脂肪酸代谢在肾脏疾病中的作用及中药干预研究进展

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摘 要 脂肪酸代谢主要包括脂肪酸氧化(fatty acid oxidation, FAO)和脂肪酸合成,其在信号转导、能量产生及炎症调节等过程均发挥重要作用。急性肾损伤(acute kidney injury, AKI)、慢性肾病(chronic kidney disease, CKD)与肾癌(renal cell carcinoma, RCC)是典型的肾脏疾病,发病机制复杂、易诱发多种并发症且临床尚无特异性干预措施。现有研究揭示,脂肪酸代谢与多种肾脏疾病的发生发展密切相关。文章综述了肾脏中脂肪酸的代谢特征、脂肪酸代谢失调与AKI、CKD及RCC等肾脏疾病的内在关系,总结了靶向脂肪酸代谢通路缓解肾脏疾病的中药及相关活性成分,为深入研究肾脏疾病脂肪酸代谢相关机制、寻找靶向干预手段提供理论参考。

关键词 脂肪酸代谢;急性肾损伤;慢性肾病;肾癌;中药

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Role of fatty acid metabolism in kidney disease and therapeutic intervention by traditional Chinese medicine

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Abstract Fatty acid metabolism, including fatty acid oxidation (FAO) and fatty acid synthesis, plays critical roles in signal transduction, energy production and inflammation regulation. Acute kidney injury (AKI), chronic kidney disease (CKD) and renal cell carcinoma (RCC) are typical renal diseases with complex pathogenesis, susceptibility to multiple complications, and still no effective measure for clinical intervention. Current studies reveal that fatty acid metabolism is closely related to the occurrence and development of a variety of kidney diseases. This article reviews the metabolic characteristics of fatty acid in the kidney, the relationship between fatty acid metabolism disorder and renal diseases (i. e., AKI, CKD and RCC), and summarizes traditional Chinese medicines and related active ingredients targeting fatty acid metabolic pathway to alleviate renal diseases, aiming to provide theoretical reference for the in-depth study of mechanisms related to fatty acid metabolism in renal diseases as well as the development of effective interventions.

Key words fatty acid metabolism; acute kidney injury; chronic kidney disease; renal cell carcinoma; traditional Chinese medicine

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据统计,全球大约有8.5亿人患有不同类型的肾脏疾病[1]。临床上常见的肾脏疾病主要包括急性肾损伤(acute kidney injury, AKI)、慢性肾病(chronic kidney disease, CKD)与肾癌(renal cell carcinoma, RCC)。流行病学研究显示,全球每年约1 300万人患AKI[2-3];CKD全球发病率为9.1%,预计到2040年将成为全球第五大死亡原因[1,4];而RCC是最常见的成人肾脏恶性肿瘤,其发病率约占全球癌症新发病例的2.2%[5],晚期RCC患者的五年生存率仅为11.7%[6]。肾脏疾病诱发因素较多且发病机制复杂,目前临床尚无特异性的干预措施。脂肪酸是一类重要的内源性小分子代谢物,在机体能量稳态调节、维持细胞膜结构和功能完整性、调节炎症反应、激素调控及信号转导等方面发挥重要作用。组学(代谢组学、蛋白质组学)及机制研究表明,脂肪酸代谢失衡与肾脏疾病关系密切,脂肪酸相关代谢酶或可作为肾脏疾病的潜在干预靶点[7-8]。本文针对脂肪酸代谢与肾脏疾病的内在关系、靶向脂肪酸代谢治疗肾脏疾病的中药或单体进行系统综述,以期为肾脏疾病的机制研究和干预调控提供新思路。

1 脂肪酸代谢概述

正常肾小管上皮细胞具有丰富的线粒体供应和旺盛的代谢活性,优先通过消耗脂肪酸供能[9]。脂肪酸的代谢过程主要包括脂肪酸氧化和脂肪酸合成,在信号转导、能量代谢和炎症调节中扮演着重要的角色。

