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综 述

陆利民，复旦大学上海医学院生理与病理生理学系教授，博士生导师；副主任；上海市肾脏发育和儿童肾脏病研究中心副主任。中国生理学会肾脏专业委员会副主任委员兼秘书长；中国生理学会教育工作委员会委员；中华医学会糖尿病学分会糖尿病微血管并发症学组委员；《生理学报》副主编；《复旦大学学报 (医学版)》编委。陆利民教授长期从事肾脏生理与病理生理研究，科研工作集中在糖尿病致肾脏慢性损伤机制、急性肾损伤发生机制及肾脏纤维化发生机制等。以通讯或第一作者在 *Kidney Int*、*Circ Res*、*Hypertension*、*Nephrol Dial Transplant*、*Am J Physiol Renal Physiol*、*J Mol Med (Berl)*、*Acta Pharmacol Sin* 等杂志发表研究论文 70 多篇；主编、参编《生理学》教材、参考书及专著十多部。曾获中国高校科学技术进步二等奖；教育部科技进步奖二等奖；上海市科学技术进步二等奖等。

调节性细胞死亡与急性肾损伤

倪佳芸，陆利民*

复旦大学基础医学院生理与病理生理学系，上海 200032

摘 要：急性肾损伤(acute kidney injury, AKI)是指各种病理因素引起的肾功能短期内出现急速下降的临床综合征。在AKI发展过程中，具有重吸收和排泌功能的肾小管是损伤的重要靶点，极易因病理刺激发生细胞死亡，肾小管上皮细胞的丢失是肾功能受损的重要原因。近年来，多种细胞死亡方式被逐渐认识，研究者发现坏死性凋亡、焦亡与铁死亡等调节性细胞死亡(regulated cell death, RCD)方式都参与AKI的发生和发展。本文就各类RCD参与AKI进展的研究现状进行概述，试图加深对AKI发生机制的认识，并为探索AKI的临床治疗新思路提供思考。

关键词：急性肾损伤；调节性细胞死亡；坏死性凋亡；焦亡；铁死亡

Acute kidney injury and regulated cell death

NI Jia-Yun, LU Li-Min*

Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Fudan University, Shanghai 200032, China

Abstract: Acute kidney injury (AKI) refers to a clinical syndrome in which renal function declines rapidly in a short period of time caused by various pathological factors. During the development of AKI, renal tubules with the functions of reabsorption and excretion are prone to cell death due to external pathological stimuli, which is an important cause of impaired renal function. In recent years, a variety of new cell death pathways have been gradually recognized. Researchers have now found that regulated cell death (RCD), such as necroptosis, pyroptosis and ferroptosis, are important regulatory mechanisms of AKI. This article will summarize the research advances of various types of RCD involved in the process of AKI, aiming to deepen the understanding of AKI and provide innovative thoughts for the clinical treatment of AKI.

Key words: acute kidney injury; regulated cell death; necroptosis; pyroptosis; ferroptosis

急性肾损伤 (acute kidney injury, AKI) 通常是指短期内肾功能突然或持续下降，引起氮质血症、水电解质紊乱和酸碱平衡紊乱，致使全身各系统出现并发症的临床综合征。目前，AKI 已成为针对人类

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*Corresponding author. Tel: +86-21-54237285; E-mail: lulimin@shmu.edu.cn

健康的又一重大威胁。全球每年的 AKI 患者可达 1 330 万，其中 85% 在发展中国家 [1]。一项多中心队列研究结果显示，中国成年住院患者中 AKI 的总体发病率高达 11.6%，而其中 8.8% 的患者面临着死亡的风险 [2]。在亚洲，约有 7%~16% 的 AKI 患者可能在后期发展为终末期肾病 (end stage renal disease, ESRD)[3]。一旦进入 ESRD，患者只能依靠透析或肾移植维持生命，不仅承受严重的经济负担，生活质量也明显下降。缺血再灌注 (ischemia-reperfusion, I/R)、横纹肌溶解症以及肾毒性药物是导致 AKI 发生的常见致病因素 (详见表 1)，这些致病因素在 AKI 发生、发展的过程中导致肾小管损伤，严重受损的肾小管不可避免地会出现细胞死亡，丧失其原有功能，并最终导致肾脏功能的下降 [4]。深入了解细胞死亡的相关机制有望为缓解 AKI 患者肾功能下降、降低 AKI 死亡率提供新的治疗靶点和思路。

2018 年，细胞死亡命名委员会 (Nomenclature Committee on Cell Death, NCCD) 就细胞死亡的分类及命名方式发布了最新指南，将细胞死亡分为意外性细胞死亡 (accidental cell death, ACD) 和调节性细胞死亡 (regulated cell death, RCD) 两大类 [17]。ACD 是指细胞在受到外界极端物理、化学或机械刺激后发生的瞬时性细胞死亡 [18, 19]。通俗来讲，就是指极端条件下，细胞结构迅速崩溃，细胞呈现出坏死 (necrosis) 的形态学特征，细胞死亡过程不存在可控性，对各类干预措施都不敏感。与之相对，RCD 在

