphate receptor type 3, ITPR3)降低细胞内钙离子的表达,并抑制铁死亡[50]。Fang等[51]研究发现,使用慢病毒载体敲减lncRNA SNHG1的表达可通过miR-16-5p/酰基辅酶A合成酶长链家族成员4(acyl-CoA synthetase long-chain family member 4, ACSL4)轴抑制铁死亡,改善DN。Li等[52]也表明在DN小鼠的血清和肾脏以及体外模型中,circ ASAP2的表达下调,而miR-770-5p的表达上调,进一步研究表明,circ ASAP2解除了miR-770-5p对SOX2的抑制并上调其表达,而SOX2作为转录因子直接结合到SLC7A11的启动子区激活转录并增加其表达,最终减轻了炎症、氧化应激和铁死亡。circNSD1能够通过组蛋白H3第36位赖氨酸(histone H3 lysine 36, H3K36)甲基化下调ACSL4和溶质载体家族39成员14(SLC39A14)表达,从而减轻肾小管上皮细胞中的铁死亡减缓急性肾损伤(acute kidney injury, AKI)到CKD的进展,提示其可作为早期检测CKD转变的诊断标志物和治疗靶点[53]。新出现的证据表明,tsRNA也可以靶向铁死亡的关键成分充当其调节因子,在多种疾病中铁死亡的激活或抑制产生关键影响。在DN小鼠中,过表达tRF3-IleAAT通过与锌指蛋白281(zinc finger protein 281, ZNF281)的3'-UTR结合靶向下调其表达,抑制铁死亡蛋白ACSL4的活性,上调GPX4和溶质载体家族7成员11的表达,从而减轻铁死亡和肾小球系膜细胞中细胞外基质(extracellular matrix, ECM)的合成,最终缓解肾纤维化和功能障碍[54]。

近年来的研究使用生物信息学的方法鉴定了疾病中铁死亡相关的基因,这将有助于识别潜在的生物标志物和治疗靶点,并构建起疾病预后预测模型,为个体化治疗提供新的策略[55]。Sone等[56]通过反复给予低剂量的顺铂来诱导小鼠的CKD模型,并使用高通量测序技术鉴定损伤过程中的miRNA及其靶标mRNA,结果发现,顺铂诱导的miR-429-3p抑制了近端肾小管中有助于分解代谢细胞的支链氨基酸的mRNA,通过上调受伤肾脏中的ACSL4和转铁蛋白受体1来促进铁死亡。CKD患者往往伴有舒张性心力衰竭,这显著影响了患者的预后并增加了临床中管理策略的复杂性,学者使用生物信息学分析筛选该类患者的生物标志物,并构建了涉及376个miRNAs和12个转录因子的miRNA-mRNA调控网络,同时进一步确定了与铁死亡、自噬和免疫过程相关的关键基因[57]。此外,Hu等[58]使用加权基因共表达网络分析确定了与DN铁死亡相关的枢纽基因以及与它们相互作用的ncRNA(has_mi572、hsa_miR-29a-3p、hsa_miR-29b-3p、hsa_miR-208a-3p、hsa_miR-153-3p和hsa_miR-29c-3p)。随着计算生物学和测序技术的不断发展,使用生物信息学分析预测ncRNA与疾病之间的关联将为理解CKD的分子机制提供新的可能性。

5 坏死性凋亡与泛凋亡

坏死性凋亡是指细胞凋亡受到抑制时所发生的一种"替代"死亡形式,虽然它与坏死具有相同的形态特征,例如质膜破裂、细胞器肿胀和核分裂,但它受类似于细胞凋亡的信号通路所调节[59]。CKD中坏死性凋亡通过激活关键信号分子受体相互作用蛋白激酶1(receptor-interacting protein kinase 1, RIPK1),RIPK3和混合谱系激酶样蛋白(mixed

表4　ncRNA调控铁死亡影响CKD的相关靶点和机制

Table 4　The pertinent targets and mechanisms through which ncRNAs regulate ferroptosis in CKD