脂肪酸氧化(fatty acid oxidation, FAO)主要发生在线粒体或过氧化物酶体,主要包括3个阶段:脂肪酸酯化、脂酰辅酶A(coenzyme A, CoA)的转移和脂酰CoA的β氧化。首先,脂肪酸在胞液中被CoA酯化成水溶性较强的脂酰CoA,长链脂酰CoA在肉碱棕榈酰转移酶系统介导下转运至线粒体基质,发生β氧化产生大量乙酰CoA。乙酰CoA一方面进入三羧酸循环氧化供能,另一方面为酮体和类固醇等化合物的合成提供原料[10]。其中,肉碱棕榈酰转移酶1A(carnitine palmitoyltransferase 1A, CPT1A)是FAO的限速酶,受脂质合成中间体丙二酰CoA负反馈调节。过氧化物酶体增殖物激活受体α(peroxisome proliferators-activated receptor α, PPARα)是调节肾脏FAO的关键转录因子,脂肪酸是其内源性配体[11]。

脂肪酸合成的直接原料是乙酰CoA,它来源于糖、酮体和蛋白质等的分解代谢。乙酰CoA不易透过线粒体外膜,需通过柠檬酸-丙酮酸循环将乙酰CoA转运至胞液中。随后,乙酰CoA被乙酰CoA羧化酶(acetyl-CoA carboxylase, ACC)转化为丙二酰CoA,新生的脂肪酸链被脂肪酸合成酶(fatty acid synthase, FASN)不断延长,直至合成诸如棕榈酸等产物。在此过程中,ACC和FASN受到固醇调节元件结合蛋白(sterol-regulatory element binding protein, SREBP)的直接调控,而SREBP是一种公认的介导肾脏脂毒性、促进肾脏疾病发展的转录因子[12]。

2 脂肪酸代谢失调与肾脏疾病

脂肪酸摄取、氧化和合成失衡与多种肾脏疾病进展密切相关[13],且不同类型的脂肪酸(如碳链长度、不饱和度等)在相同疾病中变化趋势不一(表1),如AKI小鼠肾脏及CKD患者血清中饱和脂肪酸水平升高,多不饱和脂肪酸水平降低,而单不饱和脂肪酸水平显著增加且与CKD的进展和恶化程度密切相关[14-15]。基于2型糖尿病肾病(diabetic kidney disease, DKD)小鼠模型的原位代谢组学研究也发现,不同碳链长度和双键数的脂肪酸在损伤肾脏中的丰度和位置不同[16]。此外,短链和中链脂肪酸水平与RCC分级呈负相关,但长链饱和脂肪酸的水平与RCC分级呈正相关[17]。提示长链脂肪酸的蓄积是肾脏疾病进展的促进因素之一。

2.1 AKI

AKI是由败血症、缺血再灌注、肾毒性药物等引起的7 d内血清肌酐和尿素氮的迅速升高,伴随排尿量骤减的一种临床综合征。据统计,住院患者中AKI的发病率高达20%[18]。除具有较高发病率和病死率之外,AKI还是心血管疾病、CKD和终末期肾病(end stage renal disease, ESRD)的重要风险因素[19]。

已有代谢组学研究表明，多种诱因引起的AKI均伴随脂肪酸代谢紊乱，如一项基于34例AKI患者的血清代谢组学研究发现，乙酰肉碱和3种中链酰基肉碱（辛酰肉碱、癸烯酰肉碱及癸酰肉碱）水平在AKI患者血清中显著升高[20]。另一项基于LC-MS的代谢组学研究提出，血浆中升高的酰基肉碱可作为顺铂所致AKI的早期诊断生物标志物，其敏感性比临床常用肾功能指标（如肌酐、血尿素氮）更高[21]。缺血再灌注AKI的肾脏代谢组学揭示，AKI发生后肾脏内游离脂肪酸增加，而脂酰CoA和酰基肉碱水平却显著下降[14]。本课题组前期非靶向代谢组学研究也证实，顺铂所致AKI大鼠肾脏中长链脂肪酸及酰基肉碱的水平与顺铂剂量呈正相关[22]。此外，本课题组开发了一种靶向38种脂肪酸的LC-MS/MS定量方法，并利用该法对顺铂所致AKI大鼠血清分析发现，十三烷酸、肉豆蔻酸及十五烷酸等多种长链脂肪酸水平在AKI发生后显著降低[23]。

