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蛋白尿在慢性肾脏病进展中的新认识

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[摘 要] 慢性肾脏病(chronic kidney disease，CKD)是肾脏结构或功能的不可逆性改变。蛋白尿不仅是大多数CKD患者共同的临床表现，而且在CKD的进行性发展中起重要作用。蛋白尿可通过诱导足细 胞损伤和凋亡等导致肾小球硬化；通过直接毒性作用、激活补体和炎性小体、诱导氧化应激、促 进凋亡等途径导致肾小管萎缩和间质纤维化。了解蛋白尿及其在CKD进展中的作用对于研究CKD 治疗新靶点和延缓CKD的进展具有重要意义。

[关键词] 蛋白尿；慢性肾脏病；肾小管间质纤维化

New understanding of proteinuria in the progression of chronic kidney disease

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Abstract Chronic kidney disease (CKD) is irreversible change in the structure or function of the kidney. Proteinuria is not only a common clinical manifestation in most CKD patients, but also plays an important role in the progressive development of CKD. Proteinuria can cause glomerular sclerosis by inducing podocyte damage and apoptosis; it can cause renal tubular atrophy and interstitial fibrosis through direct toxicity, activation of complement and inflammasome, inducing oxidative stress, and promoting apoptosis. Understanding proteinuria and its role in the progression of CKD is of great significance to the study of new therapeutic targets for CKD and the progression of delaying CKD.

Keywords proteinuria; chronic kidney disease; renal tubule interstitial fibrosis

近年来，全球慢性肾脏病(chronic kidney disease，CKD)的患病率正在逐渐增加。据报道，在美国和澳大利亚等第一世界国家中，CKD的患病率约为11%[1]，中国成年人的患病率约为10.8%[2]。因此，CKD已成为全球关注的重要公共卫生问题。人体研究[3]表明蛋白尿是CKD进展的独立预测因子。终末期肾病(end-stage renal disease，ESRD)的发生风险和心血管病死率也会随蛋白尿的增加而增加[4-5]。因此，更好的了解蛋白尿及其在CKD进展中的作用，对延缓CKD进展及研究CKD

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治疗新靶点至关重要。

1 蛋白尿的产生机制

正常的肾小球滤过膜允许分子量小于2~4万D的蛋白质顺利通过，经肾小球滤过的原尿中90%以上的蛋白质被近曲小管重吸收。故尿蛋白的出现大部分是由肾小球和/或肾小管功能异常引起的。

1.1 肾小球滤过屏障

肾小球滤过屏障(glomerular filtration barrier，GFB)由内皮细胞、基底膜(glomerular basement membrane，GBM)以及足细胞3层结构组成[6](图1)。除上述3层结构外，还有内皮细胞表层(endothelial surface layer，ESL)和足细胞下间隙(subpodocyte space，SPS)，ESL和SPS均具有溶质分子筛选特征，对肾小球滤过功能具有重要影响[7]。GFB的作用包括分子屏障和电荷屏障，任一屏障损伤均可引起蛋白尿。

1.2 肾小管重吸收

经肾小球滤过的血浆蛋白质主要通过megalin和cubilin介导的内吞作用从近端小管重吸收，内吞摄取后，蛋白质被转移到溶酶体中进行降解[8]。对于肾脏中白蛋白的重吸收，Megalin和cubilin缺一不可，否则会导致蛋白尿[9]。megalin是属于LDL受体家族的600 kD多配体内吞受体，由LRP2基因编码，LRP2基因突变可引起以低分子量蛋白尿和神经发育异常为特征的极为罕见的DB/FOAR综合征[10]。Cubilin由CUBN基因编码，CUBN基因突变可导致Imerslund-Gräsbeck综合征(IGS)，其特征是肠道对维生素B12吸收不良，还会出现蛋白尿[11]。据文献[12]报道，在近端肾小管上皮细胞中还存在其他潜在的蛋白质受体，如新生儿Fc受体和CD36。