表1. AKI的简单分类及其特征

Table 1. Major types of AKI and their brief characteristics

Syndrome	Characteristics	Causes	Pathological features	Animal model
Pre-renal azotaemia	Pre-renal	Hypotension Fluid loss Drug administration	Primary glomerular haemodynamic alterations No parenchymal injury	Hemorrhagic shock model [5] Drug administration [6]
Drug nephrotoxicity	Renal	Drug administration	Acute tubular necrosis Secondary glomerular haemodynamic alterations Secondary inflammation	Drug-induced kidney injury [7]
Metal toxicity	Renal	Exposure to metals (environmental, accidental or professional causes)	Acute tubular necrosis Secondary glomerular haemodynamic alterations Secondary inflammation	Metal administration (mercury salts or uranium oxides) [8]
Contrast-induced nephropathy	Renal	Iodinated contrast media administration	Acute tubular necrosis Secondary glomerular haemodynamic alterations Secondary inflammation	Iodinated contrast media administration [9]
Ischemic AKI	Renal	Surgery Transplant Renal artery occlusion	Acute tubular necrosis Primary glomerular haemodynamic alterations Secondary inflammation	Ischemia-reperfusion (IR) model [10]
Septic AKI	Renal	Sepsis Septic shock	Acute tubular necrosis Primary glomerular haemodynamic alterations Primary inflammation	Cecal ligation and puncture (CLP) model [11] Lipopolysaccharide (LPS) i.p. injection [12]
Rhabdomyolytic AKI	Renal	Rhabdomyolysis	Acute tubular necrosis Secondary glomerular haemodynamic alterations	Glycerol i.m. injection [13]
Nephritis	Renal	Systemic infections Genitourinary infections Autoimmunity	Acute tubular necrosis Primary infiltration Primary inflammation	Heymann nephritis model [14] Anti-Thy1.1 glomerulonephritis model [15] Masugi nephritis model [16]

AKI: acute kidney injury; i.p.: intraperitoneal; i.m.: intramuscular.

生理或病理情况下都可能发生，细胞死亡过程受到各类信号通路的调控，通过药理学或遗传学方式可对 RCD 进行干预，因而成为近期 AKI 研究的热点。坏死性凋亡 (necroptosis)、焦亡 (pyroptosis) 和铁死亡 (ferroptosis) 等死亡方式都属于 RCD (见图 1)，是目前 RCD 在 AKI 研究领域最受关注的方向 [20]。免疫性细胞死亡 (immunogenic cell death)、有丝分裂死亡 (mitotic death) 与 PARP1 依赖性细胞死亡 (Parthanatos) 等新型 RCD 方式是否参与调节 AKI 目前仍未知。本文将主要就坏死性凋亡、焦亡和铁死亡等 RCD 方式在 AKI 中的研究进展进行简要概述。

1 坏死性凋亡与AKI

21 世纪初，Degterev 等人最先报道了他们在研究大脑缺血性损伤时注意到一种有别于凋亡的程序性细胞死亡方式，并将这种细胞死亡方式命名为“坏死性凋亡” [21]。细胞发生坏死性凋亡时，形态学上表现为细胞膜通透性增加、细胞器肿胀，细胞体积增大，进而导致细胞破裂，释放细胞内容物等。由于在细胞死亡过程中，形态与坏死颇为相似，被称为坏死性凋亡。坏死性凋亡也被视为一种主动的“调节性坏死” [22, 23]。坏死性凋亡始于死亡受体 (death receptors, DRs) 或病原识别受体 (pathogen recognition receptors, PRRs)(见图 2)。当配体与上述受体结合后，启动了下游信号转导通路，使受体相互作用蛋白激酶 1 (receptor-interacting protein kinase 1, RIPK1) 和 3 (RIPK3) 通过磷酸化形成坏死小体 (necrosome)，坏死小体进而使混合谱系激酶结构域样蛋白 (mixed lineage kinase domain-like, MLKL) 磷酸化并发生寡聚化，寡聚化的 MLKL 易位至细胞膜，破坏膜的完整性，诱导细胞死亡的发生 [24, 25]。

2012 年，Tristão 等人的研究首次报道坏死性凋亡参与 AKI [26]。在顺铂诱导的 AKI 模型中，他们发现在使用凋亡抑制剂的基础上，坏死性凋亡特异性抑制剂 Necrostatin-1 (Nec-1) 可以进一步缓解顺铂诱导的肾损伤模型中肾小管上皮细胞的死亡，提示坏死性凋亡参与这一 AKI 模型中细胞死亡的发生。2013 年，Linkermann 等人在 I/R 引起肾脏损伤模型中进一步研究了坏死性凋亡扮演的角色 [27]。他们在 I/R 引起肾脏损伤的动物模型中观察到坏死性凋亡参与肾损伤过程，并且证实，肾损伤过程中坏死性凋亡的发生是肾脏固有细胞自身发生的病理过程，并非由免疫系统引起。与野生型小鼠相比，敲除坏死性凋亡通路上的 *Ripk3* 基因可明显提高 I/R 小鼠

