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铁死亡

·专题报道·

铁死亡在糖尿病肾病中的作用

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［摘　要］ 糖尿病肾病是常见的糖尿病微血管并发症，也是糖尿病患者死亡的主要原因之一。铁死亡是一种铁依赖性调节性细胞死亡，其在糖尿病肾病的发生发展中具有一定作用。腺苷一磷酸活化的蛋白质激酶（AMPK）介导的铁死亡相关信号通路可以延缓糖尿病肾病的进程，但AMPK信号过度激活可能会诱导细胞发生自噬性死亡；激活核转录因子红系2相关因子（Nrf）2和血红素加氧酶（HO）-1介导的信号通路能够抑制细胞铁死亡并改善糖尿病肾病，但HO-1在铁死亡中的调节作用是双向的，激活HIF-1α/HO-1信号通路可能导致细胞内铁过载，最终促进铁死亡；转化生长因子（TGF）-β1介导的信号通路通过下调SLC7A11/GSH/GPX4的表达加快细胞脂质过氧化；外泌体lncRNA/circRNA/miRNA介导的铁死亡相关信号通路也参与了糖尿病肾病的发生发展；此外，新型铁死亡启动子酰基辅酶A合成酶长链家族1以及干扰素基因刺激因子等介导的信号通路可诱导细胞铁死亡从而加速糖尿病肾病的进程。本文重点阐述了铁死亡通过AMPK、Nrf2/HO-1、TGF-β和外泌体等介导的信号通路在糖尿病肾病中发挥重要作用，以期为阐明糖尿病肾病的病理机制提供新的依据，为有效治疗糖尿病肾病提供新的靶点。

［关键词］ 糖尿病肾病；铁死亡；细胞死亡；信号通路；综述
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Roles of ferroptosis in the development of diabetic nephropathy

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[**Abstract**]　Diabetic nephropathy is a common microvascular complication of diabetes mellitus and one of the main causes of death in patients with diabetes mellitus. Ferroptosis is a newly discovered iron-dependent regulated cell death, which may contribute to the pathogenesis and development of diabetic nephropathy. Adenosine monophosphate-activated protein kinase (AMPK)-mediated ferroptosis-related signaling pathways can slow down the progression of diabetic nephropathy, but excessive activation of AMPK signaling pathway may induce cells to undergo autophagic death. Activation of the signaling pathway mediated by nuclear factor-erythroid 2-related factor (Nrf) 2 and heme oxygenase (HO)-1 can inhibit ferroptosis of cells and alleviate diabetic nephropathy. However, the regulatory effect of HO-1 on ferroptosis is bidirectional, and activation of HIF-1α/HO-1 pathway may lead to intracellular iron overload and ultimately promote ferroptosis. Transforming growth factor (TGF)-β1 mediated signaling pathways can accelerate lipid peroxidation by down-regulating the levels of SLC7A11/GSH/GPX4. The ferroptosis-related signaling pathways mediated by exosome lncRNAs/circRNAs/miRNAs are also involved in the pathogenesis and development of diabetic nephropathy. In addition, signaling pathways mediated by stimulator of interferon gene (STING) and the novel ferroptosis promoter acyl-CoA synthetase long-chain family (ACSL) 1 can induce ferroptosis to promote the progression of diabetic nephropathy. In this review, we focus on the roles of ferroptosis in diabetic nephropathy through the signaling pathways mediated by AMPK, Nrf2/HO-1, TGF-β and exosomes, to elaborate the pathogenesis and development of diabetic nephropathy, and the potential therapeutic target for diabetic nephropathy.

[**Key words**]　Diabetic nephropathy; Ferroptosis; Cell death; Signaling pathway; Review

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[**缩略语**]　谷胱甘肽过氧化物酶(glutathione peroxidase,GPX);腺苷一磷酸活化的蛋白质激酶(adenosine monophosphate-activated protein kinase,AMPK);核转录因子红系2相关因子(nuclear factor-erythroid 2-related factor,Nrf);血红素加氧酶(heme oxygenase,HO);转化生长因子(transforming growth factor,TGF);长链非编码RNA(long noncoding RNA,lncRNA);环状RNA(circular RNA,circRNA);微RNA(microRNA,miRNA,miR);溶质载体家族(solute carrier family,SLC);缺氧诱导因子(hypoxia-inducible factor,HIF);Sma和Mad相关蛋白(Sma- and Mad-related protein,Smad);小核仁RNA宿主基因(small nucleolar RNA host gene,SNHG);酰基辅酶A合成酶长链家族(acyl-CoA synthetase long-chain family,ACSL);干扰素基因刺激因子(stimulator of interferon gene,STING)

