Hans Journal of Biomedicine 生物医学, 2022, 12(3), 241-246
Published Online July 2022 in Hans. http://www.hanspub.org/journal/hjbm
https://doi.org/10.12677/hjbm.2022.123029

Hans汉斯

细胞焦亡参与糖尿病肾病发生和发展的研究进展

黄璐璐*，巴应贵#

青海大学附属医院肾病科，青海 西宁

收稿日期：2022年5月27日；录用日期：2022年6月30日；发布日期：2022年7月7日

摘 要

糖尿病肾病(diabetic nephropathy, DN)是糖尿病的主要并发症和死亡原因。随着人们对糖的摄入量的增多，糖尿病患者人数快速增长，DN的发病率也呈逐年上升的趋势，在一些国家或地区已经成为终末期肾病(end stage renal disease, ESRD)的首位原因，DN除了是发生ESRD的重要原因外，还会大幅增加糖尿病患者脑血管疾病发生的风险以及全因死亡风险，总的来说如果管理不佳，会严重影响患者的生活质量、家人的幸福指数以及给社会医疗体系带来巨大的负担。早期的DN治疗方法主要是降压、降糖等，晚期的DN治疗主要以是血液透析、腹膜透析、肾脏移植等肾脏替代治疗方法，但治疗效果并不理想。DN的发病机制复杂，目前尚未明确。因此深入了解DN发生发展的各个环节，发现新的治疗靶点显得尤为重要。既往认为DN是由代谢和血流动力学改变引起的，近年来的深入研究表明DN的病因是多因素的，炎症机制在DN的发展过程中也起着关键作用。细胞焦亡作为一个新发现的程序性细胞死亡方式近年来被广泛报道参与多种炎症性疾病的发生发展，同样被认为是DN发生发展的重要因素，近年来受到广泛关注。在这篇综述中，就细胞焦亡的特征、分子机制和与DN的关系，阐明其作为DN潜在治疗靶点的研究价值。

关键词

细胞焦亡，糖尿病肾病，炎症小体

Research Progress on the Role of Cell Pyroptosis in the Occurrence and Development of Diabetic Nephropathy

Lulu Huang*, Yinggui Ba#

Department of Nephrology, Affiliated Hospital of Qinghai University, Xining Qinghai

Received: May 27th, 2022; accepted: Jun. 30th, 2022; published: Jul. 7th, 2022

*第一作者。
#通讯作者。

文章引用: 黄璐璐, 巴应贵. 细胞焦亡参与糖尿病肾病发生和发展的研究进展[J]. 生物医学, 2022, 12(3): 241-246.
DOI: 10.12677/hjbm.2022.123029

Abstract

Diabetes nephropathy is the main complication and death cause of diabetes. With the increase of people's sugar intake, the number of diabetes patients has increased rapidly, and the incidence rate of diabetes nephropathy has also increased year by year. In some countries or regions, diabetes nephropathy has become the leading cause of end-stage renal disease. In addition to being an important cause of end-stage renal disease, it will also significantly increase the risk of cerebrovascular disease and all-cause death in diabetes patients. In general, poor management will seriously affect the quality of life of patients, the happiness index of their families and bring a huge burden to the social medical system. The early treatment of diabetes nephropathy is mainly to reduce blood pressure and glucose, while the late treatment of diabetes nephropathy is mainly renal replacement therapy such as hemodialysis, peritoneal dialysis and kidney transplantation, but the treatment effect is not ideal. The pathogenesis of diabetes nephropathy is complex, and it is not clear yet. Therefore, it is particularly important to deeply understand the occurrence and development of diabetes nephropathy and find new therapeutic targets. In the past, it was thought that diabetes nephropathy was caused by metabolic and hemodynamic changes. In recent years, in-depth studies have shown that the etiology of diabetes nephropathy is multifactorial, and the inflammatory mechanism also plays a key role in the development of diabetes nephropathy. As a newly discovered programmed cell death mode, pyroptosis has been widely reported to participate in the occurrence and development of a variety of inflammatory diseases in recent years. It is also considered to be an important factor in the occurrence and development of diabetes nephropathy, and has been widely concerned in recent years. In this review, the characteristics, molecular mechanism of cell death and its relationship with diabetes nephropathy were discussed to clarify its research value as a potential therapeutic target for diabetes nephropathy.