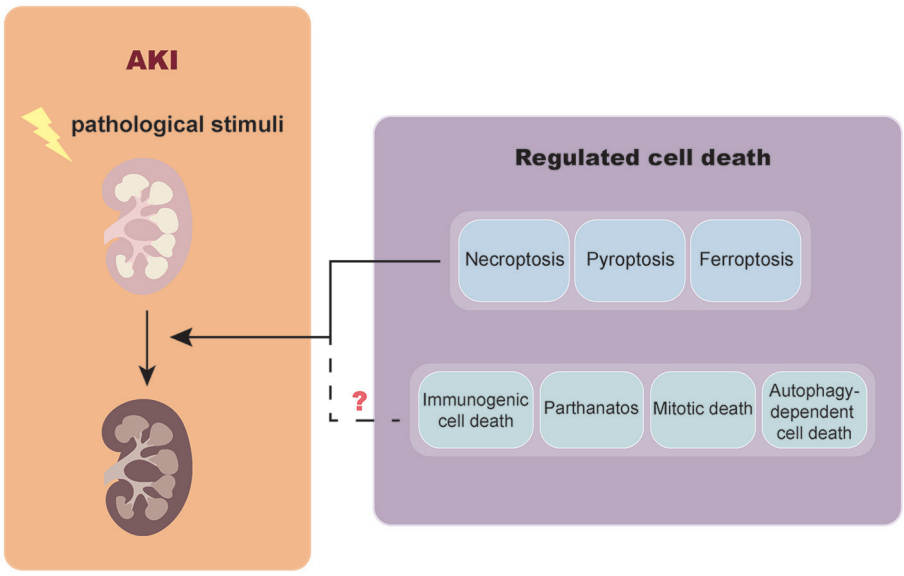

图 1. 调节性细胞死亡的分类及其与急性肾损伤的关系

Fig. 1. The classification of regulated cell death (RCD) and its relationship with acute kidney injury (AKI). RCD consists of multiple forms of cell death, including necroptosis, pyroptosis, ferroptosis, immunogenic cell death, Parthanatos, mitotic death, autophagy-dependent cell death, etc. Among all these forms, necroptosis, pyroptosis and ferroptosis have been proved to be involved in the process of AKI, while the role of immunogenic cell death, Parthanatos, mitotic death and autophagy-dependent cell death in AKI remained to be clarified.