糖尿病肾病、IgA肾病、局灶节段性肾小球硬化、高血压肾损伤等CKD患者，因免疫和/或非免疫因素导致肾小球滤过屏障或肾小管损伤，从而导致蛋白尿的产生。

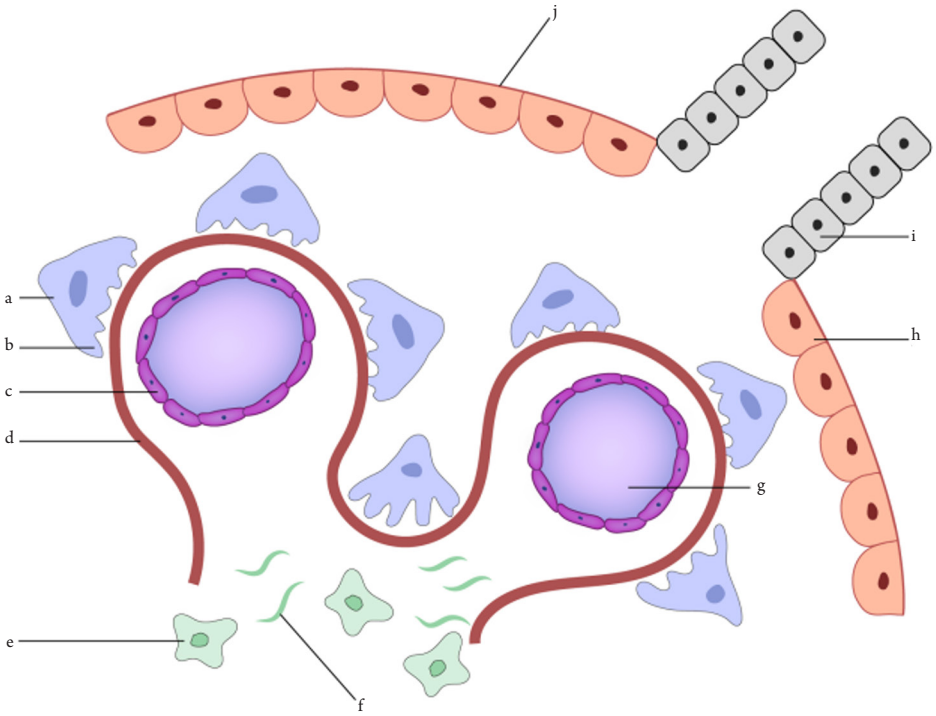

图1 肾小球示意图

Figure 1 Glomerulus map

(a)足细胞；(b)足突；(c)内皮细胞；(d)基底膜；(e)系膜细胞；(f)系膜基质；(g)肾小球毛细血管；(h)壁层上皮细胞；(i)近端小管；(j)包曼氏囊。

(a) Podocytes; (b) Podocyte foot process; (c) Endothelial cells; (d) Basement membrane; (e) Mesangial cells; (f) Mesangial matrix; (g) Glomerular capillaries; (h) Parietal epithelial cells; (i) Proximal tubule; (j) Bowman's capsule.

2 蛋白尿导致肾小球损伤

过量滤过的血浆蛋白质对肾小球损伤的具体机制研究较少。有研究[13]指出：足细胞损伤不仅与蛋白尿的程度有关，而且与肾小球硬化的发展和肾功能下降有密切关联。

Cheng等[14]采用原代培养的大鼠足细胞进行实验，证明白蛋白超载可以诱导足细胞产生活性氧(reactive oxygen species，ROS)，ROS的产生导致内质网应激，下调整合素-β1的前体和成熟形式，导致足突与肾小球基底膜的黏附性降低，并导致更多的血浆蛋白质渗入尿液，从而产生恶性循环。然而，介导白蛋白诱导内质网应激的信号通路尚未在足细胞中被揭示。Gonçalves等[15]将足细胞分别在无牛血清白蛋白(bovine serum albumin，BSA)的培养基中和BSA浓度递增的培养基中培养，采用流式细胞术记录足细胞凋亡，证明白蛋白以浓度和时间依赖的方式诱导足细胞损伤和凋亡，这与足细胞内白蛋白超载、内质网应激、PKC-δ、p38MAPK和caspase-12上调有关。

张丽萍等[16]研究了足细胞损伤对IgA肾病进展的影响，发现IgA肾病患者足细胞数量减少与肾小球硬化呈显著正相关。此外，足细胞数量减少也参与糖尿病肾病、高血压肾损伤、局灶节段性肾小球硬化等疾病中的肾小球硬化过程。足细胞数量减少致肾小球硬化的机制是：足细胞数量减少导致局部GBM区域裸露，使肾小球形成“高压、高灌注、高滤过”，导致裸露区域的GBM向外膨胀。当裸露的GBM与壁层上皮细胞和包曼氏囊接触时，形成同步性附着，从而逐渐导致肾小球硬化的发生[17]。

