PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2024, 51(5): 1067~1078
www.pibb.ac.cn

脂代谢紊乱在肾脏衰老和肾纤维化中的作用*

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摘要 肾间质纤维化是终末期肾脏病的病理基础，肾脏衰老是肾间质纤维化的危险因素。越来越多的研究证明，脂代谢紊乱会导致肾脏衰老和肾间质纤维化。脂代谢紊乱引起的脂质堆积，会造成脂毒性和细胞应激性损伤，从而诱发衰老与细胞外基质（extracellular matrix，ECM）的分泌。维持脂代谢稳态有助于减轻肾脏衰老与肾间质纤维化的发生发展。脂代谢途径的关键酶和调控蛋白有望成为改善肾脏衰老和肾间质纤维化的潜在靶点。本综述概括了脂代谢紊乱在肾脏衰老和间质纤维化中的作用，并对脂代谢中肾脏衰老和间质纤维化的预防靶点和策略进行了总结，为治疗肾纤维化发现新靶点提供了参考。

关键词 肾脏衰老，肾间质纤维化，脂代谢，肾小管上皮细胞
中图分类号 R365，R692 **DOI**：10.16476/j.pibb.2023.0305

衰老是指生物体在其生命过程中结构的退行性改变、功能储备的逐渐丧失、对外部或内部压力的适应能力显著下降，常常伴随着疾病发生，甚至有死亡的风险[1]。在过去几十年中，由于生活条件、社会经济状况和医疗保健的改善，人类的预期寿命显著增加，人口的快速老龄化将是全球的必然趋势。目前，65岁及以上的人口约占世界人口总数的8.5%，预计2050年达到17%[2]。中国65岁及以上的人口预计2050年将增加到4亿，占人口总数的26.9%，80岁或以上人口数量将达到1.5亿[3]。随着人口老龄化进程的加快，各类衰老相关疾病的发生率也逐渐升高，给社会带来了沉重的经济和医疗负担。据估算，慢性肾脏病（chronic kidney disease，CKD）会影响全球10%~14%的人口[4]，而在60岁以上人群中的发病率则高达25%[5]。年龄增长造成的肾脏衰老和肾功能储备受损，增加了个体对CKD的易感性[6]。肾间质纤维化被认为是CKD发展至终末期的主要病理基础，CKD的高发为肾纤维化的防治带来很大的挑战。脂质代谢紊乱是指体内血液及其他组织器官中脂质及其代谢产物质和量的异常。脂质代谢紊乱与肾脏疾病密切相关，它既是许多原发或继发性肾脏病的常见临床表现，同时也参与了肾脏病的进展。随着肾脏能量代谢的研究越来越多，人们对脂代谢紊乱在肾脏疾病发生发展过程中扮演的角色有了新的认识，本文将针对这些研究进展进行综述，阐述肾脏脂代谢异常产生的原因、脂质累积对细胞造成的影响，梳理脂代谢异常在肾脏衰老和肾间质纤维化中的作用，并加深对其分子机制和生物学意义的理解。

1 肾脏衰老与肾间质纤维化

1.1 肾脏衰老

随着年龄的增长，个体的各类器官发生退行性病变。肾脏特别容易受到年龄相关变化的影响[7]，被认为是正常衰老过程中变化最显著的器官之一[8]。肾脏衰老的特征是肾皮质的减少和肾功能受损，组织学的改变包括肾小球硬化、肾小管萎缩、肾纤维化及肾血管硬化[9]，功能上的变化主要表现为肾小球滤过率（glomerular filtration rate，eGFR）的下降。慢性炎症、氧化应激和肾素-血管紧张素-醛固酮（renin-angiotensin-aldosterone

* 国家自然科学基金（81971329，82200821）和广东省基础与应用基础研究基金（2023A1515012838）资助项目。
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收稿日期：2023-08-03，接受日期：2023-10-26

system，RAAS）系统活性改变造成的细胞损伤和修复能力下降是诱发肾脏衰老的重要驱动因素[10]。细胞衰老的常见分子变化在衰老的肾脏中也被鉴定出来，包括衰老相关-β-半乳糖苷酶（SA-β-gal）活性增加、细胞周期抑制蛋白上调、衰老分泌相关表型（senescence associated secretory phenotype，SASP）的增多和端粒缩短。肾脏的衰老会引发高血压、胰岛素抵抗等一系列问题[11]，还会增加个体对急性肾损伤和慢性肾病的易感，并在肾纤维化的发生和发展过程中发挥关键作用。衰老的肾小管上皮细胞（tubular epithelial cells，TECs）是区分患病肾脏和正常肾脏的关键[12-13]。最近研究表明，不断清除衰老细胞可减轻与年龄相关的肾功能减退和肾小球硬化[14]。