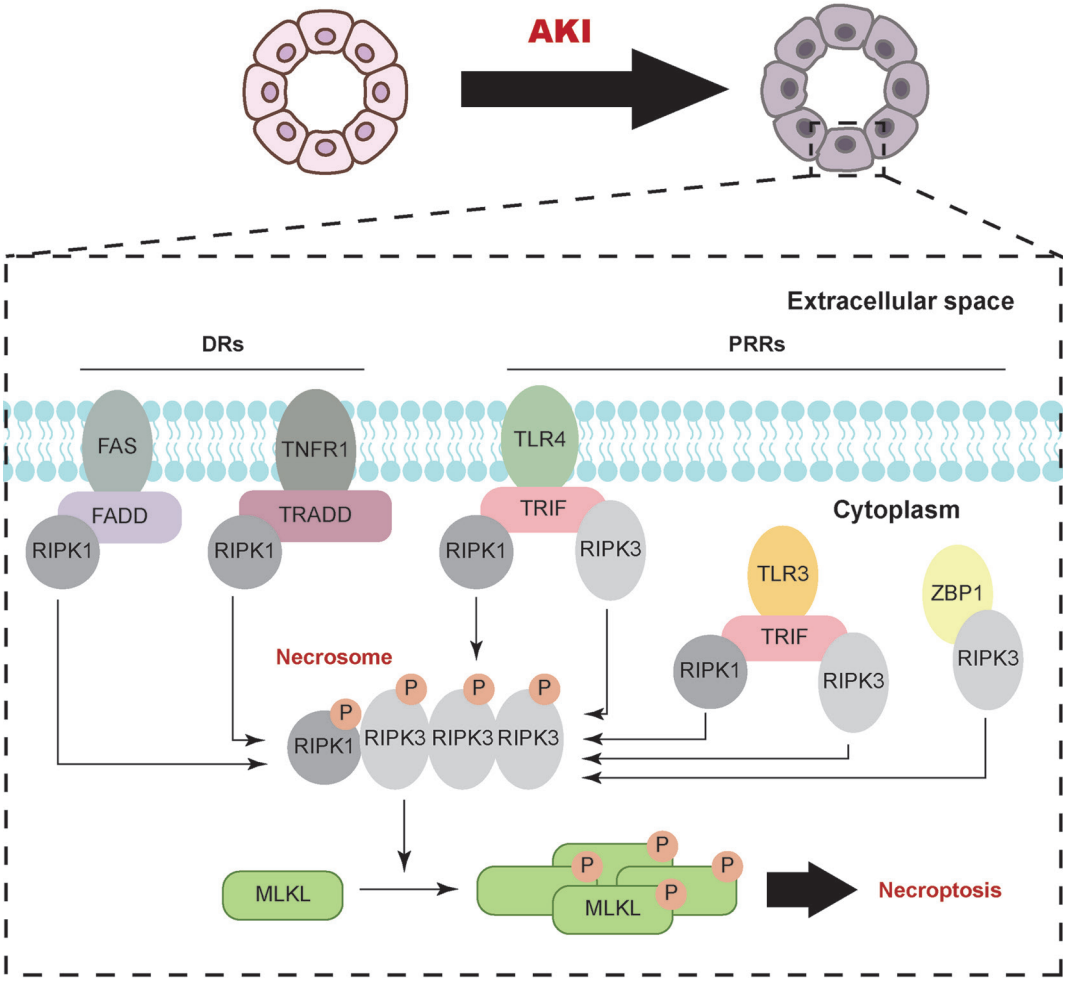

图 2. AKI过程中坏死性凋亡分子机制示意图

Fig. 2. Molecular mechanism of necroptosis in the process of AKI. Necroptosis is a newly discovered type of cell death which requires the activation of RIPK1 and RIPK3, and the formation of necrosome. Necrosome mediates the phosphorylation of MLKL, resulting in MLKL oligomerization and cell death as final consequence. During AKI, necroptosis usually occurs in tubular epithelial cells, of which the death may cause a wide range of metabolic and cellular dysfunction. AKI: acute kidney injury; DRs: death receptors; PRRs: pathogen recognition receptors; RIPK1: receptor-interacting protein kinase 1; RIPK3: receptor-interacting protein kinase 3; MLKL: mixed lineage kinase domain-like; FADD: Fas-associating protein with a novel death domain; TNFR1: tumor necrosis factor receptor 1; TRADD: TNFR1-associated death domain protein; TLR3/4: Toll-like receptor 3/4; TRIF: TIR-domain-containing adaptor inducing interferon-β.

的存活率，肾功能也优于野生型小鼠。同时，该研究团队也观察到凋亡抑制剂与 Nec-1 的联合使用能够进一步改善 I/R 小鼠的肾脏组织形态与肾功能，这些结果同样提示细胞凋亡和坏死性凋亡同时参与了 I/R 引起的肾脏损伤过程。结石是导致肾损伤的重要原因，草酸盐是人肾结石中最常见的成分。Mulay 等人的研究揭示了肾小管内各类晶体的沉积可以通过坏死性凋亡导致细胞死亡 [28]。在结石相关 AKI 肾病的活检样本中，研究者通过免疫荧光法检测到了磷酸化的 MLKL。在随后的细胞实验中，研究者发现晶体可诱导肾小管上皮细胞中 RIPK1 和 RIPK3 蛋白表达升高。无论是否使用凋亡抑制剂，Nec-1 都可以减少晶体引起的肾小管上皮细胞死亡，提示坏死性凋亡参与晶体引起的细胞死亡。在小鼠草酸盐肾病模型中，*Ripk3* 基因敲除小鼠和 *Mlkl* 基因敲除小鼠的血浆肌酐水平低于野生型小鼠，这两种基因敲除小鼠肾脏中的中性粒细胞数量与肾小管损伤标志物表达水平也明显降低。Stoppe 等人的观

察性研究显示，巨噬细胞迁移抑制因子 (macrophage migration inhibitory factor, Mif) 可以降低心脏病术后 AKI 的发生率，其保护机制可能与 Mif 减轻肾小管上皮细胞坏死性凋亡有关 [29]。Huang 等人的研究表明，在庆大霉素诱导的 AKI 模型中，除了近端小管外，集合管 (collecting ducts, CDs) 上皮细胞也会发生坏死性凋亡 [30]。电子显微镜观察到 CDs 主细胞发生明显肿胀，胞质澄清透亮，同时细胞膜发生破裂，呈坏死性凋亡的典型表现。在小鼠肾脏中，CDs 中 MLKL 总蛋白表达量与磷酸化 MLKL 的含量升高，提示 CDs 中出现坏死性凋亡。总之，现有的证据表明，在多种因素造成的 AKI 模型中，都观察到有坏死性凋亡发生，抑制坏死性凋亡能够缓解肾损伤，但对于诱发和启动坏死性凋亡的上游机制，目前探究较少。