糖尿病肾病是糖尿病严重且重要的微血管并发症,也是终末期肾病的最常见原因[1]。尽管近年来围绕糖尿病肾病的机制研究不断深入,但目前仍缺乏可靠有效的治疗方法。因此,探索新的治疗策略已成为预防和治疗糖尿病肾病的当务之急。临床研究发现,糖尿病肾病患者血清铁蛋

白表达水平明显升高[2],肾脏活检标本中GPX4表达降低导致脂质过氧化物积累[3],提示糖尿病肾病与铁死亡密切相关。

铁死亡定义为一种铁依赖性调节性细胞死亡[4],其主要特征为活性氧的铁依赖性积累和质膜多不饱和脂肪酸的消耗[5]。铁死亡的调控机制较为复杂,主要涉及铁代谢[6]、脂质代谢[7]、氨基酸代谢[8]途径,以及辅酶Q[9]、P53[10]、鸟苷三磷酸环水解酶1[11]和线粒体电压依赖性阴离子通道[12]介导的相关信号通路。细胞铁死亡有独特的形态学特征,主要表现为线粒体明显收缩或肿胀,膜密度增加,线粒体嵴减少或消失[6, 13]。这些特征有助于区分铁死亡与其他细胞死亡方式。多项研究表明,铁死亡在糖尿病肾病的进程中发挥重要作用[14-15]。本文讨论了铁死亡通过AMPK、Nrf2/HO-1、TGF-β和lncRNA/circRNA/miRNA等介导的相关信号通路参与糖尿病肾病发生发展的机制,以期为糖尿病肾病的预防和治疗提供潜在的靶向策略。

1 腺苷一磷酸活化的蛋白质激酶介导的信号通路

AMPK是新陈代谢和线粒体稳态的守护者[16]。近年来,越来越多的研究发现AMPK可以作为癌症、肥胖和糖尿病等疾病的治疗靶点[17-18]。AMPK具有抗氧化和降脂作用,因此成为改善糖尿病肾病症状的一种选择。

研究显示,AMPK可以明显增加肌肉、肝脏和脂肪中的葡萄糖摄取,从而减轻胰岛素抵抗[19-20]。Shen等[21]提出,胰高血糖素样肽1受体激动剂可通过巨胞饮作用增强下游靶标AMPK表达,激活线粒体中的脂肪酸氧化,抑制脂质合成和糖酵解,从而抑制有毒脂质积累和肾小管细胞铁死亡。此外,AMPK可以与Nrf2发挥协同效应以减轻糖尿病肾病。近期研究报道,五味子甲素A能够通过靶向AMPK抑制Nrf2/HO-1/GPX4和ROS/TXNIP/NLRP3信号通路从而减轻肾小球内皮细胞的铁死亡和焦亡,最终缓解糖尿病肾病[14]。Lu等[22]发现恩格列净可增加AMPK磷酸化、促进Nrf2核转位,加入AMPK激动剂能增强Nrf2核易位并激活靶基因,上调铁蛋白重链1、SLC7A11和GPX4蛋白表达,减弱脂质过氧化以及肾小管上皮细胞铁死亡,最终改善糖尿病肾病。值得注意的是,AMPK过度激活可能会诱导细胞发生自噬性死亡,而不是自噬性存活[23]。总之,AMPK介导的信号通路可以改善糖尿病肾病的病理生理过程,如何精准靶向AMPK并研发出理想的药物是未来研究的方向。

2 核转录因子红系2相关因子2和血红素加氧酶-1介导的信号通路

Nrf2是公认的能维持氧化还原稳态的重要因子[24],也是调节细胞功能的关键介质,是一个备受关注的药物靶点[25]。Nrf2及其下游HO-1在抗氧化反应中发挥重要作用[26]。众多研究表明,Nrf2和HO-1介导的信号通路与铁死亡密切相关[27-28]。