1.2 肾间质纤维化

肾间质纤维化是所有慢性和进行性肾病的共同病理特征，也是导致肾功能衰竭的主要决定因素[15]。它的定义是细胞外基质（extracellular matrix，ECM）在小管和管周毛细血管之间的过度沉积[16]，主要表现为致纤维化细胞因子分泌增多和ECM的胶原成分聚集，伴有肾小管萎缩和扩张变形、肾单位破坏及肾小球过滤能力减弱[4，17]。在轻度损伤的情况下，纤维化基质沉积有助于组织修复，其会在组织修复过程中被吸收[15]。然而，在CKD的后期，纤维化基质沉积过多，降低了组织修复的能力，则会破坏器官结构，减少血液供应，扰乱器官功能，最终导致肾衰竭[15]。CKD过程中肾脏的持续损伤通过不同的信号通路激活肌成纤维细胞，激活的肌成纤维细胞很大一部分是由TECs转化而来的。TECs脱离细胞接触，失去上皮特征，获得成纤维细胞表型，也可产生ECM，促进纤维化过程[18]。转化生长因子β1（transforming growth factor beta-1，TGF-β1）被认为是这一过程的主要调节因子[19]。由于肾纤维化的发病机制较为复杂[20]，阐明肾脏发生纤维化的分子调控机制，对于肾纤维化的防治具有重要的意义。

1.3 肾脏衰老与肾间质纤维化的关系

肾间质纤维化是肾脏衰老的微观表现，衰老的肾脏细胞也可在肾间质纤维化中发挥关键作用[21]。TECs衰老伴随着SASP的表达上调，引起促纤维化细胞因子分泌增加，进而推动肾间质纤维化的发生发展[22]。TECs中纤维化标志物α-SMA的蛋白质水平与SA-β-gal的活性以及衰老相关的p16和p21的表达呈正相关[23-24]。缺血再灌注6周的老年小鼠有广泛的肾纤维化和白细胞浸润，这与肾小管中p53表达及SA-β-gal阳性细胞的增加有关[25]。急性肾损伤诱导近端肾小管上皮细胞衰老产生的促纤维化生长因子，能够刺激成纤维细胞增殖和胶原的形成[26]。在人肾小管上皮细胞系HK-2和TECs中，Wnt9a能够上调p16、p19、p53和p21的表达，促进TGF-β1的分泌，进而加快肾成纤维细胞的增殖和活化[27]。以上数据揭示了肾脏衰老和肾纤维化之间的内在联系，提示延缓肾脏衰老可能是预防肾间质纤维化的有效途径。

2 肾脏脂代谢紊乱的诱发因素

在正常情况下，体内的脂质会被储存于脂肪组织中[28]。然而过量的脂质也会在其他组织中沉积，其中就包括肾脏[29]。肾脏脂质代谢失调主要源于3条途径的破坏：循环中脂肪酸（fatty acid，FA）摄取、脂质合成和分解。一旦脂质的摄取/合成超出了与分解的平衡，肾脏脂质就会累积。因此，肾脏脂代谢紊乱常见的原因主要是血脂异常、脂质合成过多和脂质分解的减少。

考虑到大量血液经过，肾脏易受循环中的游离脂肪酸（free fatty acid，FFA）影响[30-31]。血液中的FFA主要来源于食物中脂质的吸收或白色脂肪组织中甘油三酯（triglyceride，TG）的分解。脂肪组织中的甘油三酯脂肪酶（adipose triglyceride lipase，ATGL）催化脂肪细胞中TG水解的初始步骤，ATGL缺失小鼠的肾脏TG水平显著升高，并伴有蛋白尿[32]。细胞对FFA的摄取能力在很大程度上取决于血浆FA浓度以及膜结合脂肪酸转运蛋白（fatty acid transporter proteins，FATPs）和分化抗原36（cluster of differentiation，CD36）的表达水平[33]。FATP2的表达减少会引起TECs脂质含量降低，并抑制细胞凋亡[34-35]。在肾脏疾病的发生发展中，CD36表达增加会导致脂质过载从而产生脂毒性[36]。体内研究发现，CD36缺失的小鼠能够抵抗高脂饮食（high-fat diet，HFD）引起的肾脏脂质蓄积和炎性细胞浸润[37]。

基于肾脏细胞能量代谢的研究表明，肾损伤过程伴随着内皮细胞、足细胞和近端小管上皮细胞的脂肪生成增加[38-39]。胆固醇调节元件结合蛋白1（sterol-regulatory element binding proteins，SREBP-1）和脂肪酸合成酶（fatty acid synthase，FAS）是FA从头合成的关键调节因子和限速酶。糖尿病肾病（diabetic nephropathy，DN）大鼠的肾组织以及棕