2 焦亡与AKI

细胞焦亡是一种与固有免疫相关的 RCD 形式，在抵抗外源性感染和对抗内源性稳态丧失时发挥重要的作用 [31]。发生焦亡的细胞在形态学上表现为细胞不断膨胀，其细胞膜上出现气泡状突出物，细胞膜上形成孔隙，细胞膜失去完整性，最终导致细胞破裂，释放细胞内容物并引起炎症反应的发生 [31, 32]。“焦亡”一词最初由 Brad T. Cookson 等人创造，被视为一种由天冬氨酸特异性半胱氨酸蛋白酶 1 (Caspase-1) 介导的炎症性细胞死亡方式，当时的研究者认为模式识别受体通过感知外源性或内源性病理刺激，形成炎症小体 (inflammasomes)，招募并活化 Caspase-1，切割白介素 18 (interleukin 18, IL-18) 和白介素 1β (interleukin 1β, IL-1β) 等炎症因子，使之激活并启动细胞焦亡 [33, 34, 35]。随着研究的不断深入，人们意识到除了 Caspase-1 相关的经典通路外，鼠源的天冬氨酸特异性半胱氨酸蛋白酶 11 (Caspase-11) 和人源的天冬氨酸特异性半胱氨酸蛋白酶 4/5 (Caspase-4/5) 在不切割炎症因子的情况下也可引发焦亡 [36, 37](见图 3)。Caspase-1 以及 Caspase-11/4/5 都能切割共同的底物消皮素 D (Gasdermin D, Gsdmd)，切割形成的 Gsdmd 的 N 端 (N-terminal of Gsdmd, Gsdmd-N) 为 Gsdmd 的激活形式，Gsdmd-N 可与膜结构结合，并通过寡聚化在细胞膜上形成膜孔，破坏细胞膜的完整性 [38, 39]。目前，Gsdmd 已被视为细胞焦亡过程中的关键蛋白，细胞焦亡本身也被重新定义，Gsdmd 激活介导的膜孔形成成为判断焦亡发生与否的关键。

依赖 Caspase-11/4/5 的细胞焦亡通路被称为非经典途径，这一途径在 AKI 过程中所扮演的角色受到广泛关注。Yang 等人的研究最早观察到 AKI 的发展过程涉及细胞焦亡 [40]。在小鼠 I/R 肾损伤模型中，Caspase-11 及其它焦亡相关蛋白的表达水平在术后 6 h 已有明显升高，并于术后 12 h 达到巅峰。动物模型中焦亡的发生伴随着小鼠肾脏形态学改变以及肾功能下降。在细胞模型中，缺氧 - 复氧 (hypoxia-reoxygenation, H/R) 可诱导大鼠肾小管上皮细胞发生焦亡，Caspase-11 表达水平在受到刺激 3 h 后明显升高，并伴随着细胞膜完整性的破坏以及乳酸脱氢酶释放的增加。进一步的机制研究显示，H/R 可以使肾小管上皮细胞的内质网过度激活，导致 C/EBP 同源蛋白 (C/EBP homologous protein, Chop) 表达增加，是促使焦亡发生的重要原因之一。Chop 可诱导细胞发生焦磷酸化 (pyrophysphrite)，从而增强 Caspase-11 的活性，启动细胞焦亡的非经典途径。Zhang 等人的研究指出焦亡参与造影剂介导的 AKI [41]。在肾小管上皮细胞中，碘化造影剂通过上调 Caspase-11/4/5 蛋白的表达水平启动非经典焦亡程序，导致弥漫性肾小管损伤以及肾内炎症，并最终引起肾功能衰竭。Miao 等人的研究则以更加直观的方式阐述了 Caspase-11 与 Gsdmd 在发生 AKI 时的变化及其相关机制 [42]。研究者发现，在顺铂及 I/R 引起的 AKI 模型中，小鼠肾脏 Caspase-11 和 Gsdmd 的蛋白表达水平均升高，而敲除 Caspase-11 基因则可以明显改善小鼠肾功能，并减轻肾小管炎性损伤。就其机制而言，在 AKI 过程中，肾小管上皮细胞中上调的 Caspase-11 通过切割 Gsdmd 形成 Gsdmd-N，Gsdmd-N 从胞浆转移至胞膜并形成膜孔，膜通透性的改变导致细胞肿胀，在细胞表面形成气泡状突出物，同时释放细胞内容物以及 IL-18 等炎症因子，敲除 Caspase-11 有助于维持肾小管上皮细胞膜的完整性，减轻肾脏的炎性损伤。Caspase-11 表达的升高、Gsdmd 的切割、膜转位以及炎症因子的释放是细胞焦亡的重要特征，这为细胞焦亡参与 AKI 提供了更加有力的证据。该研究首次清晰地展现了 Gsdmd 在 AKI 细胞焦亡中的变化及其相关机制，强调了 Caspase-11 及 Gsdmd 具有成为 AKI 治疗靶点的潜力。除了非经典途径外，Caspase-1 相关的经典细胞焦亡通路也参与 AKI 过程中的细胞焦亡。在小鼠 I/R 肾损伤模型及肾小管上皮细胞 H/R 模型中，Caspase-1