3 蛋白尿导致肾小管间质损伤

蛋白尿是肾小管间质炎症和纤维化的驱动力[18]。这是通过多种细胞内信号转导途径介导的，但其确切作用机制仍不清楚。

3.1 蛋白尿的直接毒性作用

蛋白尿致肾小管间质损伤的一种广泛接受的机制是通过滤过的血浆蛋白质的直接毒性作用引起的[19]。研究最多的是尿中白蛋白对肾小管间质损伤的作用。近年来发现，白蛋白结合的游离脂肪酸是肾小管间质炎症和疾病进展的重要介质[20]。白蛋白结合的游离脂肪酸在体外可通过产生线粒体ROS来激活人近端小管上皮细胞中的炎性小体，导致肾小管细胞损伤[21]。Khan等[22]利用小鼠模型，将脂肪酸转运蛋白2(fatty acid transport protein 2，FATP2)定位到近端小管的管腔膜上，发现在进行性蛋白尿肾病中，白蛋白结合的非酯化脂肪酸(non-esterified fatty acid，NEFA)经受损的肾小球滤过，通过FATP2介导近端小管NEFA的重吸收，从而导致肾小管上皮细胞(proximal tubular epithelial cells，PTEC)凋亡和肾小管萎缩。

此外，还有研究[23]发现白蛋白可以通过表观遗传机制直接降低培养的肾小管细胞中Klotho表达。Klotho是一种参与体内磷酸盐平衡的肾脏蛋白，在肾脏疾病中被下调[24]。Klotho也被认为是一种抗衰老的肾脏分泌激素，Klotho缺乏症小鼠会发生肾功能衰竭，这表明Klotho缺乏对肾脏有害，并可能导致CKD进展[23]。最近，Delitsikou等[25]研究发现，蛋白尿可以在mRNA水平特异性下调Klotho表达，这种调节作用部分与内质网应激途径的激活有关，抑制内质网应激可以逆转Klotho的下调。

3.2 蛋白尿与补体激活

蛋白尿可以激活肾小管腔内的补体[26]，并且在蛋白尿性肾病模型中，抑制补体或缺乏补体成分具有抗纤维化作用[27]，表明补体激活可导致肾小管间质损伤。

补体过敏毒素C3a是肾小球和肾小管间质损伤的重要介质，可诱导PTEC向上皮间充质转化[28]。而上皮间充质转化可直接促进肾小管间质纤维化中成纤维细胞的积累[29]，这可能是导致肾纤维化的重要机制。

在糖尿病肾病中，C5a可通过导致脂肪酸代谢失调和促进PTEC纤维化而发挥致病作用，用NOX-D21抑制C5a信号转导可部分改善脂质代谢异常，改善肾功能并减弱肾纤维化的进程[30]。高浓度的C5a还可通过C5aR/ROS/线粒体依赖途径诱导小鼠肾脏内皮细胞凋亡[31]。

最近，Alghadban等[32]利用典型的蛋白尿小鼠模型，发现人甘露糖结合凝集素相关丝氨酸蛋白酶-2(mannan-binding lectin-associated serine protease 2，MASP-2)缺陷和用MASP-2抑制剂处理野生型小鼠，可明显改善蛋白尿肾脏的组织学形态，减少肾小管间质凋亡。表明MASP-2在蛋白尿肾损伤的发展过程中起重要作用。

3.3 蛋白尿与氧化应激

大量证据表明氧化应激在慢性肾脏病的发病机制中占有重要地位[33]。蛋白尿能诱导近端肾小

管细胞产生ROS，而ROS是导致NF-κB活化并随后诱导依赖NF-κB的炎症信号的主要原因[34]。Souma等[35]研究表明：受体-白蛋白复合物可以激活PKC信号通路，从而导致NAD(P)H氧化酶介导的ROS的形成。ROS的增加对促纤维化信号的转导有积极影响[36]。