棕榈酸（palmitic acid，PA）诱导的HK-2细胞中SREBP-1和FAS的表达均显著升高；抑制SREBP-1、FAS表达可以减轻DN大鼠肾小管异位脂质沉积，并改善PA诱导的TECs脂质积累[40]。另一关键的脂质合成调节因子糖应答元件结合蛋白（carbohydrate response element binding protein，ChREBP）的过表达会驱动HK-2细胞中活性氧（reactive oxygen species，ROS）产生[41]。

脂质分解减少也是肾脏脂代谢失衡的关键因素。ATGL和激素敏感脂肪酶（hormone-sensitive lipase，HSL）是TG分解的关键酶，上调肾脏中ATGL和HSL的表达可以减轻肾小管中的脂质累积[40]。脂肪酸氧化（fatty acid oxidation，FAO）受阻也会导致TECs内脂质积累，并能促进上皮-间质转化（epithelial-mesenchymal transition，EMT）和炎症[42]。FFA的β氧化是近端肾小管细胞ATP产物的主要来源，抑制脂肪酸β氧化关键酶肉毒碱棕榈酰转移酶1α（carnitine palmitoyltransferase 1α，CPT1α），造成近端肾小管细胞内脂质沉积增加、ATP耗竭和细胞死亡。过氧化物酶体增殖物激PPAR活受体α（peroxisome proliferators-activated receptors，PPARα）的激活可诱导线粒体FAO相关基因的转录，如CPT1α和酰基辅酶a氧化酶1（acyl-coenzyme A oxidase 1，ACOX1），从而减少脂质蓄积[43]。

综上所述，肾脏脂质沉积是FA摄取、脂质合成和分解之间不平衡的结果，想要改善肾脏的脂质累积则需要打破这种不平衡状态，重新建立3条脂代谢途径之间的稳态，为肾脏正常功能的维持提供能量。脂质稳态的破坏会促进组织和器官的病理变化，从而导致生物衰老和与年龄相关的疾病。

3　脂代谢紊乱引发肾脏衰老的机制

3.1　脂肪酸摄取、脂质合成与肾脏衰老

FA摄取和脂质合成异常增多是肾脏衰老的风险因素。D-半乳糖构建的衰老动物模型的肾组织中CD36的表达远高于正常组，CD36的缺失则能够减轻衰老相关的肾损伤[44]。调节FA从头合成的关键转录因子SREBP的激活不仅会造成肾损伤，还会引发肾脏衰老[45]。长期HFD造成机体血脂异常的同时也可加快肾脏细胞的衰老[46]。研究表明，HFD促进肾脏p16、p19和p53的表达以及SA-β-Gal的活性，诱导肾脏衰老[22]。茶多酚中最有效的活性成分表没食子儿茶素没食子酸酯给药导致肥胖大鼠模型的血脂水平降低，血清中白介素-6（interleukin-6，IL-6）、肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）等SASP因子减少，并能够改善肾损伤以及延长动物模型的寿命[47]。

3.2　脂质分解与肾脏衰老

肾脏功能的维持主要依赖于FAO途径产生的能量[48]，大多数的肾脏疾病模型中都能检测到FAO障碍，其中就包括衰老的肾脏[29]。研究发现，衰老状态的TECs的FAO途径受到损害，进而加重肾脏脂质积累及肾小管损伤[49]。PPAR活性的降低与肾脏疾病中的脂质代谢紊乱直接相关[11]，衰老肾脏中PPARα的转录活性和蛋白质水平降低，PPARα/β受损与衰老过程中的慢性炎症有关[49]。PPARα/β的激活剂MHY2013可以显著增加FAO相关基因的表达，改善衰老SD大鼠TECs的脂质紊乱，并下调*TGF-β*等基因的表达[50]。上述研究表明，FAO障碍是肾脏衰老过程中脂质代谢失调的关键因素。而在非FAO障碍造成的脂质累积的动物模型中，脂质过氧化则可能是造成肾脏细胞损伤和衰老的驱动因素。例如，4-羟基壬烯醛（4-hydroxynonenal，4-HNE）的染色结果显示，18月龄的小鼠肾脏中脂质过氧化水平明显高于12月龄的小鼠[51]。

