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线粒体自噬调控慢性肾脏病细胞焦亡与铁死亡

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[摘 要] 慢性肾脏病(chronic kidney disease，CKD)是一种肾损伤或肾功能下降的慢性进展性疾病，具有发病隐匿、危害大的特点，现已成为危及人类健康的世界公共卫生问题。异常的细胞死亡可能直接或间接导致肾受损，其中过度的细胞焦亡与铁死亡是CKD病理进程中的核心事件，且二者可能通过活性氧释放等方式交互作用，从而加重肾损伤。线粒体自噬作为一种选择性清除受损线粒体的特殊自噬过程，在维持机体稳态方面发挥重要作用。CKD中线粒体自噬机制受损，增强线粒体自噬信号通路的表达可减缓肾细胞中的炎症反应、减少铁蓄积与脂质过氧化等，表明线粒体自噬信号通路可能是调控肾细胞焦亡与铁死亡的关键，有望成为预防、诊断与治疗CKD的新靶点。

[关键词] 慢性肾脏病；细胞死亡；焦亡；铁死亡；线粒体自噬

Regulation of pyroptosis and ferroptosis by mitophagy in chronic kidney disease

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ABSTRACT Chronic kidney disease (CKD) is a chronic progressive disease characterized by kidney injury or declining renal function. With its insidious onset and significant harm, CKD has become a major global public health concern. Abnormal cell death can directly or indirectly contribute to kidney injury, among which excessive pyroptosis and ferroptosis are central events in CKD pathogenesis. These two forms of cell death may interact through mechanisms such as reactive oxygen species release, further aggravating renal damage. Mitophagy, a selective autophagic process that removes damaged mitochondria, plays an

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important role in maintaining cellular homeostasis. In CKD, mitophagy is impaired; however, enhancing mitophagy signaling pathways can alleviate inflammation, reduce iron accumulation and lipid peroxidation in renal cells. This suggests that mitophagy may be a key regulator of pyroptosis and ferroptosis in kidney cells and holds potential as a novel target for the prevention, diagnosis, and treatment of CKD.

KEY WORDS chronic kidney disease; cell death; pyroptosis; ferroptosis; mitophagy

慢性肾脏病(chronic kidney disease，CKD)指由各种病因导致的病程超过3个月的肾结构或功能异常，包括糖尿病肾病、高血压肾病、肾小球肾炎、狼疮性肾炎等，常见病理表现为血尿指标、肾病理学与影像学异常，或伴肾小球滤过率降低。研究显示，CKD已成为世界公共卫生负担，全球患病率11%~13%[1]，国内患病率约8.2%[2]。2018—2019年，中国成人CKD患者数量高达8 200万；在2022年亚洲CKD患病率的荟萃分析中，中国成人CKD患者数量已位居亚洲第一[3]。CKD早期因症状不明显，常被忽视，导致诊断及治疗延误，直至发展为晚期或终末期肾病，严重危害患者健康，增加家庭与社会的医疗负担。

CKD的发病机制十分复杂，尚未完全阐明。现有研究[4-5]表明，肾异常的细胞死亡已成为肾病发病机制的核心事件，细胞死亡可直接或间接通过募集免疫细胞和刺激炎症反应导致肾损伤。CKD中存在多种细胞死亡模式，以炎症为核心的焦亡和以铁蓄积、脂质过氧化为标志的铁死亡异常被认为是CKD病理进程中的重要一环[6-7]。线粒体作为细胞死亡的信号中枢，具有调控细胞死亡的能力[8]。近年研究认为，线粒体自噬与CKD的发生和发展密切相关[9]，可能通过调控细胞焦亡与铁死亡参与肾病进程，进一步加重肾损伤[10]。

1 焦亡与铁死亡参与CKD的发生和发展

1.1 肾细胞焦亡

持续的低度炎症是CKD发生和发展的关键环节[11]，多种炎症生物标志物与CKD发病率相关，在先天免疫反应和适应性免疫反应中可能损害肾功能[12]。细胞焦亡是一种由炎症小体引发的细胞程序性死亡，死亡过程中伴随大量促炎性细胞因子释放，加重肾损伤。

胱天蛋白酶-1(cysteinyl aspartate acid specific protease-1，Caspase-1)是经典焦亡途径中的关键分子，可由核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体3(nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3，NLRP3)炎症小体激活，一方面切割消皮素D(gasdermin D，GSDMD)，诱导细胞破裂，释放内容物，产生炎症反应；另一方面促进白细胞介素(interleukin，IL)-1β前体和IL-18前体活化，使IL-1β和IL-18释放到胞外，扩大炎症反应[13-14]。