AKI中脂肪酸代谢紊乱提示调控通路中的相关代谢酶可能发挥潜在疾病干预作用（图1）。有研究表明，顺铂所致AKI小鼠肾脏中PPARα和MCAD（medium-chain acyl-CoA dehydrogenase）表达降低，肾近端小管中FAO明显受阻。机制研究发现，线粒体亲环蛋白D（cyclophilin D, CypD）可与PPARα作用，阻止其核易位而导致FAO受阻，最终引发肾功能障碍[24]。PPARα配体Wy14643可通过恢复MCAD的活性及表达，改善其介导的FAO过程而发挥缓解顺铂AKI的作用[25]。此外，脂肪酸结合蛋白（fatty acid binding protein 4, FABP4）在多种AKI模型中显著升高，抑制FABP4可通过减轻线粒体功能障碍、细胞炎症和凋亡水平而恢复肾脏功能[26-27]。因此，对脂肪酸摄取、氧化和合成过程代谢酶的调控有望成为干预AKI的新策略。

2.2　CKD

临床上CKD定义为肾脏结构或功能的持续异常（如体表面积每1.73 m^2肾小球滤过率小于60 mL/min或白蛋白尿≥30 mg/24 h）超过3个月，常见诱因包括糖尿病、高血压和感染等[28]，其中糖尿病因素占全部CKD诱因的30%~50%，影响全球约6.4%的成年人[29]。当肾功能损伤达到体表面积每1.73 m^2肾小球滤过率小于15 mL/min时，CKD将转化为ESRD。此外，肾纤维化作为CKD进展至

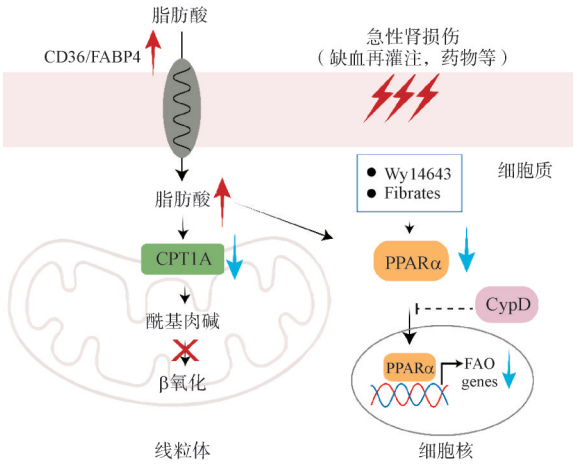

图1　急性肾损伤（AKI）中的脂肪酸代谢失调

CD36：脂肪酸转位酶；CPT1A：肉碱棕榈酰转移酶1A；CypD：线粒体亲环蛋白D；FABP4：脂肪酸结合蛋白4；FAO genes：脂肪酸氧化基因；Fibrates：贝特类；PPARα：过氧化物酶体增殖物激活受体α

ESRD的重要病理过程，与肾功能恶化密切相关，抑制肾纤维化对延缓或预防CKD至关重要[30-31]。

CKD患者的脂肪酸代谢紊乱主要表现为（图2）：（1）FAO相关酶活性或表达降低引起FAO受阻，而脂肪酸合成代谢增强。基于肾脏样本的全基因组分析显示，CKD患者肾脏PPARα及下游代谢酶表达显著降低，而这种降低归因于转化生