3.3　应激性损伤与肾脏衰老

脂质的持续蓄积产生脂毒性，诱发氧化应激、内质网应激和线粒体功能障碍，造成TECs损伤[52-53]。大量研究表明，TECs损伤和衰老会导致肾功能障碍，与肾脏疾病的发病密切相关，包括DN和肾脏衰老等[10，54-55]。抑制小鼠TECs内质网应激可减轻DN进程中细胞的过早衰老[56]。氧化应激可引起DNA氧化损伤和线粒体功能障碍，对TECs的衰老有很大的影响[57]。研究指出，醛固酮可以诱导TECs的氧化应激和衰老，提高细胞的自噬则可通过改善氧化应激减轻细胞衰老[58]。氧化应激可诱导脂质过氧化，形成高度反应性和亲电性的化合物，这些化合物攻击蛋白质中的游离氨基使其共价修饰，并导致高级脂氧化终产物（advanced lipoxidation endproducts，ALEs）的产生[59]，氧化应激诱导的ALEs形成与衰老有关[60]。作为诱导HK-2细胞衰老的常用试剂，H_2O_2增加了氧化应激和导致线粒体功能障碍[61]。线粒体是ROS产生的主要场所，线粒体ROS可以激活Jun-N端激酶，促进染色质片段向胞质释放以及SASP的分泌[62]。同时，小鼠线粒体中具有抗氧化作用的超氧化物歧化

酶（superoxide dismutase 2，SOD2）的缺失则会导致细胞衰老[63]。

4　脂代谢紊乱与肾纤维化的发生发展密切相关

在肥胖相关的肾脏疾病和肾纤维化进展中可以观察到，脂质过载会产生脂毒性，同时产生ROS、释放促炎和促纤维化因子以及导致细胞周期阻滞，促进细胞凋亡[64]。血浆中脂蛋白的含量对肾纤维化有很大的影响。CKD患者往往伴随着高甘油三酯血症、高的低密度脂蛋白胆固醇（low density lipoprotein cholesterol，LDL-C）和低的高密度脂蛋白胆固醇（high-density lipoprotein cholesterol，HDL-C）水平[65-66]。接受肾脏移植的CKD患者的LDL水平与移植肾的脂质含量和纤维化密切相关[67]。氧化LDL（ox-LDL）促进TECs的EMT过程，引起ECM积累，最终导致肾间质纤维化的发生[68]。同样地，LDL受体、乙酰化LDL和CD36水平的升高与DN的进展和eGFR的降低有关[69]。临床数据表明，HDL-C水平升高能明显改善肾功能[70-71]。补充HDL可以降低黏附分子表达，减少炎性细胞浸润以及细胞氧化应激，并减轻肾小管损伤和肾纤维化，提高肾缺血再灌注动物模型的eGFR[72]。对高血脂有显著疗效的他汀类药物可明显减轻受试者的肾损伤[73]。

脂质代谢紊乱引起的脂毒性通过各种致病机制损害TECs、足细胞和肾小管间质细胞，导致肾功能不全[74]。在小鼠纤维化模型中，miR-21介导的PPARα下调会导致肾纤维化和肾小管上皮损伤[75]。过表达CPT1α可以增强TECs的FAO，降低炎症因子的表达，并显著减轻纤维化[76]。同样有研究指出，SREBP-1/2/AMPK途径可启动肾脏中脂肪生成，并通过上调CD36的表达加快脂质摄取，双重作用下肾脏中脂质发生堆积，造成肾损伤和肾纤维化[67]。芝麻油中的有效活性成分芝麻素给药可介导脂质代谢，改善高脂血症大鼠模型中脂质代谢紊乱引起的肾损伤以及下调大鼠肾脏中α-SMA和四型胶原蛋白（Col-IV）的表达[77]。

因此，肾脏中脂质过量累积会导致脂代谢紊乱，产生脂毒性。同时产生内质网应激，细胞内的活性氧和线粒体活性氧增加。脂毒性会诱发TECs应激性损伤和衰老，衰老TECs分泌的SASP因子（包括促纤维化因子和促炎因子）进一步加速其衰老以及炎症和EMT的发生，促进成纤维细胞活化和ECM的分泌，最终导致肾间质纤维化的发生（图1）。

