中国临床研究 Chin J Clin Res, September 2025, Vol.38, No.9

Cite as: Wu C, Xu J, Peng HY, Zhang XL, An K. Role of neutrophil extracellular traps in the development and progression of chronic kidney disease [J]. Chin J Clin Res, 2025, 38(9): 1310-1313,1318.

DOI: 10.13429/j.cnki.cjcr.2025.09.003

Role of neutrophil extracellular traps in the development and progression of chronic kidney disease

WU Cai*, XU Jun, PENG Hongying, ZHANG Xiaoli, AN Ke

*School of Clinical Medicine, Guizhou Medical University, Guiyang, Guizhou 550000, China

Corresponding author: XU Jun, E-mail: carryxu@163.com

Abstract: Neutrophil extracellular traps (NETs) is a network structure composed of DNA, histone and granular protein released by neutrophils stimulated by their own or external pathogens. The correlation between NETs and the development and progression of chronic kidney disease (CKD) has been concerned and studied, and an excess of NETs may indicate the progression of CKD. Therefore, this article reviews the formation and clearance mechanism of NETs, as well as their mechanism and clinical application in the pathogenesis of CKD, in order to provide new ideas for the application of NETs in early diagnosis, disease progression prediction and treatment of CKD.

Keywords: Neutrophil extracellular traps; Chronic kidney disease; Diabetic kidney disease; Lupus nephritis; Glomerulonephritis; Autoimmune kidney disease; Membranous nephropathy

Fund program: Science and Technology Fund Project of Guizhou Provincial Health Commission (gzwkj2021-129)

Chronic kidney disease (CKD) is a chronic disease caused by various primary or secondary etiologies, characterized by impaired renal function with gradual progression of the condition, and symptoms lasting for more than 3 months [1]. In 2017, there were 697.5 million cases of CKD worldwide, with a prevalence rate of 9.1%, and it is increasing year by year [2]. CKD is difficult to diagnose in the early stage, with an awareness rate of only about 10%. Moreover, it is difficult to cure during its development, with a poor prognosis and a large number of comorbidities. CKD is mainly classified into subtypes such as diabetic kidney disease (DKD), lupus nephritis (LN), and membranous nephropathy (MN), characterized by a decrease in glomerular filtration rate, and may also present with symptoms such as proteinuria, hypertension, edema, anemia, and hypoglycemia. Clinically, serum creatinine is currently used as an indicator to evaluate renal function [2-5].

When neutrophils are stimulated, they release a reticular structure containing components such as DNA, histones, and neutrophil granule proteins to capture pathogens and other substances. This reticular structure is called neutrophil extracellular traps (NETs) [6]. Excessive formation or abnormal clearance of NETs can cause dysfunction of the body, leading to kidney damage, exacerbated inflammation, upregulation of coagulation function, and the occurrence of diseases such as autoimmune diseases, malignant tumors, thrombosis, and inflammation. In some diseases, excessive NETs may indicate the occurrence and development of the disease. This article discusses the formation and elimination mechanisms of NETs, as well as the pathogenic mechanism of CKD, reviews the role of NETs in the occurrence and development of CKD, and their potential clinical application value in the early diagnosis and prediction of disease progression of CKD, aiming to provide new strategies for the treatment of CKD.

1 Formation and mechanism of action of NETs

NETs begin to form when neutrophils are stimulated by various physiological stimuli. Antibodies, immune complexes, chemokines [interleukin (IL)-8, tumor necrosis factor (TNF)-α, interferon (IFN)-γ], as well as calcium and potassium ions, can induce the release of NETs by neutrophils [7]. The scaffold of NETs is formed by decondensed and diffused chromatin DNA, and neutrophils die due to the release of chromatin DNA, a process termed NETosis [8-9]. Adhered to the NET scaffold are citrullinated histones and primary/secondary granule proteins, such as myeloperoxidase (MPO)-DNA, neutrophil elastase (NE), cathepsin G, and lactoferrin [10-11].

Studies have shown that the generation of reactive oxygen species (ROS) induced by reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is the initiating step in NET scaffold formation. Thus, inhibiting NADPH oxidase or neutralizing ROS can suppress NET formation. Activation of NADPH oxidase converts oxygen molecules into superoxide anion radicals (a type of ROS), exacerbating ROS production. These ROS first convert to hydrogen peroxide, which is then catalyzed by MPO to form halogenated acids [12]. MPO, together with the aforementioned granule proteins NE, cathepsin G, and several other proteins, constitutes azurophilic granules. Among these, NE and cathepsin G belong to serine proteases. Hydrogen peroxide can induce the dissociation

of azurophilic granules, releasing serine proteases upon dissociation [13]. After translocating into the nucleus, serine proteases cleave histones, promoting chromatin decondensation in the nucleus and further facilitating NET formation [13]. MPO also exerts a synergistic effect on the promotion of chromatin decondensation by serine proteases [14]. Therefore, reducing hydrogen peroxide production, inhibiting MPO, and suppressing serine proteases (e.g., NE, cathepsin G) can all inhibit NET formation. During NET formation, large amounts of histones are released into tissues, which are not only toxic to pathogens but also cause significant tissue damage [15]. The abundant double-stranded DNA in NETs can be degraded by DNases, then endocytosed by macrophages, and further lysed under lysosomal mediation [16]. Abnormalities in NET clearance also lead to excessive NET accumulation, further exacerbating inflammatory states or organismal damage. The mechanisms of NET formation and clearance are illustrated in **Figure 1**, which was drawn by the authors using Figdraw.