Item	ncRNA	Mechanism of action	Role in ferroptosis	Impact on CKD	Reference
miRNA	miR-223-3p	Downregulates ITPR3 expression	Inhibition	/	[50]
lncRNA	lncRNA SNHG1	Downregulates miR-16-5p expression to upregulate ACSL4 expression	Activation	Aggravates renal tubular injury and renal fibrosis	[51]
circRNA	circ ASAP2	Downregulates miR-770-5p expression to activate the SOX2/SLC7A11 pathway	Inhibition	Alleviates renal injury	[52]
	circ NSD1	Downregulates ACSL4 and SLC39A14 expression through H3K36 methylation	Inhibition	Attenuates the AKI-to-CKD transition	[53]
tsRNA	tRF3-IleAAT	Binds to the 3′-UTR of ZNF281 to downregulate its expression	Inhibition	Alleviates renal fibrosis	[54]

ITPR3: inositol 1, 4, 5-trisphosphate receptor type 3; ACSL4: acyl-CoA synthetase long-chain family member 4; SOX2: SRY-box transcription factor 2; SLC7A11: solute carrier family 7 member 11; H3K36: histone H3 lysine 36; AKI: acute kidney injury; CKD: chronic kidney disease; 3′-UTR: 3′-untranslated region; ZNF281: zinc finger protein 281.

lineage kinase domain-like protein, MLKL)，导致细胞膜破裂和损伤相关分子模式(damage associated molecular patterns ，DAMP)的释放，从而介导肾小管细胞死亡并导致免疫细胞的募集和肾脏炎症的持续存在，触发成纤维细胞的激活和ECM的沉积。随后，坏死性凋亡、炎症和肾纤维化相互作用构成恶性循环将导致肾功能进行性丧失和终末期肾病的发生[60]。国外学者使用二代测序技术调查了DN小鼠肾脏中miRNA的差异表达模式，发现miR-802、miR-34a、miR-132、miR-101a、mir-379上调最为显著，随后对其潜在靶点进行计算机模型预测，表明炎症、免疫、脂肪生成和坏死性凋亡是与这些miRNA相关的途径[61]。这提示了坏死性凋亡在DN发病机制中的重要性。随后的研究进一步表明，miR-30e可以通过调节RIPK1和RIPK3影响坏死性凋亡，加重DN[62]。

新发现的PCD模式泛凋亡强调了不同类型PCD之间的相互作用，它被定义为先天免疫、炎症和裂解性细胞死亡，其整合了细胞凋亡、焦亡和坏死性凋亡的关键特征，代表着一种高度协调和动态平衡的PCD新模式[63]。Guo等[64]的综述指出，泛凋亡正在成为肾脏疾病发病机制的关键调节因子。通过协调不同的PCD途径，失调的泛凋亡可能通过DAMP(如高迁移率组蛋白1和IL-1β)驱动肾组织损伤，并可能导致肾功能丧失和慢性炎症，提示其可作为肾脏疾病新的治疗靶点和生物标志物。使用生物信息学的初步研究表明，has_miR-101-3p可能在CKD后泛凋亡的调控中具有重要潜力[65]。尽管取得了一定的成就，支持ncRNA通过调控坏死性凋亡和泛凋亡影响CKD过程的科学证据仍较少，未来需借助基因编辑技术、单细胞转录组学、合成生物学等新技术进一步深入研究。

6　新兴研究方向

铜是人体必需的微量元素之一，也是多种关键酶的辅助因子，然而当其浓度超过进化保守的稳态机制维持的阈值时，会产生毒性。当过量的Cu^{2+}进入细胞时，它会易位到线粒体中并还原为Cu^{+}，从而诱导细胞死亡，这个途径被称为铜死亡，其受线粒

体铁氧还蛋白1介导的蛋白质脂酰化的调节[66]。肾脏是铜积累的重要靶器官,一项中国老年人群的横断面研究显示,血铜水平与CKD患病率间存在剂量依赖性正相关[67],当血铜水平升高时肾小球滤过率降低,进一步损害肾功能并加速CKD的进展[68]。双硫死亡是指溶质载体家族7成员11的高表达会加速消耗细胞质中的烟酰胺腺嘌呤二核苷酸磷酸,导致胱氨酸和其他二硫键的异常积累,进而诱导二硫键应激和细胞快速死亡的过程。研究表明,双硫死亡在维持细胞稳态和抵抗应激方面起着重要作用[69]。目前,多项转录组学和单细胞测序研究揭示了DN患者差异性的双硫死亡基因,表明双硫死亡可作为DN的特定靶点,为其发病机制提供了新的见解[69-70]。尽管初步研究已证明了铜死亡和双硫死亡与CKD之间存在关联,但ncRNA是如何通过调控铜死亡和双硫死亡参与CKD进展的直接证据有限,ncRNA与二者之间的关系目前在肾癌领域研究较为广泛,而在CKD领域仍需进一步的研究。