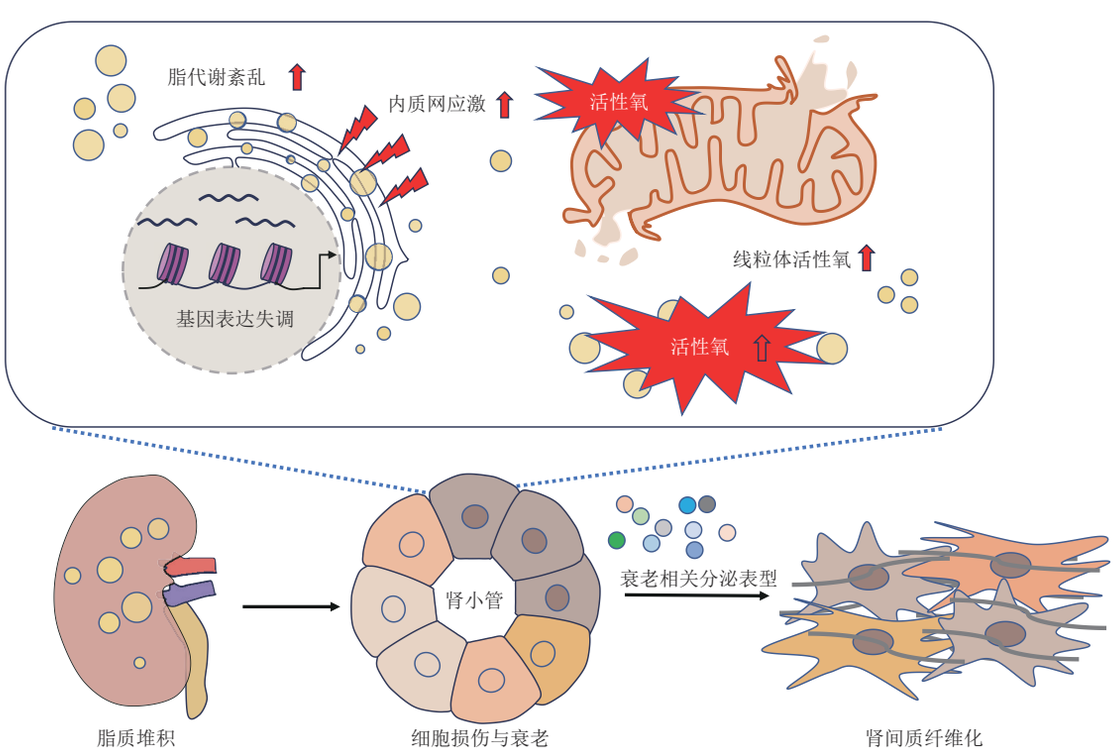

Fig. 1　Association of disorders of lipid metabolism with renal ageing and renal interstitial fibrosis

图1　脂代谢异常与肾脏衰老和肾间质纤维化的关系

5　基于脂代谢调控预防肾脏衰老与肾纤维化的潜在靶点和策略

5.1　潜在分子靶点类型

目前关于抑制甚至扭转肾间质纤维化的研究，多数停留在实验动物阶段，仅个别被应用到临床[78-79]。延缓肾脏衰老的有效药物尚未见报道。现已明确脂质紊乱可以促进肾脏衰老与肾间质纤维化的发生发展。因此，靶向脂质代谢相关酶、转运蛋白、转录因子有望成为预防或治疗肾间质纤维化的有效途径[80]。

5.1.1　PPARs

PPARs是配体激活的核受体/转录因子的一个亚家族，属于核受体超家族[81]。PPARα或PPARβ是细胞内脂质代谢的重要调节因子，主要调控过氧化物酶体和线粒体FAO途径、FA摄取和TG分解代谢相关基因的转录[82]。老年大鼠肾脏中PPARα和FAO相关酶的水平降低，伴随着脂质堆积和肾纤维化的显著增加[50]。研究表明，PPARα缺失造成的脂代谢失衡在衰老相关的肾纤维化发展中发挥重要作用。PPARα敲除的老年小鼠的肾脏表现出脂质积聚、损伤加重以及纤维化水平升高，miR-21也可通过下调PPARα表达加快小鼠模型的肾小管上皮损伤和纤维化[49]。PPARα/β激活剂则能够减少细胞内脂质积聚并下调细胞中衰老和纤维化相关基因的表达，如*p65*、*IL-1*、*IL-6*和*TNF-α*等[50]。多酚类中药单体白藜芦醇通过调节PPARα途径预防HFD小鼠肾脂毒性[83]。研究表明，核受体PPARγ的活性随着年龄的增长而降低[84]。可保护人体细胞免受氧化应激和衰老的影响[85-87]。

5.1.2　PGC1α

PGC1α是转录共激活因子家族的一员，是PPARs等转录调控蛋白的共激活因子。它在能量代谢组织中广泛表达[30]，参与调节能量代谢、线粒体生物发生以及其他生物过程[88]。在CKD患者肾脏中，PGC1α表达下调，其表达与eGFR呈正相关，与纤维化呈负相关[89]。肾小管特异性过表达PGC1α可恢复线粒体含量并减轻纤维化[48]。在衰老或发生纤维化肾脏中，PGC1α和相关转录因子的缺乏会导致FAO障碍、脂质堆积、过量ROS的产生、线粒体膜电位的丧失和线粒体损伤[90]。研究表明，沉默信息调节因子1（silent information regulator 1，Sirt1）可以通过激活PGC1α来改善线粒体的生物发生从而延长寿命[91]。*PGC1α*还是Notch的靶基因，上调*PGC1α*基因表达可以预防Notch介导的肾损伤和纤维化[89]。考虑到调控脂代谢和线粒体生物发生的重要作用，PGC1α是极具潜力的一个治疗肾脏疾病分子靶点。