Keywords

Pyroptosis, Diabetic Nephropathy, Inflammatory Corpuscle

1. 引言

全球糖尿病肾病都呈增加的趋势，国际糖尿病联合会(International Diabetes Federation, IDF)曾指出：糖尿病是21世纪增长最快的全球突发卫生事件之一，其作为重大的健康问题已经达到了令人担忧的程度[1]。据IDF推测，13年后成年人的患病比例可能达到八分之一，糖尿病患者中有30%~40%会同时患有DN [2] [3]。DN发病机制复杂，尚未完全阐明。目前认为DN的发病机制除了血液动力学改变、糖代谢异常、氧化应激、遗传因素以外，也是一种炎症性疾病。大量研究证实，细胞因子的激活参与了DN的发生、发展，相关的细胞因子主要有TG转化生长因子β1 (TGFβ1)、结缔组织生长因子(CTGF)、血管紧张素Ⅱ、血管内皮生长因子(VEGF)、内皮素(ET)、前列腺素(PG)及一氧化氮(NO)等。它们相互影响和制约，促进肾纤维化和肾小管萎缩的发展[4]。细胞焦亡作为近年来发现的一种炎症性细胞死亡模式，也被发现存在于DN的发生及发展过程。大量研究证明，高糖、氧化应激、糖基化终产物等均可激活细胞炎症因子从而诱发细胞焦亡，促进疾病的进展[5]。

2. 细胞焦亡概述

细胞焦亡(pyroptosis)是近年来发现的一种由gasdermin介导的依赖炎性半胱天冬酶(主要为caspase-1、4、5、11)的程序性细胞死亡方式，细胞发生焦亡的同时会伴随着炎性因子的释放[6] [7]。在光镜下主要表现为细胞的膨胀，在电镜下可以观察到细胞膜上形成孔洞导致细胞破裂、胞质流出，最终发生焦亡。细胞焦亡分为经典通路和非经典通路，两种通路都是通过切割GSDMD后，在细胞膜上形成孔洞，导致细胞破裂从而释放大量分泌炎性因子，包括IL-1β和IL-18 [8]。

目前，越来越多的研究证实细胞焦亡在慢性炎性疾病的发生发展中也有不可忽视的作用。Caspase家族、GSDMD、炎性小体都是焦亡反应中的重要参与部分[9] [10]。细胞焦亡的经典通路中，标志分子Nod样受体蛋白3 (Nod-like receptor protein 3, NLRP3)、caspase-1以及gasdermin D的N端结构域(GSDMD-N)等的高表达是细胞焦亡的重要特征[11]。细胞焦亡参与许多疾病的发生发展过程，Shahzad首次在糖尿病小鼠的模型中通过两种caspase抑制剂的作用对比，发现抑制caspase-1延缓了DN的进展，该研究结果表明在DN中细胞焦亡起了关键作用。NLRP3作为一种模式识别受体，不但存在于天然免疫细胞中，也存在于肾脏固有细胞，如足细胞、肾小球系膜细胞、肾小球内皮细胞和肾小管上皮细胞中。虽然很多疾病都可能有细胞焦亡的存在，但其具体机制并不一定完全相同。一是因为焦亡本身就具有多条通路参与调控；二是因为很多疾病的产生也是多因素的。