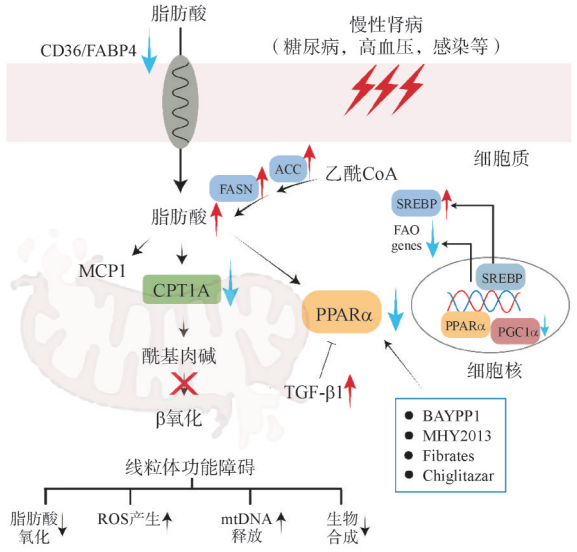

图2　慢性肾病（CKD）中的脂肪酸代谢失调

ACC：乙酰CoA羧化酶；Chiglitazar：西格列他钠；CPT1A：肉碱棕榈酰转移酶1A；FASN：脂肪酸合酶；MCP1：单核细胞趋化蛋白1；mtDNA：线粒体DNA；PGC1α：过氧化物酶体增殖物激活受体γ共激活因子1α；ROS：活性氧；SREBP：固醇调节元件结合蛋白；TGF-β1：转化生长因子β1

长因子β1(transforming growth factor β, TGF-β1)水平的升高[32]。另外,5/6肾切除CKD大鼠残余肾脏中脂肪酸生物合成酶FASN和ACC表达上调,而FAO相关酶表达下调[33]。(2)肾脏FAO受阻导致饱和脂肪酸蓄积,通过诱导线粒体活性氧(reactive oxygen species, ROS)生成、内质网应激和自噬等损伤小管细胞[34]。一项横断面研究揭示,从CKD的2期到5期,患者血浆饱和脂肪酸的含量逐级增加,而长链与中间链酰基肉碱比值逐级降低[35]。Chen等[34]通过Logistic回归分析发现晚期CKD患者血清饱和脂肪酸的含量与肾小球滤过率呈负相关。CKD的加剧则归因于脂肪酸蓄积引起的小管细胞中单核细胞趋化蛋白1(monocyte chemoattractant protein1, MCP1)的释放和蛋白激酶C的活化等[36]。(3)随着CKD的发展,蓄积的脂肪酸进一步损伤肾脏线粒体从而形成恶性循环。研究表明,线粒体DNA拷贝数与CKD进展风险高度相关[37]。DKD小鼠的肾小管细胞和足细胞中线粒体碎片增加,并伴随细胞氧化应激和凋亡水平的升高[38]。此外,线粒体生物发生调节因子过氧化物酶体增殖物激活受体γ共激活因子1α(peroxisome proliferator-activated receptor γ coactivator 1α, PGC1α)的表达在CKD小鼠和CKD患者的肾脏中均显著降低[30],提示线粒体功能障碍是CKD脂肪酸氧化受阻的原因之一,促进肾脏线粒体生物发生进而恢复FAO或将成为缓解CKD的潜在措施。

研究证实靶向调控PPARα及其下游代谢酶可有效缓解CKD。例如,在叶酸和单侧输尿管结扎诱导的肾纤维化模型中,PPARα激动剂非诺贝特通过恢复FAO相关代谢酶的表达改善肾损伤和纤维化[32]。新型PPARα激动剂BAYPP1在5/6肾切除诱导的肾纤维化模型中也观察到类似的结果[39]。近年研究也发现,PPARα/β激动剂MHY2013可显著增加PPARα/β的核易位和活性,增强FAO相关基因的表达,进而预防衰老过程中的肾纤维化[40]。2021年10月,全球首个PPARs全激动剂西格列他钠在我国获批上市,成为一个新型2型糖尿病有效药物治疗手段[41]。另有包括吉非罗齐、苯扎贝特、非诺贝特等在内的6个PPARα激动剂已经进入临床试验[42],但其对CKD的治疗作用还有待进一步验证。

2.3 RCC

据癌症中心的最新数据,2015年我国新发RCC为66.8万例,死亡人数为23.4万人[43]。近期研究揭示,几乎所有类型的RCC都与三羧酸循环、脂肪酸和葡萄糖的代谢重编程密切相关[44],其中脂肪酸代谢在RCC侵袭性中发挥重要作用。