5.1.3　CPT1/2

CPT家族成员CPT1和CPT2位于线粒体外膜和内膜中，CPT1/2是FAO的一种关键限速酶，对脂质分解代谢至关重要[92]。FA进入线粒体是由CPT1介导的，该酶的作用是使FA与肉碱结合。CPT1的下调会抑制FAO，造成脂质堆积，进而导致CKD和肾纤维化[48]。在衰老相关的肾纤维化患者中，CPT1α的表达与纤维化程度呈负相关[93]。研究表明，敲除CPT1会降低近端肾小管上皮细胞的FAO和ATP产生能力，加剧肾小管损伤和肾纤维化，并减弱肾脏的修复能力[42]。CPT1的过表达则可以保护线粒体呼吸并防止叶酸诱导的肾病小鼠模型的肾小管细胞损伤[94]。同样，在单侧输尿管结扎或腺嘌呤诱导的肾纤维化小鼠模型的TECs中过表达CPT1，引起上皮细胞损伤减轻、炎症反应减弱以及纤维化标志物的表达减少[76]。间充质干细胞细胞外小泡通过恢复CPT1α的表达，增强肾脏线粒体FAO，修复了线粒体的结构，在减轻肾损伤和肾纤维化方面表现出优越的治疗效果[75]。DN小鼠模型中CPT2及其调控分子的表达较低，细胞内脂质沉积较多[95]。CPT2的过表达使FAO和纤维化相关基因恢复到正常水平[95]，表明靶向CPT2有助于预防和治疗肾纤维化。

5.1.4　TGF-β

TGF-β超家族在衰老、组织稳态、纤维化疾病和免疫功能障碍等一系列病理变化中起重要的作用[96]。参与EMT和ECM积累的众多通路，TGF-β1被认为在肾纤维化中发挥主要作用[97]。TGF-β1已被确定为细胞和器官衰老的关键调节因子，TGF-β信号传导以多种方式与衰老过程相互作用。TGF-β信号传导的下游靶点包括许多参与衰老过程的调节因子，如细胞增殖、细胞周期调节、ROS产生、DNA损伤修复、端粒调节和自噬[98]。人们普遍认为脂毒性代谢物的生成通常与脂质积累同时发生，这在肾脏衰老和肾间质纤维化的发病机制中起着关键作用。脂毒性易使肾脏产生过多的ROS和氧化应激，可引起细胞坏死和凋亡[99]。在TGF-β刺激的TECs中，谷胱甘肽浓度降低，脂质过氧化增强，暗示了TGF-β也可能通过调节肾脏细胞的脂代谢过程促进肾纤维化进程[100]。

5.1.5 Sirt1

肾脏中Sirt1水平降低与肾功能减退有关[87]。在肥胖的DN大鼠模型中，饮食限制（dietary restriction，DR）会上调Sirt1的表达，加强抗炎作用，改善自噬失调，从而改善肾损伤[101]。Sirt1的过表达还能降低ROS、FN和TGF-β1水平[102]。黄芩苷可以通过Sirt1/AMPK/HNF4A途径缓解*db*/*db*小鼠肾脏的脂代谢异常，发挥肾脏保护作用[103]。此外，Sirt1对氧化应激介导的肾纤维也有重要的作用[102]，同样的结果在HK-2细胞中也得到证实[104]。Sirt1是一种抗衰老分子[105]。衰老过程中Sirt1的表达水平与线粒体生物发生保持一致[106]。骨髓来源的间充质干细胞通过Sirt1/Parkin轴促进TECs的自噬，改善脓毒症诱导的急性肾损伤[107]。Sirt1过表达和SRT1720治疗均降低了肾脏脂质含量和脂肪生成、氧化应激和炎症标志物的表达，并在一定程度上减轻肾间质纤维化[108]。白藜芦醇给药能通过激活Sirt1防止HFD小鼠高糖高脂引发的肾脏损伤和细胞衰老[109]。

5.2 相关治疗策略

5.2.1 运动干预和热量限制

运动可以降低BMI、腰围和脂肪量[110]。定期运动可以降低ROS和血清糖基化终产物（advanced glycation end product，AGE）水平，减轻衰老引起的氧化应激以及p16、p21的表达，从而达到延缓衰老，延长寿命的目的[111]。AGE是指在非酶促条件下，蛋白质、氨基酸、脂类或核酸等大分子物质的游离氨基与还原糖的醛基经过缩合、重排、裂解、氧化修饰后产生的一组稳定的终末产物，其过量产生会引发的细胞功能改变和机体病变，坚持运动则能够减少这一情况的发生。在HFD小鼠模型中，运动减少了衰老细胞的比率以及SASP因子的分泌，并改善了机体功能[112]。运动可以增强端粒酶逆转录酶基因的表达和端粒酶活性，减轻端粒的磨损，从而延缓细胞衰老[113]。