抑制肾炎症可以防治CKD。在高脂肪和高果糖诱导的CKD模型小鼠中，木兰花碱可通过促进帕金蛋白(Parkin)/同源性磷酸酶张力蛋白诱导激酶1[phosphatase and tensin homologue (PTEN)-induced putative kinase 1，PINK1]依赖性线粒体自噬来抑制NLRP3/Caspase-1介导的焦亡，从而改善肾损伤[15]。敲低长链非编码RNA(long noncoding RNA，lncRNA)X染色体失活特异转录因子(X inactive specific transcript，XIST)能够抑制焦亡，缓解糖尿病肾病[16]。使用VX-765治疗糖尿病肾病小鼠可降低其体内Caspase-1表达水平，抑制炎症细胞浸润并下调焦亡相关蛋白质表达水平，减轻肾小管间质纤维化，从而改善肾功能[17]。在糖尿病肾损伤小鼠中，葛根素通过抑制足细胞中Caspase-1介导的细胞焦亡来减轻肾小球病变和足细胞损伤，从而发挥保护作用[18]。在高血糖状态下，吡咯喹啉醌可通过缓解小鼠肾线粒体功能障碍、减少活性氧(reactive oxygen species，ROS)产生和抑制核因子κB(nuclear factor kappa-B，NF-κB)/焦亡途径的激活来缓解肾纤维化[19]。和厚朴酚通过抑制NLRP3/IL-33/生长刺激表达基因2蛋白(growth stimulation expressed gene 2，ST2)轴活化，减轻狼疮性肾炎中细胞焦亡通路异常激活引发的肾小管上皮细胞炎症，从而发挥防治作用[20]。

1.2 肾细胞铁死亡

铁死亡是由于细胞内铁蓄积而导致毒性脂质过氧化物升高的非凋亡性细胞死亡模式。铁蓄积和脂质过氧化增加是铁死亡的标志[21]，也是促进CKD发

生的重要决定因素[22]。

正常情况下，人体内大部分铁以铁蛋白的形式储存，少数铁转运至细胞质中的不稳定铁池(labile iron pool，LIP)。当体内铁蓄积时，细胞LIP中的游离铁(Fe^{2+})增加，而过多Fe^{2+}能通过芬顿反应产生大量羟基自由基，参与脂质过氧化，导致铁死亡[23]。其中，脂酰辅酶A合成酶长链家族成员4(acyl-CoA synthetase long chain family member 4，ACSL4)被视为铁死亡的关键参与者，参与酯化游离多不饱和脂肪酸(polyunsaturated fatty acids，PUFAs)，使PUFAs氧化成有毒的脂质过氧化物[24]。

铁死亡还表现为抗氧化系统的损伤。细胞内谷胱甘肽(glutathione，GSH)耗竭或谷胱甘肽过氧化物酶4(glutathione peroxidase 4，GPX4)失活会降低磷脂过氧化物(phospholipid hydroperoxide，PL-OOH)等有毒脂质过氧化物的清除率，导致铁死亡[25]。

抑制铁死亡可减轻肾损伤程度。细胞抗氧化反应的关键调节因子核转录因子红系2相关因子2(nuclear factor-erythroid 2-related factor 2，Nrf2)已被证实具有调节GPX4、防止脂质过氧化和Fe^{2+}蓄积的能力，下调Nrf2将导致细胞铁死亡增加[26]。高糖诱导的肾小管上皮细胞铁死亡异常激活，重链铁蛋白1(ferritin heavy 1，FTH1)表达下降，给予槲皮素干预后细胞铁死亡受到抑制[27]。使用db/db小鼠联合链脲佐菌素建立糖尿病肾病动物模型发现，小鼠肾ACSL4表达增加，肾Fe^{2+}蓄积，从而诱导了肾铁死亡，加剧肾损伤[28]。在糖尿病患者肾活检样本和糖尿病小鼠肾中，*GPX4* mRNA表达显著降低，脂质过氧化增加；使用铁死亡抑制剂铁抑素-1(ferrostatin-1，Fer-1)治疗糖尿病小鼠后，上述指标得到改善[29]。恩格列净可能通过促进腺苷酸活化蛋白激酶[adenosine 5'-monophosphate (AMP)-activated protein kinase，AMPK]介导的Nrf2途径激活，从而降低糖尿病肾病患者肾小管铁死亡水平[30]。在高盐饮食诱导的高血压肾病小鼠中，桃红四物汤能够通过下调p53/Nrf2/p21通路抑制铁死亡，从而减轻肾损伤[31]。