Excessive NETs in the body, particularly components like histones with cytotoxicity, cause tissue damage. Meanwhile, the large quantities of proteins present activate the body's immune response, leading to immune dysregulation and further contributing to the pathogenesis of autoimmune diseases. Additionally, studies have shown that DNA within NETs can enhance the procoagulant activity of proteases, while histones can inhibit thrombomodulin and plasma anticoagulant activity, thereby inducing platelet aggregation and further promoting microthrombus formation, fibrin deposition, and platelet deposition in *vivo* [16-17]. By inducing inflammatory responses, NETs release large amounts of IL-4, IL-6, and TNF-α; these inflammatory factors exhibit fibrinolytic resistance [18].

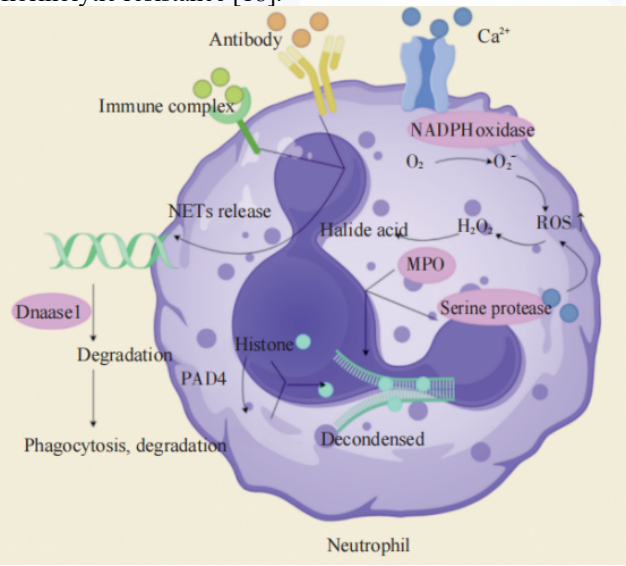

Fig.1 Formation and clearance mechanism of NETs

2 Mechanism of action of NETs in the development and progression of chronic kidney disease

The main manifestations of CKD include decreased glomerular filtration rate, as well as proteinuria, hypertension, edema, anemia, and hypoglycemia. Clinically, serum creatinine is currently used as an indicator to evaluate renal function [3-5]. Excessive formation or abnormal clearance of NETs can cause systemic dysfunction, leading to kidney damage, exacerbated inflammation, upregulated coagulation function, and the development of CKD. The level of NETs is expected to serve as an auxiliary indicator for evaluating the progression stage of CKD.

2.1 Mechanism of action of NETs in the development and progression of DKD

DKD is the most common microvascular complication of diabetes [19]. Its pathological features include glomerular mesangial expansion, glomerulosclerosis, and Kimmelstiel-Wilson nodules [20], with clinical manifestations of massive proteinuria. A key characteristic of DKD pathogenesis is elevated glucose levels. Studies have shown that high glucose levels can upregulate protein kinase C (PKC) activity, further inducing increased NADPH oxidase levels, thereby promoting excessive NET formation [21]. This process induces oxidative stress, activates coagulation pathways, and leads to fibrinolytic resistance [22-23]. Although there is no direct evidence that DKD exerts fibrinolytic resistance through NETs, this effect is highly consistent with the role of NETs. Additionally, studies have indicated that in DKD, inflammatory signaling pathways and insulin signaling pathways are activated, leading to the production of numerous inflammatory factors that promote NET release [24]. Research has demonstrated that under high glucose conditions, glycolysis promotes macrophage polarization into the pro-inflammatory M1 phenotype, exacerbating inflammatory responses and releasing extracellular DNA, which further aggregates and accelerates disease progression [25]. Follow-up studies in diabetic patients have found that the concentration of DNA (a major component of NETs) is positively correlated with the risk of developing DKD, suggesting that NET levels may predict the onset of DKD [26-27].

2.2 Mechanism of action of NETs in the development and progression of CGN

The pathogenesis of CGN is primarily associated with immune-inflammatory injury. Thus, its role in NET formation is mainly mediated by substances such as inflammatory factors. For example, inflammatory factors like IL-2 and IL-6 can stimulate neutrophils to release NETs into the inflammatory microenvironment [28-29]. Therefore, in CGN, levels of NETs can partially indicate the extent of kidney damage.