2.1. 足细胞的焦亡与糖尿病肾病

随着DN的发展，足细胞和内皮细胞、基底膜共同作为肾小球滤过屏障的受损越来越严重，其中足细胞是避免机体内蛋白丢失的最后一道屏障。足细胞是终末分化细胞，具有较差的分裂增殖能力，足细胞的存活有赖于对应激的处理能力[12]。Dimas GG等研究发现DN蛋白尿的产生与足细胞数量减少及结构的破坏有明显相关性，提示肾小球足细胞的损伤是DN的关键因素[13]。已有研究发现在DN早期，足细胞与肾小管上皮细胞的线粒体功能严重障碍时，细胞内的ATP含量急剧下降，足细胞标志物nephrin和podocin (位于足细胞裂孔隔膜上的蛋白分子)的表达降低，足细胞足突融合、消失，细胞发生焦亡。此外，DN患者随着NLRP3的活化，胰岛素抵抗(insulin resistance, IR)加强，这也是肾脏固有细胞损伤的病理机制之一。足细胞作为胰岛素高度敏感的效应细胞，其功能和结构的改变与肾组织胰岛素信号通路活性，尤其是与IRS1/PI3K/Akt信号通路活性低下密切相关[14] [15]。另外也有实验报道了足细胞焦亡中也有caspase-11/caspase-4的介导，高糖状态下caspase-11/caspase-4、GSDMD-N、NF-κB、IL-1β和IL-18的表达显著增加。因此，足细胞的焦亡有多种通路介导，靶向干预足细胞焦亡、IR、IRS1/PI3K/Akt等信号通路活性可能改善炎症性足细胞损伤，延缓DN的进展。

2.2. 系膜细胞焦亡与糖尿病肾病

肾小球系膜细胞(GMCs)是肾脏固有细胞，在高糖状态下可诱导的炎症反应并引起肾小球系膜细胞肥大、细胞外基质生成过度、基底膜增厚等表型改变和系膜细胞活性丧失的功能改变，最终导致肾功能减退，可见GMCs在DN的进程中起着重要的作用。TLR4/NF-κB/NLRP3信号轴在高糖刺激下诱导大鼠系膜细胞增殖增加，应用NLRP3炎症体拮抗剂MCC950可以抑制NLRP3炎症体活化，降低系膜细胞增殖，阻止纤维化发展。冯红等通过观察高糖状态下NLRP3在肾系膜细胞的表达，发现高脂高糖可通过ROS-TXNIP-NLRP3-IL-1β炎症小体信号通路介导DN炎症反应的发生。王盈盈等课题组在研究前发现，高糖状态下GMCs和足细胞之间可能存在相互作用，这种相互作用对DN的发生发展可能具有主要意义，但其具体机制尚不明确。遂通过分离GMCs来源的外泌体作用于足细胞的实验得出外泌体可以介导GMCs与足细胞之间的相互作用及小檗碱可以改善高糖诱导GMCs来源的外泌体对足细胞的损伤，同时

也发现小檗碱可能通过外泌体调节 TGFβ1-P13k/AKT 通路发挥对足细胞的保护作用[16]。也有实验研究用 MCC950 抑制 NLRP3 炎症体激活，从而减轻了高糖状态下的肾小球系膜增生以及肾脏的纤维化。

2.3. 肾小管上皮细胞焦亡与糖尿病肾病

国内已有文献报道了 NLRP3/caspase-1/IL-1β 信号通路介导的高糖缺氧富复氧诱导人肾小管上皮细胞的损伤[6] [17]。在糖尿病肾病模型小鼠及人肾近曲小管上皮细胞(HK-2)中，肾小管上皮细胞的活性氧(ROS)过量产生，超过线粒体抗氧化酶清除的限度，导致 ROS 过量蓄积伴 NLRP3、IL-1β 和 TGF-β 的高表达，抑制 ROS 则会逆转上述变化，线粒体 ROS 还可能介导激活硫氧还蛋白相互作用蛋白(TXNIP)/NLRP3 通路诱导肾小管上皮细胞焦亡，引起 DN 小管间质损伤[18] [19]。因此，可证明 ROS/TXNIP/NLRP3 信号通路介导肾小管上皮细胞焦亡。有研究表明，DN 中肾小管上皮的焦亡是通过 TLR4/NF-κB 信号通路诱导 GSDMD 所介导。TLRs 的激活是炎症体形成和细胞焦亡的触发因素，GSDMD 作为细胞焦亡的执行者，在 DN 患者中 TLR4 和 GSDMD 的上调是肾小管损伤的主要原因[20]。研究确定了一种新的 circRNA 即 circACTR2，它可以调节高葡萄糖诱导的近端肾小管细胞的焦亡[21]，可见明确 DN 的发病机理可为 DN 提供新的治疗策略提供了新的见解。