1.3 焦亡与铁死亡的交互作用

焦亡相关的多种信号通路激活可诱导铁死亡，同时铁死亡的发生常常伴随着炎症、焦亡的产生[32]。在微塑料诱导的肝损伤中，细胞同时表现出焦亡和铁死亡，并伴有氧化应激和肝炎症[33]。在脓毒症小鼠中，焦亡与铁死亡可能存在交互作用，二者共同参与急性肺损伤进程，激活线粒体醛脱氢酶2(aldehyde dehydrogenase 2，ALDH2)可通过抑制细胞焦亡与铁死亡改善肺部损伤[34]。在心肌纤维化小鼠中，混合谱系激酶3(mixed lineage kinase 3，MLK3)可参与调控心肌细胞的焦亡和铁死亡，抑制MLK3对压力超负荷引起的心肌纤维化具有改善作用[35]。人脐带间充质干细胞衍生的外泌体可通过PINK1/Parkin介导的线粒体自噬对抗细胞焦亡和铁死亡，抑制创伤性脑损伤，从而保护神经[36]。在焦亡与铁死亡共同参与以上疾病进程的研究中，氧化应激与脂质过氧化被视为同时调控焦亡与铁死亡的关键环节，例如敲除抗氧化因子*GPX4*不仅能诱发铁死亡，还可导致GSDMD裂解，激活细胞焦亡[37]。最新研究[38]表明，锌、铜等过渡金属与焦亡、铁死亡之间存在相互作用，破坏金属稳态将改变细胞生存状态，其中ROS的释放是主要交互方式之一。此外，损伤相关分子模式(damage-associated molecular patterns，DAMP)是焦亡和铁死亡的共同特征，由铁死亡产生的DAMP可以反过来触发细胞焦亡[39]。

肾病中同时存在焦亡与铁死亡。在糖尿病肾病中，五味子A可通过脂联素受体1(Adiponectin receptor 1，AdipoR1)/AMPK信号通路减轻线粒体损伤，进而降低肾的焦亡与铁死亡水平[40]。在镉诱导的绵羊肾损伤中，硒能够提高GPX4表达水平，缓解肾细胞焦亡与铁死亡[41]。敲除小鼠焦亡相关基因*Nlrp3*可减轻脂多糖诱导的肾炎症与铁死亡[42]，而抑制铁死亡可阻断吡虫啉诱导的小鼠肾细胞焦亡[43]，提示肾损伤中的焦亡与铁死亡可能存在交互作用。然而，目前有关CKD中焦亡与铁死亡交互作用的研究较少，有待深入探讨。

2 线粒体自噬调控焦亡与铁死亡

肾线粒体具有清除废物、调节体液与电解质平衡的作用，因此肾线粒体功能失调成为肾相关疾病的病因之一[44]。已有研究[45-46]表明，在糖尿病肾病患者与小鼠的肾皮质中均发现了线粒体碎片的积累，这提示慢性损伤状态下的肾线粒体清除机制受损，而破碎的线粒体持续积累将进一步加重细胞内氧化应激和肾结构功能障碍。自噬作为最主要的线粒体清除机制，可将受损的线粒体通过自噬系统选择性地运输到溶酶体进行降解，以维持线粒体质量与数量[8]。现有研究[10]发现，线粒体自噬调节的细胞死亡在人类疾病中起着重要作用。有效清除受损线粒体是维持细胞生理功能的关键，异常的线粒体自噬将促使CKD进一步恶化[47]。线粒体自噬可能通过同时调控焦亡与铁死亡改善肾或肾细胞慢性损伤，是CKD治疗干预的新靶点(图1)。