值得注意的是,本研究所讨论的ncRNA主要为miRNA、lncRNA和circRNA。随着高通量测序的发展,一种新兴的ncRNA—tsRNA的生物学作用正逐渐被揭示。Khurana等[71]表明,CKD患者尿液外泌体中tRF-Val、tRF-Leu、tRN-ACys、tRNA-Pro以及tRNA-Glu丰度显著低于健康对照者。本研究提示,tsRNA可能参与CKD后细胞自噬与铁死亡的调控过程。然而该领域研究有限,未来需进一步探讨tsRNA是否可以调控其他PCD过程,从而作为CKD新型生物标志物和治疗靶点。

7 慢性肾脏病中非编码RNA介导的程序性死亡串扰

CKD的发病机制十分复杂,尽管目前尚未完全阐明,但异常的肾脏细胞死亡是其发病机制的核心事件之一。然而需要注意的是,上述所提到的PCD途径在标志物、时程等多方面存在串扰,ncRNA作为整合性枢纽,通过精细调控各种PCD途径,构成了一个复杂的交互网络。其中自噬与其他PCD途径之间的交互作用已被证明。Liu等[72]发现在慢性间歇性缺氧诱导的CKD大鼠中,lncRNA-GAS5的抑制可以减弱体内肾小管上皮细胞凋亡和纤维化,抑制氧化应激,促进自噬,从而减轻大鼠肾损伤。多数研究探讨了足细胞自噬与凋亡的交互作用。例如,抑制miR-383-5p通过激活DN小鼠的足细胞自噬从而减轻高葡萄糖诱导的足细胞凋亡[73]。敲低lncRNA-SNHG17的表达可以通过调节哺乳动物不育系20样激酶1,促进线粒体自噬并减少足细胞的凋亡,最终提供独立于血糖下降的特异性肾脏保护作用[74]。miR-769-5p能够通过转录调节抑制lncRNA SPAG5-AS1的表达,并通过调节AKT/mTOR信号通路抑制足细胞自噬并加重足细胞凋亡[75]。综上所述,未来研究应继续阐明ncRNA介导不同PCD途径间整合性串扰的机制,旨在开发新的CKD治疗靶点。

8 靶向非编码RNA调控程序性死亡的慢性肾脏病疗法

8.1 外泌体疗法

细胞外囊泡是指由各类细胞释放的纳米级脂质双层结构,主要包含外泌体、微囊泡和凋亡小体3种类型,其能够携带蛋白质、脂质和核酸等并被局部或远端细胞摄取,既能作为细胞间通信的介质,也可充当药物递送载体[76]。在肾脏疾病动物模型中,源自细胞培养基的外泌体研究较为广泛,其递送的分子能够减轻炎症反应、抑制肾纤维化和ECM生成,并促进组织再生[77]。

其中间充质干细胞(mesenchymal stem cells,MSCs)因其具有免疫调节和组织修复的特性,是用于肾脏再生的研究最广泛的干细胞。多项研究探讨了MSCs来源的外泌体对CKD后肾纤维化的治疗作用。例如,MSCs来源的外泌体能够将miR-186-5p递送至UUO小鼠的肾脏中,从而减少ECM的积累,并通过TGF-β1/Smad5信号通路减轻细胞上皮间质转化与细胞凋亡,最终改善肾纤维化[78]。人脐带MSCs来源的外泌体通过miR-874-3p靶向RIPK1调节坏死性凋亡,从而减轻肾小管上皮细胞损伤并增强修复,减慢CKD的转化过程[79]。母乳MSCs来源的外泌体能够通过分泌抗纤维化的miRNA如miR-29b、miR-181和Let-7b来减少腺嘌呤诱导的肾损伤,并通过lncRNA-NBR-2调节SNHG7表达来增强肾自噬[80]。脂肪MSCs来源的外泌体能够增加CKD模型中miRNA-145的表达,