2.4. 肾小球内皮细胞焦亡与糖尿病肾病

肾小球内皮细胞是参与组成机械屏障，同时它与血液直接接触也是参与肾小球选择性滤过的重要成员，更容易受到高糖及炎症刺激的影响。Shahzad 等在糖尿病患者和 db/db 小鼠的肾小球内皮细胞中观察到 NLRP3、caspase-1，而 NLRP3 及 caspase-1 的表达抑制可有效减轻内皮细胞的损伤[22]。也有研究发现钠-葡萄糖协同转运蛋白 2 (SGLT2)抑制剂和二肽基肽酶-4 (DPP4)抑制剂的联合使用可下调 NLRP3/ASC 炎症体的表达，丁酸钠可通过抑制核转录因子-κB 使得 caspase-1、GSDMD 的表达下调，从而抑制内皮细胞焦亡[23]。这都提示焦亡参与了 DN 中肾小球内皮细胞的损伤。因此，研制靶向 caspase-1 的药物对治疗 DN 有重要意义。

3. 展望

有研究发现肌肽通过靶向 caspase-1 介导的细胞焦亡减轻糖尿病肾病小鼠的足细胞损伤[24]。除此之外，红景天苷作为红景天属植物中广泛存在的酚苷类化合物也被发现通过活化 Akt/GSK-3β 信号通路，控制高糖、炎症和氧化应激反应，从而起到糖尿病肾病的治疗作用[25]。Wang 等研究发现红景天苷通过抑制 NLRP3 炎症小体的激活，从而抑制高糖诱导的肾小球系膜细胞增殖、氧化应激和 ECM 积累[26]。

总之，细胞焦亡作为一种新的程序性死亡是近年来的研究重点，细胞焦亡参与 DN 的发生和发展。明确细胞焦亡介导的炎症因子在 DN 各个细胞损伤方面的机制，寻找新的治疗靶点将对 DN 的治疗提供了新的思路和方法。以细胞焦亡作为干预方向利用药物靶向治疗将降低 DN 对肾脏细胞的损伤，是未来研究中的重点。

基金项目

国家自然科学基金委领域：H0510.继发性肾脏疾病，科技部领域：320.2435.肾脏病学，项目类别：应用基础研究，项目名称：研究 NLRP3/IL-1β/TGF-β1 信号轴在高原低氧环境下糖尿病肾病足细胞焦亡中的作用及红景天苷的拮抗效应。

参考文献

[1] Li, Y., Teng, D., Shi, X., Qin, G., Qin, Y., Quan, H., Shi, B., Sun, H., Ba, J., Chen, B., Du, J., He, L., Lai, X., Li, Y.,

Chi, H., Liao, E., Liu, C., Liu, L., Tang, X., Tong, N., Wang, G., Zhang, J.A., Wang, Y., Xue, Y., Yan, L., Yang, J., Yang, L., Yao, Y., Ye, Z., Zhang, Q., Zhang, L., Zhu, J., Zhu, M., Ning, G., Mu, Y., Zhao, J., Teng, W. and Shan, Z. (2020) Prevalence of Diabetes Recorded in Mainland China Using 2018 Diagnostic Criteria from the American Diabetes Association: National Cross Sectional Study. *British Medical Journal*, **369**, m997. https://doi.org/10.1136/bmj.m997

[2] Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B.B., Stein, C., Basit, A., Chan, J.C.N., Mbanya, J.C., Pavkov, M.E., Ramachandaran, A., Wild, S.H., James, S., Herman, W.H., Zhang, P., Bommer, C., Kuo, S., Boyko, E.J. and Magliano, D.J. (2022) IDF Diabetes Atlas: Global, Regional and Country-Level Diabetes Prevalence Estimates for 2021 and Projections for 2045. *Diabetes Research and Clinical Practice*, **183**, Article ID: 109119. https://doi.org/10.1016/j.diabres.2021.109119