研究发现,参芪地黄汤、阿伐他汀、伞形酮、高迁移率组蛋白质-1和沉默信息调节因子6等可通过激活Nrf2和HO-1介导的铁死亡相关信号通路来缓解糖尿病肾病[29-33]。Wang等[34]发现维生素D受体激活剂帕立骨化醇能够通过调节Nrf2/HO-1信号通路,上调铁蛋白重链1、GPX4和胱氨酸/谷氨酸逆向转运蛋白中SLC7A11的表达,从而减轻肾小管上皮细胞铁死亡。槲皮素也能通过激活Nrf2/HO-1信号通路抑制铁死亡,从而延缓糖尿病肾病的进程[15]。但另有研究显示,糖尿病肾病小鼠和高糖高脂处理的肾小管上皮细胞中存在大量脂质过氧化、抗氧化能力受损和铁过载等铁死亡典型特征,且HIF-1α和HO-1表达增加,加入达格列净能明显逆转这些症状,可见达格列净可以通过抑制HIF-1α/HO-1介导的铁死亡通路减轻糖尿病肾病[35]。肾康丸也可通过同样机制缓解糖尿病肾病[36]。总的来说,HO-1在铁死亡中的调节作用是双向:一方面通过Nrf2/HO-1信号通路抑制铁死亡,另一方面通过HIF-1α/HO-1信号通路促进铁死亡。值得注意的是,丁香树脂醇能够通过Nrf2介导的抗氧化途径抑制细胞焦亡来预防糖尿病肾病[37],可见糖尿病肾病中的细胞铁死亡和细胞焦亡在Nrf2靶点可能存在串扰现象。

3 转化生长因子β介导的信号通路

TGF能调节分化、生长、迁移、细胞外基质产生和细胞凋亡等多种细胞过程,并介导Smad和非Smad信号转导[38]。研究显示,TGF-β可通过诱导肾小管上皮细胞的铁死亡而促进糖尿病肾病发生[39]。

Liu等[40]在体内外分别建立糖尿病肾病大鼠模型和高糖诱导的肾小管上皮细胞模型,发现袖状胃切除术可显著下调糖尿病肾病大鼠肾脏中的TGF-β1/Smad3信号通路并抑制细胞铁死亡;而TGF-β1可通过TGF-β1/Smad3通路下调GSH、SLC7A11和GPX4表达来诱导肾小管上皮细胞铁死亡。因此,袖状胃切除术可能通过抑制TGF-β1/Smad3信号通路来上调SLC7A11、GSH和GPX4表达,从而减轻细胞铁死亡并缓解糖尿病肾病。最近一项研究发现,TGF-β拮抗剂骨形态发生蛋白7通过抑制经典TGF-β信号通路来减少脂质过氧化,从而减轻肾小管细胞的铁死亡并延缓糖尿病肾病的进程[41]。然而,TGF-β相关信号通路在糖尿病肾病的细胞铁死亡中的报道甚少,仍有待进一步探索。

4　长链非编码RNA/环状RNA/微RNA介导的信号通路

外泌体是一类细胞外囊泡,其作为细胞间的通信介质对稳态调节起着重要作用。外泌体非编码RNA主要包括lncRNA、circRNA和miRNA,与糖尿病视网膜病变、糖尿病肾病、糖尿病足溃疡等糖尿病并发症的发生发展密切相关[42]。研究表明,lncRNA/circRNA/miRNA介导的铁死亡相关信号通路参与了糖尿病肾病的发生发展[43-44]。

Jin等[43]在糖尿病肾病小鼠和高糖诱导的足细胞中研究发现,一种新鉴定的circRNA——mmu_circRNA_0000309可以通过靶向miR-188-3p上调GPX4表达,从而抑制铁死亡依赖性线粒体损伤和足细胞凋亡。另一项研究报道,circ ASAP2通过miR-770-5p介导的SOX2/SLC7A11减轻糖尿病肾病的炎症和铁死亡,表明circ ASAP2可能是治疗糖尿病肾病的靶标[44]。Fang等[45]通过体内外研究发现,糖尿病肾病小鼠肾组织中SNHG1和ACSL4表达增加,而miR-16-5p表达减少,加入铁死亡抑制剂Fer-1或敲低*SNHG1*可抑制高糖诱导的肾小管上皮细胞铁死亡。此外,Gao等[46]提出血清外泌体可通过miR-4449/HIC1途径促进肾小管上皮细胞焦亡,以加剧糖尿病肾病进展。可见外泌体可能是糖尿病肾病中细胞铁死亡和细胞焦亡相互联系的一个重要靶点。综上,从分子水平了解lncRNA/circRNA/miRNA有助于开发糖尿病肾病防治的新方法。