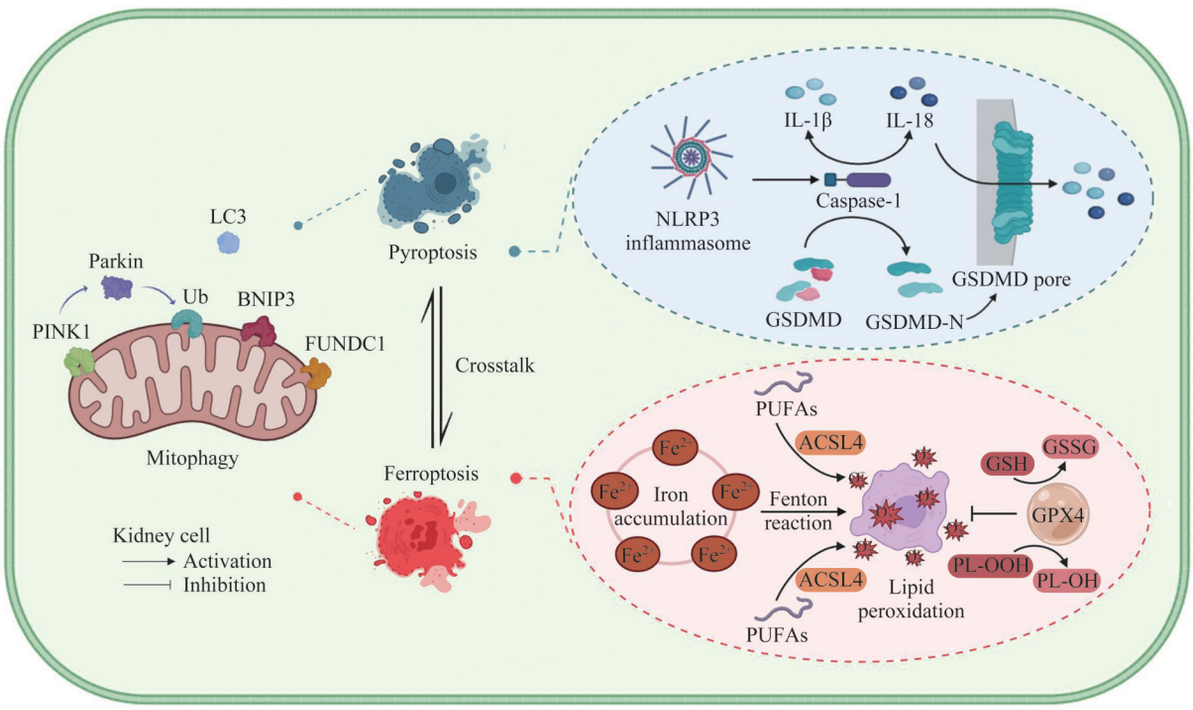

图1 线粒体自噬调控细胞焦亡与铁死亡

Figure 1 Mitophagy regulates cellular pyroptosis and ferroptosis

PINK1: Phosphatase and tensin homologue-induced putative kinase 1; Ub: Ubiquitin; BNIP3: B-cell lymphoma-2-interacting protein 3; FUNDC1: FUN14 domain containing 1; LC3: Microtubule-associated protein 1 light chain 3; NLRP3: Nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3; Caspase-1: Cysteinyl aspartate acid specific protease-1; IL-1β: Interleukin-1β; IL-18: Interleukin-18; GSDMD: Gasdermin D; GSDMD-N: Gasdermin D N-terminal fragment; PUFAs: Polyunsaturated fatty acids; ACSL4: Acyl-CoA synthetase long chain family member 4; GPX4: Glutathione peroxidase 4; GSH: Glutathione; GSSG: Oxidized glutathione; PL-OOH: Phospholipid hydroperoxide; PL-OH: Phospholipid-alcohol.

2.1 线粒体自噬的主要调控机制

长期以来，有关线粒体自噬机制探讨的研究受到广泛关注。线粒体自噬功能的正常发挥可通过泛素依赖和非泛素依赖途径实现。泛素依赖途径依靠线粒体表面蛋白质的广泛泛素化来促进线粒体自噬，是最主要的线粒体自噬途径。其中，PINK1和Parkin是该途径参与调节线粒体自噬最重要的蛋白质。当PINK1进入线粒体内膜的过程受阻时，PINK1可在线粒体外膜募集并激活Parkin，导致线粒体膜表面蛋白质泛素化[48-49]。这些泛素化的蛋白质与微管相关蛋白1轻链3(microtubule-associated protein 1 light chain 3，LC3)结合，将促使线粒体自噬发生[50]。非泛素依赖途径可直接募集自噬受体蛋白质到线粒体，随后与LC3结合，促使自噬体吞噬线粒体。在哺乳动物中，Nip3样蛋白X(Nip3-like protein X，NIX)、B细胞淋巴瘤-2互作蛋白3[B-cell lymphoma-2 (Bcl-2)-interacting protein 3，BNIP3]与FUN14结构相关蛋白1(FUN14 domain containing 1，FUNDC1)是目前研究最为广泛的3种自噬受体蛋白质[51]。