[3] Zhang, X.X., Kong, J. and Yun, K. (2020) Prevalence of Diabetic Nephropathy among Patients with Type 2 Diabetes Mellitus in China: A Meta-Analysis of Observational Studies. *Journal of Diabetes Research*, **2020**, Article ID: 2315607. https://doi.org/10.1155/2020/2315607

[4] Qiu, Y.Y. and Tang, L.Q. (2016) Roles of the NLRP3 Inflammasome in the Pathogenesis of Diabetic Nephropathy. *Pharmacological Research*, **114**, 251-264. https://doi.org/10.1016/j.phrs.2016.11.004

[5] Ni, W.J., Tang, L.Q. and Wei, W. (2015) Research Progress in Signalling Pathway in Diabetic Nephropathy. *Diabetes/Metabolism Research and Reviews*, **31**, 221-233. https://doi.org/10.1002/dmrr.2568

[6] Wen, S., Deng, F., Li, L., Xu, L., Li, X. and Fan, Q. (2022) VX-765 Ameliorates Renal Injury and Fibrosis in Diabetes by Regulating Caspase-1-Mediated Pyroptosis and Inflammation. *Journal of Diabetes Investigation*, **13**, 22-33. https://doi.org/10.1111/jdi.13660

[7] Burdette, B.E., Esparza, A.N., Zhu, H. and Wang, S. (2021) Gasdermin D in Pyroptosis. *Acta Pharmaceutica Sinica B*, **11**, 2768-2782. https://doi.org/10.1016/j.apsb.2021.02.006

[8] Aranda-Rivera, A.K., Srivastava, A., Cruz-Gregorio, A., Pedraza-Chaverri, J., Mulay, S.R. and Scholze, A. (2022) Involvement of Inflammasome Components in Kidney Disease. *Antioxidants*, **11**, Article No. 246. https://doi.org/10.3390/antiox11020246

[9] Broz, P., Pelegrín, P. and Shao, F. (2020) The Gasdermins, a Protein Family Executing Cell Death and Inflammation. *Nature Reviews Immunology*, **20**, 143-157. https://doi.org/10.1038/s41577-019-0228-2

[10] Picca, A., Calvani, R., Coelho-Junior, H.J. and Marzetti, E. (2021) Cell Death and Inflammation: The Role of Mitochondria in Health and Disease. *Cells*, **10**, Article No. 537. https://doi.org/10.3390/cells10030537

[11] Liu, P., Zhang, Z. and Li, Y. (2021) Relevance of the Pyroptosis-Related Inflammasome Pathway in the Pathogenesis of Diabetic Kidney Disease. *Frontiers in Immunology*, **12**, Article ID: 603416. https://doi.org/10.3389/fimmu.2021.603416

[12] Jiang, A., Song, A. and Zhang, C. (2022) Modes of Podocyte Death in Diabetic Kidney Disease: An Update. *Journal of Nephrology*. https://doi.org/10.1007/s40620-022-01269-1

[13] Dimas, G.G., Didangelos, T.P. and Grekas, D.M. (2017) Matrix Gelatinases in Atherosclerosis and Diabetic Nephropathy: Progress and Challenges. *Current Vascular Pharmacology*, **15**, 557-565. https://doi.org/10.2174/1570161115666170202162345

[14] Wang, M.Z., Yue, L.J., Wan, Y.G., Huang, H., Wu, W., Tu, Y., Liu, B.H., Fang, Q.J., Yuan, C.C., Wang, J., Li, H. and Wan, Z.Y. (2021) [Effects and Mechanisms of Supplemented Gegen Qinlian Decoction Formula against Podocyte Pyroptosis and Insulin Resistance in Model Rats with Diabetic Kidney Disease]. *China Journal of Chinese Materia Medica*, **46**, 4471-4479.

[15] Liu, B.H., Tu, Y., Ni, G.X., Yan, J., Yue, L., Li, Z.L., Wu, J.J., Cao, Y.T., Wan, Z.Y., Sun, W. and Wan, Y.G. (2021) Total Flavones of *Abelmoschus manihot* Ameliorates Podocyte Pyroptosis and Injury in High Glucose Conditions by Targeting METTL3-Dependent m6A Modification-Mediated NLRP3-Inflammasome Activation and PTEN/PI3K/Akt Signaling. *Frontiers in Pharmacology*, **12**, Article ID: 667644. https://doi.org/10.3389/fphar.2021.667644

[16] 王盈盈, 刘青, 唐丽琴, 魏伟. 小檗碱对高糖诱导足细胞功能及相关蛋白表达的影响[J]. 中国药理学通报, 2018, 34(8): 1158-1163.