在RCC的发展过程中,FAO途径被抑制而细胞内脂质储存大大增加(图3)。Wettersten等[17]利用蛋白质组学和代谢组学对人RCC组织分析发现,RCC细胞中酰基肉碱和脂质水平显著升高且与RCC分级呈正相关。进一步研究发现,大多数FAO代谢酶在高级RCC组织中降低,这可能是酰基肉碱累积的原因。此外,PPARα高表达的RCC患者的预后比PPARα低表达的RCC患者更好,提示PPARα也是RCC的关键调控因子[45]。Wang等[46]发现Wy14643可抑制RCC细胞的增殖和迁移,可能与激活PPARα-CPT1A轴进而减少脂质积累有关。PPARα特异性抑制剂GW6471以及小干扰RNA通过减弱与糖酵解和FAO相关的代谢重编程抑制RCC发展[47]。

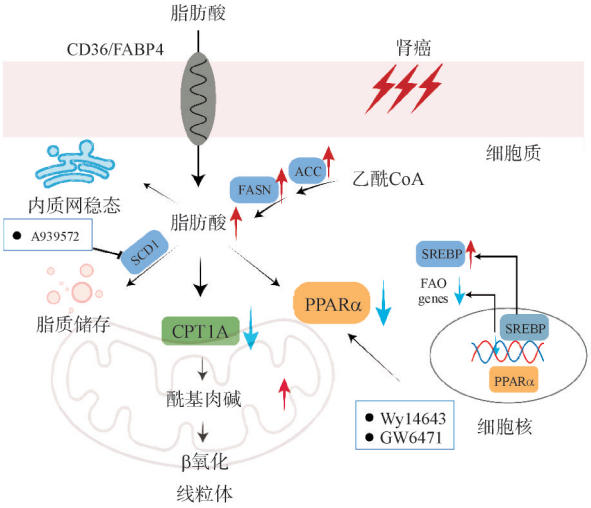

图3 肾癌(RCC)中的脂肪酸代谢失调

SCD1:硬脂酰CoA去饱和酶;红色箭头表示上调或增强,蓝色箭头表示下调或减弱

脂肪酸合成方面,有研究发现RCC中脂质的储存可通过维持内质网稳态促进肿瘤细胞的存活[48]。硬脂酰CoA去饱和酶(stearoyl-CoA desaturase-1, SCD1)主要负责脂质储存,其在RCC的所有发展阶段中均表达增加,使用小分子抑制剂A939572抑制SCD1表达可抑制RCC生长和增

殖[49]。此外，脂肪酸合成相关代谢酶的上调在一定程度上与RCC的预后不良存在相关性，有研究证明FASN表达增加与RCC侵袭性和患者生存率低有关[50]。

表1　不同肾脏疾病中脂肪酸变化及相关机制总结

疾病	临床诊断标准	数据来源	脂肪酸及相关代谢物变化趋势	机制或通路	参考文献
急性肾损伤	7 d内血清肌酐和尿素氮的迅速升高，伴随排尿量骤减（血清肌酐升高至基线值的1.5倍及以上；尿量＜0.5 mL/(kg·h)，持续6 h）	急性肾损伤患者	短/中链酰基肉碱↑	FAO↓	[20]
		缺血再灌注急性肾损伤大鼠	长链饱和脂肪酸↑ 单不饱和脂肪酸↑	脂肪酸生物合成↑	[51]
		缺血再灌注急性肾损伤小鼠	单/多不饱和脂肪酸↑ 中/长链饱和酰基肉碱↓ 多不饱和酰基肉碱↓	CPT1A↓ MCAD↓	[14]
		顺铂急性肾损伤小鼠	短链酰基肉碱↑	FAO↓	[52]
		顺铂急性肾损伤大鼠	长链饱和酰基肉碱↑ 单/多不饱和酰基肉碱↑	FAO↓ 酰基肉碱排泄↓	[21]
慢性肾病	肾脏结构或功能的持续异常（如体表面积每1.73 m^2肾小球滤过率小于60 mL/min或白蛋白尿≥30 mg/24 h）超过3个月	慢性肾病患者	长链饱和脂肪酸↑	FAO↓	[35]
		慢性肾病患者	长链饱和脂肪酸↑ 多不饱和脂肪酸↓	FAO调节因子↓	[53]
		糖尿病肾病小鼠	长链饱和脂肪酸↑ 单不饱和脂肪酸↓ 多不饱和脂肪酸↑	CPT1A↓ FASN↑	[16]
肾癌	透明细胞癌（60%～70%）：PAX8染色阳性；乳头状细胞癌（10%～20%）：AE1/3、CAM5.2染色阳性；嫌色细胞癌（5%～7%）：CD117、小白蛋白和肾脏特异性钙黏蛋白染色阳性	透明细胞癌患者	短/中链脂肪酸↓ 长链脂肪酸↑	FAO↓	[17]
		透明细胞癌患者	长链饱和脂肪酸↑ 多不饱和脂肪酸↑	CPT1A↓ FAO↓	[54]
		透明细胞癌患者	肉碱/短/长链酰基肉碱↑	脂肪酸代谢失调	[55]
		透明细胞癌患者	长链饱和脂肪酸↑ 单不饱和脂肪酸↑	脂肪酸合成↑	[56]
		肾癌转基因小鼠	单/多不饱和脂肪酸↑	脂质生物合成↑	[57]