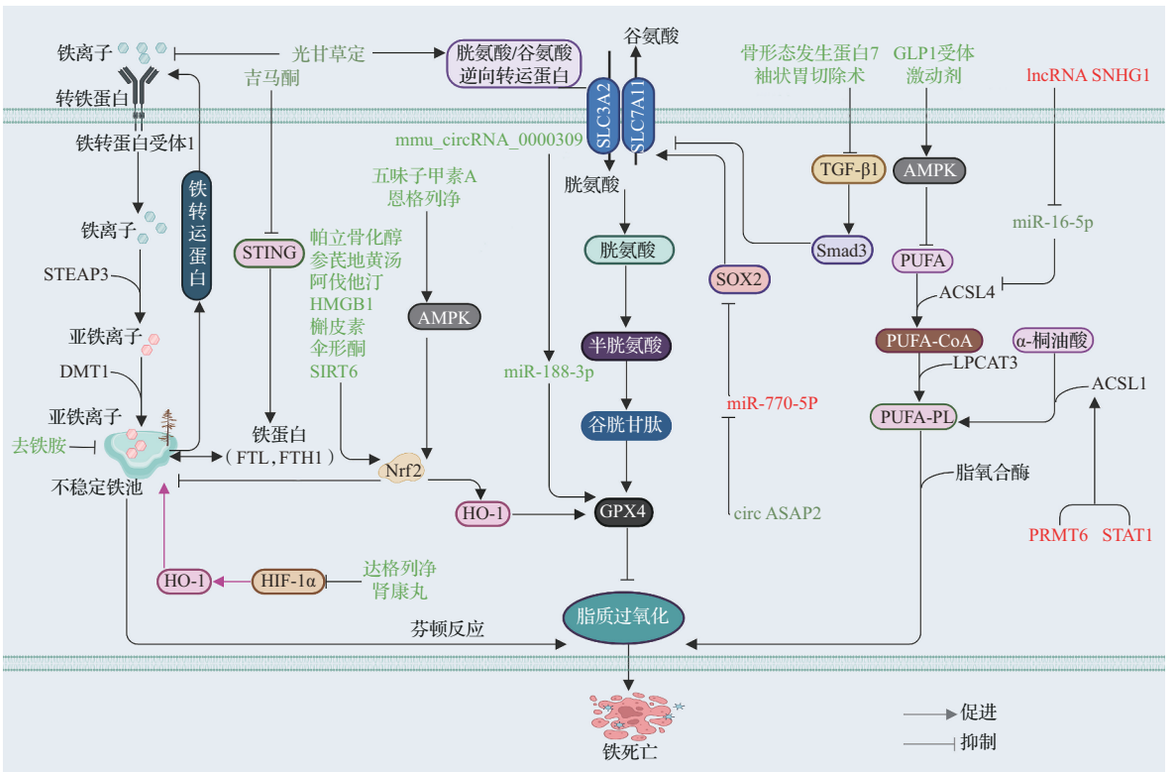
5　其他信号通路

ACSL1和STING等介导的信号通路与糖尿病肾病的细胞铁死亡密切相关[47-51]。Beatty等[47]提出ACSL1可介导α-桐油酸掺入中性脂质并促进脂质过氧化,从而触发细胞铁死亡。Hong等[48]进一步研究发现,蛋白精氨酸甲基转移酶6和信号转导及转录激活蛋白1可共同调节ACSL1转录,诱导多不饱和脂肪酸磷脂的产生,通过促进脂质过氧化来加剧糖尿病肾病的进程。ACSL1作为一种新的铁死亡启动子,有别于铁死亡的经典诱导剂ACSL4,为糖尿病肾病的治疗提供了一个新方向。Zhao等[49]提出抑制STING可通过稳定铁转运蛋白和减少氧化应激减轻肾小管上皮细胞铁死亡。此外,Tan等[50]研究证实,甘草的生物活性成分光甘草定可能通过上调GPX4、SLC7A11和SLC3A2表达及下调转铁蛋白受体表达、降低铁过载,从而抑制大鼠肾上管上皮细胞铁死亡,最终发挥对糖尿病肾病大鼠肾脏的保护作用。研究显示,吉马酮能通过激活线粒体自噬和抑制线粒体DNA-STING信号转导改善糖尿病肾病,为糖尿病肾病的治疗提供了一种可行的方法[51]。目前,糖尿病肾病与细胞铁死亡相关报道不断增加,但其具体机制尚未明确,未来仍需深入研究。

6　结　语

糖尿病肾病是引起糖尿病患者死亡的重要原因之一,病情严重且预后不良,目前尚无特异性药物预防和治疗糖尿病肾病。因此,深入了解糖尿病肾病发生发展的病理机制以设计疾病的治疗策略显得尤为迫切。铁死亡与糖尿病肾病病理机制密切相关。目前研究结果提示铁死亡通过AMPK、Nrf2/HO-1、TGF-β、lncRNA/circRNA/miRNA等介导的信号通路参与糖尿病肾病的发生和发展,而且这些信号通路相互联系,共同介导铁死亡的发生(图1)。

近年来,虽然铁死亡机制研究取得了一些关键性突破,但对糖尿病肾病中的认识还存在局限,仍待进一步探索:①HO-1在铁死亡中双向调节功能值得关注;②ACSL1作为一种新的铁死亡启动子,其通过脂质代谢参与糖尿病肾病的机制仍需进一步研究;③铁死亡在糖尿病肾病中的机制研