并通过减轻细胞凋亡、炎症和肾纤维化来改善肾损伤，当与罗氟司特联合使用时，其治疗效果更优[81]。除肾纤维化外，Liu等[82]研究表明骨髓MSCs来源的外泌体还可通过递送miR-381-3p抑制其靶基因核转录因子5的表达，从而减轻CKD大鼠血管平滑肌细胞凋亡，抑制血管钙化。此外，一些研究探究了其他细胞来源的外泌体在CKD中的治疗潜力。研究表明，系膜细胞来源的外泌体能够上调miR-4455的表达直接靶向Unc-51样激酶2，并调节LC3Ⅱ与LC3I的比例和P62水平，从而减轻足细胞自噬并加重足细胞损伤[83]。M2巨噬细胞来源的外泌体中含有高表达的miR-25-3p，能够通过抑制双特异性蛋白磷酸酶1的表达，激活足细胞自噬以减轻足细胞损伤[84]。尽管有大量的临床前研究证实了外泌体的治疗作用，但其临床证据仍有限。Nassar团队[85]的研究发现，MSCs来源的细胞外囊泡治疗3个月后，能够上调CKD患者肾组织细胞再生与分化标志物的表达，并减轻炎症反应，这一发现为其临床应用提供了重要证据。总体而言，目前证据支持外泌体作为CKD有潜力治疗方法的可能性，尽管仍需要进一步的研究来确定其最佳来源、剂量以及递送途径，并在大规模的临床试验中评估其长期安全性和有效性。此外，未来研究可考虑将外泌体疗法可以与其他组织工程技术（例如生物材料、支架、3D生物打印等）联合运用，以期获得更优的疗效。

8.2　中药及其活性成分

中药及其活性成分可以通过调控ncRNA靶向调节不同类型的PCD过程，在CKD的治疗中展现出巨大的潜力，因其成本低、副作用小的优点，正逐渐成为传统CKD疗法的补充或替代策略。

中药及其活性成分以ncRNA为分子开关，能够有效的调控肾脏细胞的凋亡和自噬过程。姜黄素是从姜黄中提取的植物多酚，研究表明姜黄素通过靶向调节circ 0008925/miR-204-5p/IL-1β信号转导轴减轻细胞凋亡和炎症，并在UUO小鼠模型中缓解肾纤维化[86]。大豆苷元是植物雌激素的主要亚类之一，研究表明大豆苷元通过调节miR-33a和miR-27a的表达及其与血管紧张素Ⅱ1型受体、血管紧张素（1-7）受体之间的相互作用，从而减轻卵巢切除术后UUO大鼠的细胞凋亡、肾功能不全、纤维化和肾小球硬化[87]。中药复方肾苏Ⅳ通过以lncRNAH19/DIRAS3/mTOR依赖性方式促进自噬，对CKD大鼠的肾小球足细胞发挥保护作用[88]。尿毒康颗粒是广东省中医院的自制方剂，研究表明其通过调节miR-214-3p/ Sirt1信号通路增加DN后自噬、减少系膜细胞增殖和炎症[89]。白藜芦醇能够增加DN小鼠miR-18a-5p的表达，而足细胞中miR-18a-5p的过表达增加了LC3II与LC3I的比例，并抑制了裂解的caspase 3蛋白表达，通过自噬途径减缓肾损伤[90]。二氢杨梅素也可以通过调节miR-155-5p/磷酸酶张力蛋白同源物（recombinant phosphatase and tensin homolog，PTEN）通路和磷脂酰肌醇3-激酶（phosphatidylinositol 3-kinase，PI3K）/蛋白激酶B（protein kinase B，Akt）/mTOR通路，促进DN大鼠的自噬，从而减轻肾间质纤维化[91]。Li等[92]发现miR-141-3p可作为PTEN/Akt/mTOR信号通路的上游，介导雷公藤内酯所诱导的自噬增强从而缓解DN小鼠的肾纤维化。