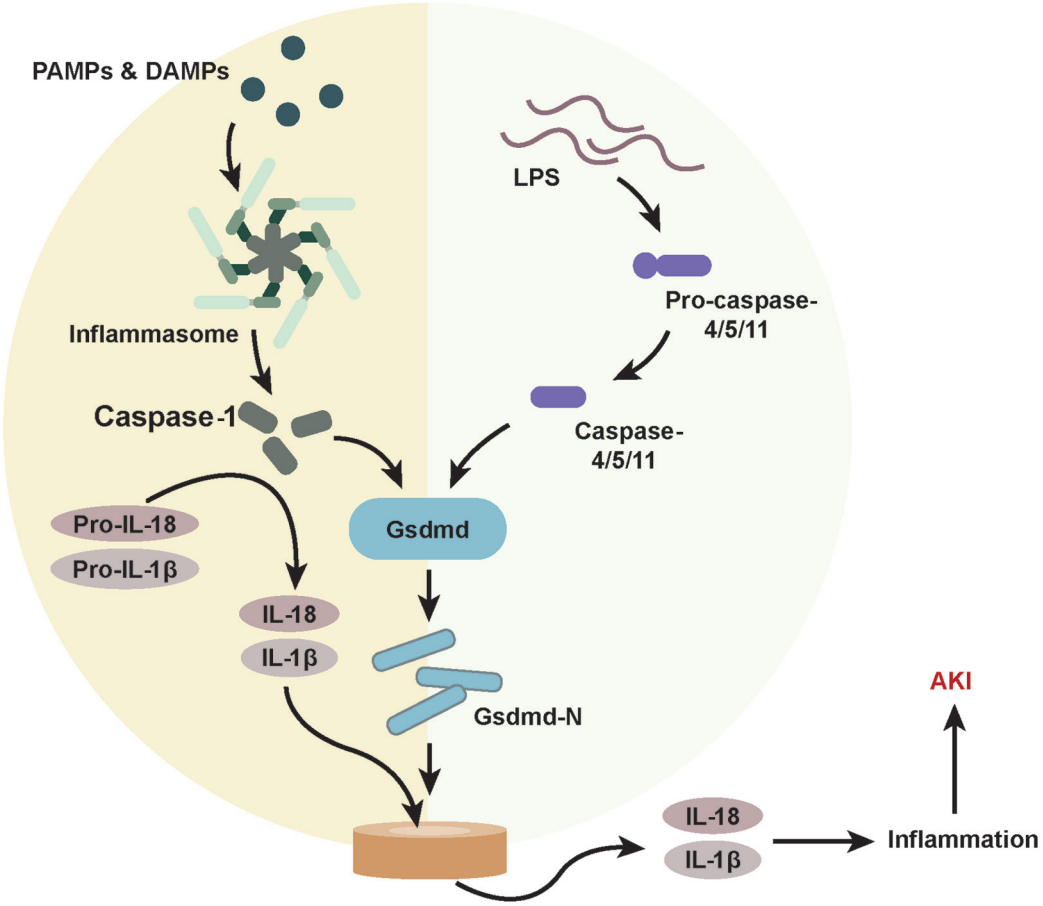

图 3. AKI过程中焦亡分子机制示意图

Fig. 3. Molecular mechanism of pyroptosis in AKI. During the process of pyroptosis, active Caspase-1 and Caspase-4/5/11 cleave Gsdmd into two domains, of which the N-terminal leads to the formation of membrane pores, resulting in extracellular release of IL-1β and IL-18. These two inflammatory factors are key drivers of renal inflammation, which can lead to the further deterioration of AKI. AKI: acute kidney injury; PAMPs: pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; LPS: lipopolysaccharide; Gsdmd: Gasdermin D; Gsdmd-N: N-terminal of Gsdmd.

及其下游炎症因子的表达水平同样明显升高[40]。Tajima等人在研究β-羟基丁酸酯(β-hydroxybutyrate, β-OHB)对缺血性组织损伤的保护作用时，发现β-OHB能够通过抑制焦亡而非凋亡减少小鼠I/R肾损伤模型中的细胞死亡[43]。叉头转录因子O3 (Forkhead transcription factor O3, FOXO3)具有调节Caspase-1相关经典焦亡通路的功能，β-OHB通过恢复FOXO3启动子处的组蛋白乙酰化水平上调其蛋白表达，从而下调Caspase-1的生成并抑制焦亡的发生，最终减轻近端肾小管上皮细胞死亡。当前，对于焦亡在AKI及其他肾损伤中的作用及发生机制还有许多问题尚未阐明。除Caspase-1及Caspase-11外，Gsdmd还能够切割包括Caspase-8在内的其它Caspase家族成员，这些切割对象是否参与AKI时焦亡发生及其在AKI中的作用目前不得而知；此外，有资料显示GSDM家族其他成员的剪切也可以引发细胞焦亡，但这些成员所引起的焦亡在AKI中的作用也尚不明确。这些问题都有待后续进一步研究验证[44, 45]。