不同化合物可以通过AMPK、Nrf2/HO-1、lncRNA/circRNA/miRNA、TGF-β等介导的信号通路来促进或抑制铁死亡，最终恶化或缓解糖尿病肾病. STEAP：前列腺六跨膜上皮抗原；DMT：二价金属离子转运体；HO：血红素加氧酶；HIF：缺氧诱导因子；STING：干扰素基因刺激因子；FTL：铁蛋白轻链；FTH：铁蛋白重链；HMG：高迁移率组蛋白质；SIRT：沉默信息调节因子；AMPK：腺苷一磷酸活化的蛋白质激酶；Nrf：核转录因子红系2相关因子；SLC：溶质载体家族；GPX：谷胱甘肽过氧化物酶；lncRNA：长链非编码RNA；circRNA：环状RNA；miR：微RNA；SOX：性别决定区Y框；TGF：转化生长因子；Smad：Sma和Mad相关蛋白；GLP：胰高血糖素样肽；SNHG：小核仁RNA宿主基因；PUFA：多不饱和脂肪酸；CoA：辅酶A；PL：磷脂；ACSL：酰基辅酶A合成酶长链家族；LPCAT：溶血磷脂酰胆碱酰基转移酶；PRMT：蛋白质精氨酸甲基转移酶；STAT：信号转导及转录活化因子.

图1　铁死亡参与糖尿病肾病的机制示意图

Figure 1　Possible therapeutic targets of ferroptosis in diabetic nephropathy

究绝大部分是动物和细胞实验，缺乏更多令人信服的临床研究；④目前铁死亡在糖尿病肾病中的临床应用主要集中在铁螯合剂去铁胺、钠–葡萄糖协同转运蛋白2抑制剂类药物、胰高血糖素样肽-1受体激动剂以及一些传统的中医药复方制剂等，下一步研究重点可放在新的铁死亡抑制剂的开发，如最新一项研究发现了一种无明显毒副作用的新型铁螯合剂铁死终结者FOT1[52]；⑤细胞铁死亡和细胞焦亡均可通过Nrf2和外泌体靶点作用于糖尿病肾病，在其他靶点是否还有联系？在糖尿病肾病发生发展过程中，铁死亡与其他细胞死亡途径是否还有互作转换？探索铁死亡在糖尿病肾病中的作用以获得防治糖尿病肾病的最佳方案，这仍是未来研究的重要方向。

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医学伦理　研究不涉及人体或动物实验

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