焦亡及铁死亡也是中药及其活性成分调控的主要作用靶点。葛根素是一种具有特异性肾保护作用的黄酮类化合物，研究发现葛根素通过调节lncRNA NEAT1，抑制caspase-1和GSDMD的表达，从而减轻CKD大鼠模型中的肾小管上皮细胞焦亡，而lncRNA NEAT1的过表达阻断了葛根素的抗焦亡作用[93]。此外，葛根素还可以靶向miR-342-3p/转化生长因子β/Smad轴，抑制CRF大鼠肾小管上皮细胞焦亡，减轻肾损伤[94]。关键成分为黄芪和三七总苷的肾痿方可以通过减少lncRNA A33的表达抑制下游的铁死亡途径，从而减轻CKD小鼠的肾纤维化[95]。吉马酮可正向调控mmu_circRNA 0000309的表达，通过靶向miR-188-3p/GPX4轴，从而减轻DN小鼠中铁死亡依赖性的线粒体功能失调和足细胞凋亡[96]。

8.3　新型药物

近年来，国内外学者广泛报道了基于ncRNA调控PCD治疗CKD的药物研究，并深入探讨了其作用机制。SIAH3是一种E3泛素连接酶，对线粒体自噬起抑制作用，在高尿酸诱导的CKD小鼠模型中，注射褪黑素可以上调miR-4516的表达从而抑制SIAH3，并增强PINK1/Parkin所介导的线粒体自噬，减少功能失调的线粒体，并减轻肾纤维化的过程，从而改善CKD[97]。此外，来自褪黑素刺激的MSCs来源的外泌体能够上调与抗炎和抗纤维化相关的miR-29b-3p、miR-7a-3p、let-7b-5p、let-7c-3p、miR-153-3p、miR-26a-2-3p、miR-846-5p基因

表达,通过抑制细胞凋亡和纤维化细胞增殖,改善CKD小鼠模型中的肾脏炎症和纤维化[98]。达格列净是一种治疗2型糖尿病的新型药物,研究表明其通过miR-155-5p/血红素加氧酶1/NLRP3轴抑制DN小鼠的足细胞焦亡[99]。药物性肾损伤可表现为进行性CKD或终末期肾病,在庆大霉素诱导肾毒性大鼠模型中,达格列净可增加miR-21表达以及降低miR-181a表达,减少氧化应激、肾小管细胞凋亡并在治疗14 d后恢复肾结构[100]。

9 总结与展望

本文系统综述了ncRNA(miRNA、lncRNA和circRNA)参与CKD后PCD(主要是细胞凋亡、自噬、焦亡和铁死亡)调控的最新研究进展,并提出ncRNA作为CKD后细胞命运的主调节因子。外泌体疗法、中药活性成分以及新型药物通过调控ncRNA的表达,能够靶向调节不同的PCD模式,从而有效缓解CKD导致肾脏代谢失衡所引起的负面影响,有助于恢复肾小球滤过功能和肾小管重吸收功能,维持肾组织的稳态。尽管如此,ncRNA在临床转化方面仍面临着体内递送效率低、组织靶向性差、免疫原性以及安全性低等诸多挑战。未来研究应注重以下方面:①探究如何实现ncRNA在特定肾脏细胞(如足细胞、肾小管上皮细胞或系膜细胞)的特异性靶向。②探讨如何优化基因编辑技术并提高ncRNA的稳定性和降低免疫原性,利用硫代磷酸酯骨架修饰、2′-O-甲基化等化学修饰策略,以及工程化外泌体、脂质纳米颗粒、靶向肽偶联物等递送平台,将有助于高效、安全的递送或敲减ncRNA,为CKD患者提供更精准和个性化的治疗方案。③不同PCD模式之间存在广泛的串扰,寻找同时参与多种PCD的关键因子并探讨ncRNA对其的调控作用,或者寻找可同时调节多种PCD的ncRNA,构建CKD后复杂的调控网络。④借助人工智能技术,使用更为先进的生物信息学分析方法探索ncRNA的调控网络,以确定新的调控因子和潜在的治疗靶点,同时开发基于ncRNA的生物标志物用于CKD的早期诊断、监测和评估过程中。

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