3.4 蛋白尿与炎性小体

炎性小体是细胞内的多蛋白复合物，可以触发宿主免疫防御反应[37]。NLRP3炎性小体是目前研究最多和表征最强的炎症体[38]。激活NLRP3炎性小体会导致casepase-1的激活，然后分泌包括IL-1β和IL-18在内的炎性细胞因子[39]，这两种细胞因子与各自受体结合后会导致其他促炎细胞因子的释放，从而在肾脏和全身内建立炎症环境[37]。典型的NLRP3/ASC/caspase-1/IL-1β/IL-18轴通过介导炎症反应促进多种肾脏疾病的病理生理过程，这可能是肾脏纤维化的重要启动机制[40]。

体内和体外实验都证明严重的蛋白尿可以激活肾小管NLRP3炎性小体[41]，并且肾小管NLRP3炎性小体的表达与患者的蛋白尿水平呈正相关，白蛋白诱导的NLRP3炎性小体的激活还会导致线粒体功能障碍，进而导致细胞表型改变和细胞凋亡，表明NLRP3炎性小体/线粒体轴介导了白蛋白诱导的肾小管损伤[42]。除此之外，NLRP3炎性小体还被证明参与了白蛋白诱导的肾小管紧密连接的损伤[43]。肾小管完整性受损可增加其对尿液成分的通透性，导致包括尿蛋白在内的尿液成分进入肾小管间质，从而进一步加重炎症和纤维化反应[44]。

3.5 蛋白尿与肾小管上皮细胞凋亡

文献[45-46]表明：近端肾小管细胞过度摄取白蛋白会导致细胞凋亡。在蛋白尿肾病进程中，蛋白尿可以激活多条PTEC凋亡途径。

Erkan等[47]研究了暴露于无内毒素白蛋白培养的人近端肾小管细胞的凋亡机制，发现白蛋白通过刺激独立于ROS产生的线粒体凋亡途径诱导人近端小管细胞凋亡，其特征是Bax易位至线粒体和细胞色素c从细胞器中释放。蛋白尿也可抑制NIX介导的肾小管上皮细胞有丝分裂，从而使细胞发生线粒体依赖的凋亡级联反应，导致肾小管损伤[48]。

越来越多的证据[41,49]表明：在蛋白尿的体外和体内模型中，内质网应激途径都显著促进了肾小管细胞的凋亡。但是对该途径中激活的信号分子的认识仍然有限。Lee等[50]证明白蛋白诱导的内质网应激是通过ROS-c-Src激酶-PPAR-γ-mTOR信号转导途径调节的。过度的内质网应激可能通过激活内质网跨膜蛋白PERK而引起细胞凋亡[51]。Ding等[52]研究表明BSA以时间和剂量依赖的方式诱导PTEC凋亡，BSA诱导的PTEC凋亡依赖于caspase-3激活；同时也证明内质网应激诱导的细胞凋亡主要由CHOP介导，Numb通过下调与内质网应激相关的CHOP/PERK信号通路对BSA诱导的PTEC凋亡起保护作用。另外，还有研究[53]表明蛋白尿可通过钙释放诱导的内质网应激来刺激脂钙蛋白2过度表达，进而导致肾小管凋亡和肾脏损伤。

3.6 蛋白尿与自噬

自噬是一种重要的细胞自降解机制，控制着细胞发育过程中的能量平衡。自噬也是去除错误折叠或聚集蛋白的一种机制，从而确保细胞存活[54]。之前已有研究[55]表明，PTEC暴露于过多的白蛋白会增加错误折叠蛋白在内质网中的积累，从而引起自噬。未能通过自噬消化的错误折叠蛋白已被证明会触发细胞程序性死亡[56]。多项研究[55,57]表明，在慢性肾脏病中，自噬对蛋白尿诱导的肾小管损伤具有保护作用。但是，有研究[58]提出过度激活自噬可能会导致细胞凋亡并加剧肾脏损伤。自噬的持续激活会导致肾小管细胞萎缩并促进肾脏纤维化[59]。

随着对蛋白尿的发病机制和蛋白尿对CKD患者病程进展影响的研究，认识到蛋白尿的产生与CKD病程发展相互促进。蛋白尿不仅是大多数CKD患者共同的临床表现，而且还可以通过诱导足细胞损伤等导致肾小球硬化；通过蛋白尿的直接毒性作用、激活补体和炎性小体、引起氧化应激和促进凋亡等途径导致肾小管间质炎症和纤维化，从而促进CKD疾病进展，部分CKD患者会进展至终末期肾病。因此，更全面地认识蛋白尿在CKD进展中的作用，对延缓CKD进展和研究CKD治疗新靶点具有重要意义。

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