3 铁死亡与AKI

铁死亡是Dixon等人定义的一种铁依赖性非凋亡细胞死亡方式，主要特征为细胞在死亡过程中伴随有大量铁离子的蓄积与脂质过氧化[46]。用电子显微镜观察发生铁死亡的细胞，可见其特征性变化有线粒体体积缩小、线粒体膜密度增高以及线粒体嵴数量减少或消失。铁死亡的发生机制主要涉及二价铁离子在细胞内的大量蓄积以及谷胱甘肽过氧化物酶4 (glutathione peroxidase 4, GPX4)的异常[47, 48](见

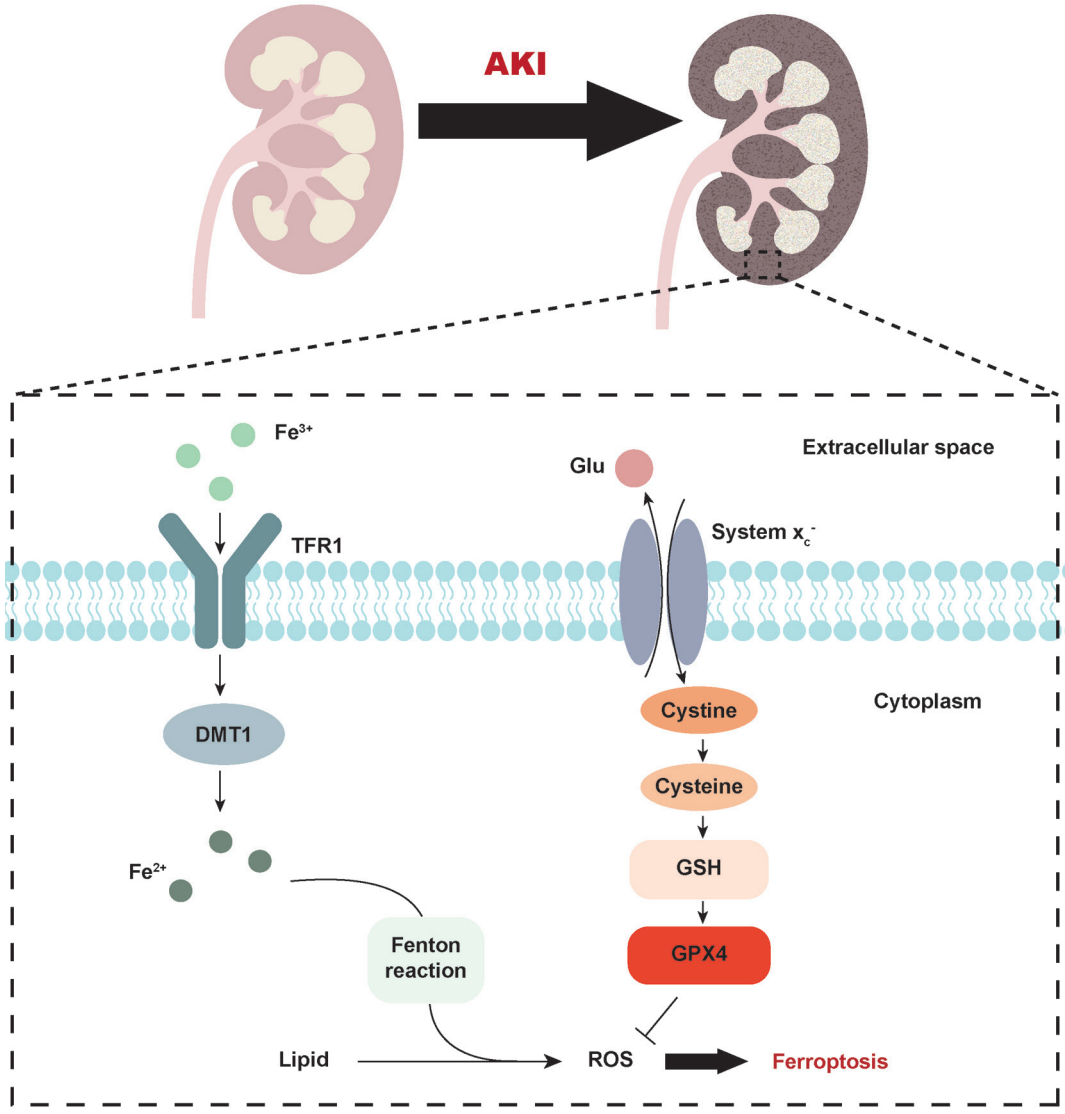

图 4. AKI过程中铁死亡分子机制示意图

Fig. 4. Molecular mechanism of ferroptosis in the process of AKI. Ferroptosis is a form of cell death characterized by the accumulation of iron and the peroxidation of lipid. During the process of ferroptosis, GPX4 is affected by several ferroptosis-associated factors, leading to a decrease in antioxidant capacity and the accumulation of ROS in cells. The elevated secretion of ROS may induce oxidative stress, which contributes to renal parenchymal damage and causes functional dysregulation of kidney. AKI: acute kidney injury; TFR1: transferrin receptor 1; DMT1: divalent metal transporter 1; Glu: glutamate; System X_c^-: cystine/glutamate antiporter; GSH: glutathione; GPX4: glutathione peroxidase 4; ROS: reactive oxygen species.