↑表示上调或增强，↓表示下调或减弱

3　干预脂肪酸代谢缓解肾脏疾病的中药及活性成分

脂肪酸代谢失调与肾脏疾病的发生发展密切相关，因此靶向调控肾脏脂肪酸代谢或可缓解肾脏损伤。此外，线粒体功能障碍所致的脂肪酸代谢紊乱亦是肾脏损伤的促进因素。长久以来，中药及其活性成分在预防和治疗各种疾病中发挥了关键作用，是新药研发、药品制备的重要来源，本文系统总结了回调脂肪酸代谢相关代谢物、调控脂肪酸代谢相关代谢酶以及改善线粒体功能障碍缓解各种肾脏疾病的相关研究（表2）。

3.1　回调脂肪酸相关代谢物

真武汤由茯苓、芍药、生姜、附子、白术组成，是临床常用方剂，具有温阳利水、健脾燥湿的功效。Li等[58]利用代谢组学方法，发现真武汤通过回调脂肪酸代谢、缓解氧化应激缓解肾纤维化。黄葵胶囊是黄蜀葵干燥花冠的乙醇提取物制剂，具有清热除湿、消肿解毒等功效。临床数据表明，黄葵胶囊治疗DKD的效果显著[59]。近期有研究基于文献挖掘与网络药理学揭示，黄葵胶囊治疗DKD的分子作用机制与亚油酸代谢和甾体激素生物合成代谢相关[60]。大黄是一味常用的泻下药材，具有清热泻火、凉血解毒、逐瘀通经的功效。Zhang等[61]结合脂质组学和代谢组学探究大黄缓解慢性肾衰的机制，发现缓解作用与脂肪酸、甘油磷脂和氨基酸代谢回调密切相关。茯苓皮为多孔菌科植物茯苓菌核的外皮，其作为一种有效的CKD传统治疗药物已有数千年历史。Zhao等[62]基于UPLC-

表2 干预脂肪酸代谢缓解肾脏疾病的中药及活性成分汇总

中药类别	名称	肾脏疾病	调控因素	参考文献
方剂/制剂	滋肾清热通络方	高尿酸血症肾病	PGC-1α↑	[64]
			PPARα↑	
			FAO↑	
	真武汤	肾纤维化	脂肪酸	[58]
	黄葵胶囊	糖尿病肾病	亚油酸	[60]
药材	大黄	慢性肾衰	脂肪酸	[61]
	茯苓皮	慢性肾病	脂肪酸	[62]
活性成分	大黄酸	肾纤维化	CPT1A↑	[66]
			FAO↑	
	三七皂苷	顺铂急性肾损伤	线粒体损伤↓	[70]
	黄芪甲苷Ⅳ	顺铂急性肾损伤	脂肪酸	[63]
	山柰酚	顺铂急性肾损伤	酰基肉碱	[64]
	雷公藤红素	顺铂急性肾损伤	线粒体功能↑	[71]
	小檗碱	糖尿病肾病	PGC-1α↑	[72]
			线粒体能量稳态↑	
	骆驼蓬碱	肾纤维化	PGC-1α↑	[67]
			PPARα↑	
			CPT1A↑	
			FAO↑	
	三七多糖	糖尿病肾病	SREBP↓	[68]
			ACC↓	
			脂质蓄积↓	
	花青素	糖尿病肾病	AMPK↑	[69]
			SREBP↓	
			ACC↓	
			脂质蓄积↓	