鉴于HFD可以加速肾脏衰老，研究人员进一步探究了减少脂质或者热量的摄入对衰老的作用，发现DR，即是在不挨饿的情况下减少能量的摄入，可以延迟健康寿命，并且降低衰老相关疾病的发病率[114]。长期以来，DR被认为可以延长从苍蝇到灵长类动物等物种的寿命，对细胞衰老机制的广泛影响。与短期DR相比，长期DR对于延缓肾脏衰老具有更佳的效果[115]。DR对CKD具有保护作用，可恢复肾脏功能，降低CKD发病率，提高生存率[116]。短期DR能够通过增加自噬活性和降低氧化应激来对肾脏衰老起到保护作用；长期DR可以改善衰老肾脏的线粒体受损、氧化应激和纤维化[117]。老年DR组的肾脏中NF-κB的磷酸化水平显著下降以及SASP尤其是细胞因子、趋化因子和生长因子表达减少[24]，提示DR通过减少降低NF-κB的转录活性来抑制SASP因子分泌，从而延缓肾脏衰老。

5.2.2 针对SASP因素的新兴干预措施

SASP因子及其相关受体的分泌可引发肾脏衰老和肾间质纤维化[118]。SASP治疗主要包括以下3种途径：a. 通过调控转录因子表达或活性阻断SASP的前信号通路；b. 使用蛋白酶抑制SASP的生物活性；c. 抑制特定的SASP因子或其受体。例如，用shRNA降低NF-κB的表达已被证明可以阻止衰老细胞中IL-6、IL-8、CXCL1和ICAM-1的分泌[119]。p38抑制剂可以通过抑制IL-6表达来减轻肾纤维化[120]。胡桃素给药通过调节NF-κB信号传导改善HFD小鼠肾脏中的脂质沉积和炎症[121]。柑橘皮中的有效活性成分川皮苷给药可以通过抑制IL-6和TGF-β来减轻肾纤维化[122]。TGF-β在纤维化过程中起着重要作用，针对TGF-β途径的各种方法已经出现，如特异性抗体、可溶性受体、TGF-β结合蛋白、TGF-β受体的小分子抑制剂，以及相关的microRNAs[123]。然而，仅阻断TGF-β1信号在CKD中的抗纤维化效果并不理想[124]，提示可能多个SASP因子在肾间质纤维化和肾脏衰老过程中共同起作用。

综上所述，脂质过度累积会细胞脂毒性和ROS含量增加，引发氧化应激、线粒体功能障碍、内质网应激等，致使肾脏细胞衰老和肾间质纤维化发生。调节FA摄取、脂质合成与分解的平衡，改善脂代谢紊乱，有助于延缓肾脏衰老和减轻肾间质纤维化。鉴于肾间质纤维化和肾脏衰老带来的后果非常严重，扭转肾间质纤维化和延缓肾脏衰老药物的成功研发和应用于临床成为极其期待的事情。但目前对肾纤维化治疗靶点的研究较为缺乏，仍需要对治疗肾纤维化的靶点进行临床试验，以评估其在患者中的安全性和有效性。此外，许多炎症和纤维化因子也是SASP成分，其表达不足以识别细胞衰老。鉴于现有的衰老指标可能因疾病和器官而异[125]，因此需要更高灵敏度和特异性的衰老检测方法，脂代谢途径的关键酶和调控蛋白有望成为改善肾脏衰老和肾间质纤维化的潜在靶点。从脂代谢

的角度，深入挖掘肾脏衰老以及肾间质纤维化的分子调控机制，寻找更多更好的治疗靶点，筛选出更多的小分子药物，对于延缓肾脏衰老以及治疗肾间质纤维化具有重要的意义以及临床使用价值。

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Role of Lipid Metabolism Disorders in Renal Ageing and Renal Fibrosis*