[17] Jia, Y., Xu, H., Yu, Q., Tan, L. and Xiong, Z. (2021) Identification and Verification of Vascular Cell Adhesion Protein 1 as an Immune-Related Hub Gene Associated with the Tubulointerstitial Injury in Diabetic Kidney Disease. *Bioengineered*, **12**, 6655-6673. https://doi.org/10.1080/21655979.2021.1976540

[18] Ao, L. and Xie, Y. (2021) Research Advance in the Mechanism for Oxidative Stress-Induced Podocyte Injury in Diabetic Kidney Disease. *Journal of Central South University. Medical Sciences*, **46**, 1403-1408.

[19] Li, N., Zhao, T., Cao, Y., Zhang, H., Peng, L., Wang, Y., Zhou, X., Wang, Q., Li, J., Yan, M., Dong, X., Zhao, H. and Li, P. (2021) Tangshen Formula Attenuates Diabetic Kidney Injury by Imparting Anti-Pyroptotic Effects via the TXNIP-NLRP3-GSDMD Axis. *Frontiers in Pharmacology*, **11**, Article ID: 623489.

https://doi.org/10.3389/fphar.2020.623489

[20] Wada, J. and Makino, H. (2016) Innate Immunity in Diabetes and Diabetic Nephropathy. *Nature Reviews Nephrology*, **12**, 13-26. https://doi.org/10.1038/nrneph.2015.175

[21] Wen, S., Li, S., Li, L. and Fan, Q. (2020) CircACTR2: A Novel Mechanism Regulating High Glucose-Induced Fibrosis in Renal Tubular Cells via Pyroptosis. *Biological and Pharmaceutical Bulletin*, **43**, 558-564. https://doi.org/10.1248/bpb.b19-00901

[22] Shahzad, K., Bock, F., Al-Dabet, M.M., Gadi, I., Kohli, S., Nazir, S., Ghosh, S., Ranjan, S., Wang, H., Madhusudhan, T., Nawroth, P.P. and Isermann, B. (2016) Caspase-1, but Not Caspase-3, Promotes Diabetic Nephropathy. *Journal of the American Society of Nephrology*, **27**, 2270-2275. https://doi.org/10.1681/ASN.2015060676

[23] Birnbaum, Y., Bajaj, M., Yang, H.C. and Ye, Y. (2018) Combined SGLT2 and DPP4 Inhibition Reduces the Activation of the Nlrp3/ASC Inflammasome and Attenuates the Development of Diabetic Nephropathy in Mice with Type 2 Diabetes. *Cardiovascular Drugs and Therapy*, **32**, 135-145. https://doi.org/10.1007/s10557-018-6778-x

[24] Zhu, W., Li, Y.Y., Zeng, H.X., Liu, X.Q., Sun, Y.T., Jiang, L., Xia, L.L. and Wu, Y.G. (2021) Carnosine Alleviates Podocyte Injury in Diabetic Nephropathy by Targeting Caspase-1-Mediated Pyroptosis. *International Immunopharmacology*, **101**, Article ID: 108236. https://doi.org/10.1016/j.intimp.2021.108236

[25] 朴敏虎. 红景天苷对糖尿病肾病大鼠的治疗作用及其机制探讨[J]. 山东医药, 2017, 57(10): 34-36.

[26] Wang, S.Y., Zhao, X.X., Yang, S.X., Chen, B.P. and Shi, J. (2017) Salidroside Alleviates High Glucose-Induced Oxidative Stress and Extracellular Matrix Accumulation in Rat Glomerular Mesangial Cells by the TXNIP-NLRP3 Inflammasome Pathway. *Chemico-Biological Interactions*, **278**, 48-53. https://doi.org/10.1016/j.cbi.2017.10.012