Q-TOF/MS的代谢组学方法考察了茯苓皮改善CKD的机制，发现改善作用茯苓皮与脂肪酸代谢、磷脂代谢和色氨酸代谢回调相关。黄芪甲苷Ⅳ是黄芪的代表性成分，近期Song等[63]基于代谢组学阐释其缓解顺铂AKI的代谢机制，结果表明黄芪甲苷Ⅳ可显著回调血清中不饱和脂肪酸、丙氨酸、天冬氨酸等的生物合成，通过改善炎症反应、氧化应激和能量代谢缓解AKI。本课题组前期整合网络药理学和代谢组学研究证实，山柰酚可通过回调酰基肉碱代谢、降低炎症水平而发挥缓解顺铂AKI的作用[64]。

3.2 调控脂肪酸相关代谢酶

滋肾清热通络方是由《金匮要略》中的白虎桂芝汤改制而来，以知母、石膏、桂枝、甘草、薏苡仁、山药配比组成，已被用于治疗高尿酸血症肾病。体内研究表明，滋肾清热通络方可通过介导TGF-β1/Smad3信号通路，显著上调PGC-1α和PPARα蛋白表达，改善肾脏FAO发挥肾脏保护作用[65]。Song等[66]通过体外研究考察了蒽醌类化合物大黄酸对肾纤维化的缓解作用与FAO的关系，结果表明大黄酸可通过SirT1/STAT3/Twist3通路恢复CPT1A介导的FAO改善肾纤维化。骆驼蓬碱是存在于植物骆驼蓬中的一种β-咔啉类生物碱，体内外研究表明，它是转录因子Twist1的新型抑制剂，这种抑制作用可通过上调PGC-1α、PPARα及其下游代谢酶CPT1A的表达恢复FAO，最终显著缓解肾间质纤维化[67]。此外，文献报道三七多糖和花青素均可通过抑制SREBP和ACC活性及表达，改善脂质代谢紊乱、缓解氧化应激进而发挥治疗DKD的作用[68-69]。

3.3 改善线粒体功能障碍

三七是常用的止血中药材，具有散瘀止血、消

肿定痛的功效。体内研究显示，其有效活性成分三七皂苷可改善顺铂诱导的线粒体损伤并增强肾细胞自噬，从而减轻顺铂肾毒性[70]。雷公藤红素是雷公藤的有效成分，临床上用于治疗免疫性疾病，文献报道其可抑制 NF-κB 活化、改善线粒体功能而缓解化疗药物顺铂所致的 AKI[71]。小檗碱是从黄连中分离的一种季铵生物碱，近期的研究发现其可通过激活 PGC-1α 信号通路，促进足细胞线粒体能量稳态和 FAO 而缓解 DKD[72]。

4　结语与展望

综上，本文以典型肾脏疾病 AKI、CKD 与 RCC 为代表，系统阐述了肾脏疾病与脂肪酸代谢的内在关系。值得注意的是，PPARα 在多种肾脏疾病中均发挥着重要的调控作用，虽然 PPARs 全激动剂西格列他钠在我国获批上市且已有多个 PPARα 激动剂获得临床批件，但这些药物在肾脏疾病中的作用有待进一步验证。

此外，调节脂肪酸代谢的中药及其活性成分已应用于治疗各种肾病，部分中药已深入分子水平的实验研究和评价，但在应用方面仍基于临床经验，或局限于动物实验研究，尚缺乏临床试验依据。因此，在传承中医药理论基础上，开发出临床上安全有效、机制明确的中药制剂或组合，有望为肾脏疾病的治疗带来新突破。

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