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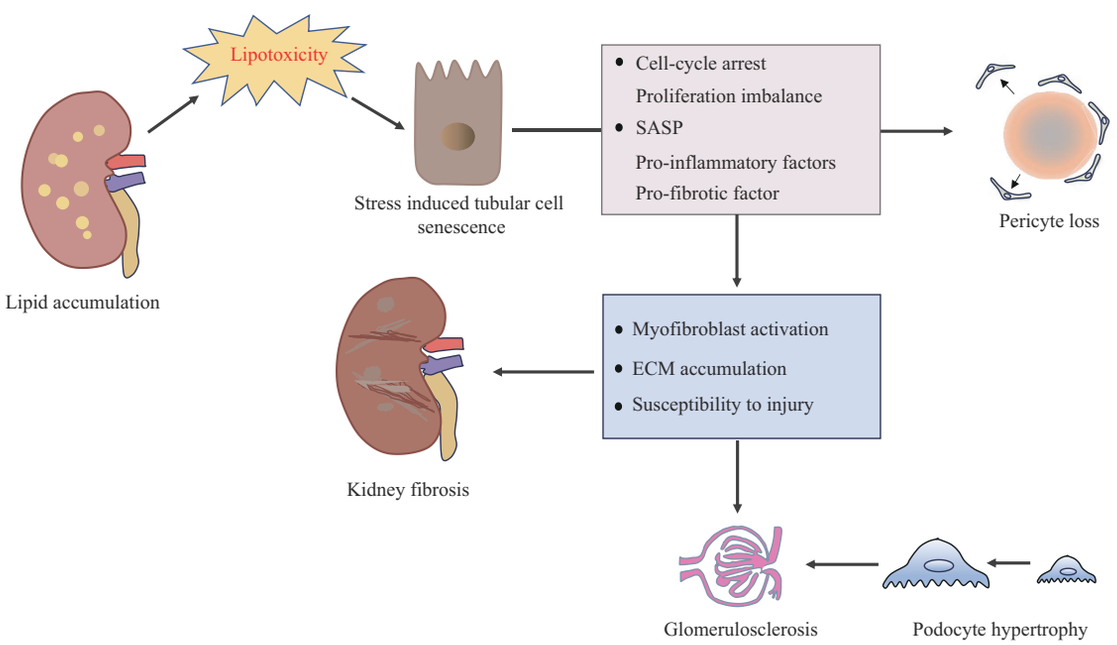
Graphical abstract



Abstract　Chronic kidney disease (CKD) has become a significant global public health problem. It is defined as chronic renal structural and functional dysfunction caused by various reasons. The prevalence of obesity and diabetes has increased dramatically in developing countries, which substantially affected the patterns of CKD observed in these regions. It's inevitable that the disease spectrum of CKD is converting to metabolic diseases. CKD is also considered an independent risk factor for renal aging and cardiovascular disease in the elderly, which usually progresses to end-stage renal disease (ESRD). Renal interstitial fibrosis is the pathological basis of ESRD and is a microscopic manifestation of renal aging. Conversely, renal aging is a risk factor for interstitial fibrosis. Although the healthy kidney has a relatively low lipid level, CKD-associated dyslipidemia has been extensively

* This work was supported by grants from The National Natural Science Foundation of China (81971329, 82200821) and Guangdong Basic and Applied Basic Research Foundation (2023A1515012838).

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Received：August 3，2023　Accepted：October 26，2023

studied. Nevertheless, less is known about the contribution of lipid disorders to the development of renal senescence and interstitial fibrosis. Recent studies have demonstrated that lipid metabolism disorders occur in the progress of renal aging and interstitial fibrosis. Renal lipids accumulate once lipid uptake and synthesis exceed the balance with lipolysis, which is mainly characterized by increased levels of triglyceride (TG) and oxidized low-density lipoprotein, and decreased levels of high-density lipoprotein. Excessive lipid accumulation in the kidney not only induces lipotoxicity and endoplasmic reticulum stress but also increases intracellular and mitochondrial reactive oxygen species, which induce stress injury and senescence in renal tubular epithelial cells. Pro-inflammatory and pro-fibrotic cytokines in a senescence-associated secretory phenotype secreted by senescent renal tubular epithelial cells further accelerate their senescence as well as the occurrence of inflammation and pericyte loss, promoting secretion of extracellular matrix (ECM) and subsequent fibrosis in the tubulointerstitial compartment. In addition, podocyte hypertrophy also leads to glomerulosclerosis. Currently, most of the studies on inhibiting or even reversing renal interstitial fibrosis are still in the experimental stage. What's more, effective drugs to slow down renal aging have not been reported. Many inflammatory and fibrotic factors are both components of the senescence-associated secretory phenotype (SASP), nevertheless, they are not sufficient to recognize cellular senescence. Given that indicators of senescence may vary from disease to disease and organ to organ, there is a need for more sensitive and specific senescence assays. Crucial enzymes and regulatory proteins of lipid metabolic pathways are expected to be potential targets for ameliorating renal aging and interstitial fibrosis. Lipid-lowering approach might represent another therapeutic in the management of kidney injury associated with metabolic dysfunction. Thus, clarifying the molecular regulatory mechanisms of lipid metabolism in kidney is extremely important for the delay of renal aging and the treatment of interstitial fibrosis. This review outlines the effects of lipid metabolism disorders on renal aging and renal fibrosis, analyses the role of lipid metabolism disorders in the development of renal diseases, and summarizes the potential targets and strategies for the prevention of renal aging and renal fibrosis based on lipid metabolism regulation, which will provide a reference for the discovery of new targets for the treatment of renal fibrosis.

Key words renal ageing, renal interstitial fibrosis, lipid metabolism, renal tubular epithelial cells
DOI：10.16476/j.pibb.2023.0305