图 4)。在生理状态下，人体内的铁主要以三价铁的形式与血浆中的转铁蛋白结合，二价铁的含量相对较少。细胞内二价铁的浓度约为 0.2~0.5 μmol/L，剩余的二价铁通常与铁蛋白结合，避免细胞发生氧化损伤。外界刺激可诱导含铁化合物释放二价铁，并通过 Fenton 反应氧化细胞内的羧酸、醇和酯类等多种有机物，进一步导致细胞膜上的不饱和脂肪酸过氧化从而启动铁死亡 [49]。谷胱甘肽 (glutathione, GSH) 是细胞内重要的抗氧化剂，而 GPX4 是 GSH 相关抗氧化体系的核心调控酶，这种酶可以抑制脂质氧化酶 (lipoxygenase, LOX) 的活性，清除因二价铁的累积而产生的脂质过氧化物，减轻细胞膜的损伤 [50, 51]。若以 GPX4 为代表的抗氧化体系组成成分表达减少或失活，则脂质过氧化进程将失去控制，亦可引起细胞的铁死亡 [52]。

Skouta 等人以小鼠原代肾小管上皮细胞为实验

对象，模拟横纹肌溶解症所致 AKI [53]。在该细胞模型中，他们发现铁死亡抑制剂 ferrostatin-1 (Fer-1) 可以通过抑制脂质过氧化减轻细胞死亡。这一实验结果首次证实了铁死亡与 AKI 的关联性。同年，Linkermann 等人在 AKI 动物模型中验证了 Fer-1 的肾脏保护功能 [54]。研究者利用小鼠 I/R 肾损伤模型和草酸盐肾病模型模拟 AKI，发现 Fer-1 在两种模型中都可以减少小鼠近端肾小管上皮细胞的死亡。Friedmann Angeli 等人构建了 Gpx4 基因敲除小鼠模型，试图探究这一铁死亡信号传导通路中的关键酶与肾脏损伤的关系 [55]。他们发现，在未进行手术造模的情况下，Gpx4 基因敲除小鼠的肾脏较野生型小鼠显得大而苍白，组织染色证实其近端肾小管上皮细胞发生广泛死亡，其中大部分细胞的死亡方式被鉴定为铁死亡。他们的研究指出，对于敲除 Gpx4 基因的细胞，铁死亡过程中的脂质过氧化主要发生于线粒体基质外部。同时，他们还发现螺喹喔啉胺衍生物 Liproxstatin-1 可以特异性抑制细胞铁死亡，并在 Gpx4 基因敲除小鼠中验证了这一观点。Deng 等人研究发现，顺铂可以诱导肾小管上皮细胞发生铁死亡 [56]。在研究相关机制时，他们观察到使用顺铂刺激人肾小管上皮细胞系 HK-2 可以使细胞中肌醇加氧酶 (Myo-inositol oxygenase, Miox) 的蛋白表达升高。Miox 通过促进溶酶体摄取铁蛋白，使细胞内游离铁含量增加，加强脂质过氧化，促进铁死亡的发生。此外，Miox 可以下调 GPX4 的活性和细胞内 GSH 的浓度，铁死亡进程因失去“刹车”而无法及时终止，最终损伤肾小管。Mishima 等人以铁死亡作为靶点，探究了多种药物对于 AKI 的治疗作用 [57]。通过筛选发现，利福平、异丙嗪和奥美拉唑等药物可以通过减少 ROS 的产生与减轻不饱和脂肪酸的过氧化缓解细胞铁死亡，这些药物的肾保护作用已在顺铂肾损伤小鼠模型中得到验证。

4 小结

现有的研究结果显示，坏死性凋亡、焦亡和铁死亡等 RCD 方式在 AKI 发展过程中起着重要的作用；但免疫性细胞死亡、有丝分裂死亡与 PARP1 依赖性细胞死亡 (Parthanatos) 等新型 RCD 方式是否参与调节 AKI 有待进一步探索。细胞死亡，特别是肾小管上皮细胞死亡，是 AKI 时肾功能下降的关键。RCD 因其具有可调控、可干预的特征，在未来针对 AKI 的临床诊断治疗过程中，无疑会成为新的方向，而对 AKI 中 RCD 方式及相关机制的揭示，将为 AKI 的预防、干预和治疗提供靶点和思路。

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