2.2 线粒体自噬调控肾细胞焦亡

线粒体是炎症反应的中心，当细胞损伤或受到病毒、细菌攻击时，线粒体可通过NLRP3炎症小体等途径激活Caspase-1参与炎症反应与细胞焦亡[52]。线粒体自噬和焦亡作为程序性死亡的不同形式，可被高糖、高脂等刺激共同激活，参与多种疾病的发生或发展。

激活线粒体自噬可有效减缓肾细胞焦亡水平。在大鼠肾小管导管上皮细胞中，黄曲霉毒素B1可通过阻碍PINK1/Parkin途径，抑制线粒体自噬，显著提高NLRP3、Caspase-1等焦亡相关蛋白质表达水平，促进细胞焦亡[53]。人参皂苷Rb1可激活PINK1/Parkin介导的线粒体自噬从而减轻氯丙醇类似物诱导的肾细胞焦亡[54]。在脓毒症诱导的急性肾损伤中，骨髓间充质干细胞可以通过上调SIRT1/Parkin来促进线粒体自噬，减轻细胞炎症反应与焦亡水平，从而使大鼠急性肾损伤得到改善[55]；Zn^{2+}通过抑制去乙酰化酶沉默信息调节因子7(silence information regulator 7，SIRT7)活性增加Parkin乙酰化，促进线粒体自噬，抑

制NLRP3炎症小体活化和细胞焦亡[56]；尿石素A能够上调BNIP3介导的线粒体自噬，部分逆转NLRP3的激活，从而减轻肾损伤[57]。

2.3 线粒体自噬调控肾细胞铁死亡

线粒体自噬可能参与了铁死亡进程，但其具体如何影响铁死亡的发生和发展尚无确切定论[58]。表观遗传调节因子泛素样PHD和无名指结构域1(ubiquitin like with PHD and ring finger domains 1，UHRF1)可抑制硫氧还蛋白互作蛋白(thioredoxin-interacting protein，TXNIP)表达，促进PINK1介导的线粒体自噬，从而抑制铁死亡[59]。AMPK磷酸化可增强PINK1/Parkin调节的线粒体自噬，进而减轻肾小管上皮细胞铁死亡[60]。激活线粒体自噬可减少铁死亡和肾损伤，而抑制PINK1/Parkin或BNIP3介导的线粒体自噬会加重ROS释放、脂质过氧化、细胞铁死亡[61]。给予抗铁性药物Germacrone不仅上调PINK1/Parkin依赖性线粒体自噬，还抑制高糖暴露下肾小管细胞中的铁蓄积，通过线粒体DNA/环鸟苷酸-腺苷酸合酶(cyclic GMP-AMP synthase，cGAS)/干扰素基因刺激因子(stimulator of interferon genes，STING)信号通路改善细胞铁死亡[62]。

然而，也有研究认为提高线粒体自噬水平会促进细胞铁死亡，例如草酸盐处理的HK-2细胞外泌体可通过调节PINK1和Parkin来增强线粒体自噬，同时上调苄氯素1(beclin 1，BENC1)增强细胞自噬并导致铁死亡的加剧[63]；金属镉和纳米塑料的联合暴露能够诱导氧化应激、铁死亡和过度的线粒体自噬，加重小鼠肾损伤[64]。

3 结　语

焦亡、铁死亡是CKD发生和发展中的核心事件，线粒体自噬可能通过同时调控焦亡与铁死亡改善肾或肾细胞慢性损伤，是CKD治疗干预的新靶点。现有针对CKD的治疗方案多以控糖、降脂、降压及配合使用肾素-血管紧张素系统阻断剂为主，后期肾功能恶化时多采取透析、肾移植，但尚无特效治疗手段。高效低毒的植物化学物在预防、治疗CKD中发挥重要作用，如安石榴苷、芍药素、槲皮素、黄芩苷、芹菜素等多种植物化学物已被证实具备改善CKD的作用，并且具有靶向线粒体自噬潜能[65-69]。未来可深入挖掘CKD进展的关键环节，同时寻找更加安全、有效的肾病干预方式，着力减少CKD带来的公共卫生问题。

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