2.3 Mechanism of action of NETs in the development and progression of systemic autoimmune kidney disease

Systemic autoimmune kidney disease is often characterized by immune dysregulation. The deposition of immune complexes composed of DNA and anti-double-stranded DNA IgG antibodies in the kidneys is also an important cause of nephritis. During NET formation, DNA is oxidized by ROS, and oxidized DNA is more resistant to nuclease degradation than unoxidized DNA. Accumulation of oxidized DNA activates the cGAS-STING signaling pathway, increases type Ⅰ interferon (IFN-Ⅰ) synthesis, and leads to immune dysregulation [30-31]. Additionally, patients with systemic autoimmune diseases have a high risk of coronary atherosclerotic disease and thromboembolic complications. Studies suggest that this may be caused by neutrophils and NETs inducing microthrombus formation, fibrin and platelet deposition, and inhibiting fibrinolysis *in vivo* [30]. Common systemic autoimmune kidney diseases include lupus nephritis (LN) and anti-neutrophil cytoplasmic antibodies associated vasculitis (AAV).

2.3.1 Mechanism of action of NETs in the development and progression of LN

The pathogenesis of LN is mediated by NETs through reactive oxygen species (ROS), DNase 1, NADPH oxidase, and other factors. Studies have shown that a typical feature of LN is the presence of a distinct population of low-density granulocytes (LDGs) in patients, which markedly differs from that in healthy individuals [32]. In LDGs, mitochondrial ROS production induces excessive formation of NETs. Moreover, NETs from neutrophils of LN patients contain more pathogenic autoantigens than those from healthy individuals, which also leads to severe tissue damage and activation of plasmacytoid dendritic cells, thereby inducing the release of IFN [33-34]. Additionally, in some LN patients, the inhibition of DNase 1 activity impairs the clearance of NETs, resulting in NET accumulation [28]. Furthermore, in histopathological sections of LN patients, NET formation is clearly observed in the tubulointerstitial compartment adjacent to the glomerular capsule, indicating that NETs may be involved in capsular rupture and crescent formation in LN patients [35].

2.3.2 Mechanism of action of NETs in the development and progression of AAV

AAV is a type of ANCA-associated vasculitis that affects small and medium-sized blood vessels and often involves the kidneys, thus classified as a form of CKD [9]. In AAV patients, MPO, as a serum marker of AAV, can activate neutrophils, leading to ROS production and NET formation, ultimately causing vascular damage and the development of extravascular inflammation [36-37]. AAV is often associated with thrombosis, and thrombus tissues are rich in NETs and their related molecules [38]. NETs play an important role in this process: histones further enhance thrombosis in a platelet-dependent manner, while serine proteases such as NE promote thrombosis by enhancing coagulation [39]. Immunostaining experiments have shown the presence of NETs and NET-related molecules in inflammatory areas, around fibrinoid necrosis areas of the kidney in necrotizing glomerulonephritis, and in the walls of lobular arteries in renal biopsy specimens of AAV patients [40-41]. This strongly indicates that NETs are involved in the pathogenesis of AAV.

2.4 Mechanism of action of NETs in the development and progression of MN

MN is an immune complex-related glomerular disease, clinically manifested as varying degrees of proteinuria, hypoproteinemia, severe edema, and hyperlipidemia. Its pathological features include subepithelial immune complex deposition along the glomerular capillary loops, diffuse thickening of the glomerular basement membrane (GBM), granular deposition of immunoglobulin G (IgG), complement membrane attack complex, and antigen-antibody immune complexes along the glomerular capillary loops, with electron-dense deposits observed subepithelially [42]. Meanwhile, studies have shown that idiopathic MN may also lead to thrombosis due to enhanced coagulation function, weakened anticoagulant effect, and increased microparticle expression [43]. Research has confirmed that highly expressed NETs in the peripheral blood of patients with idiopathic MN can reflect the degree of renal endothelial injury. The high expression of NETs causes endothelial damage, thus presenting massive proteinuria and hypercoagulable manifestations, indicating that NET-induced damage to endothelial cells and renal tubular epithelial cells may exacerbate the progression of idiopathic MN [44]. Additionally, studies have shown that the more significant the elevation of NETs, the higher the probability of thrombosis, which to some extent indicates that NETs can timely monitor the formation of hypercoagulable state in MN patients [44].

2.5 Mechanism of action of NETs in the development and progression of hepatitis B virus associated glomerulonephritis (HBV-GN)

HBV-GN is a disease occurring in parts of the body other than the liver caused by hepatitis B virus (HBV) infection [45], mainly clinically manifested as kidney damage. When HBV enters the body and is not promptly cleared, it binds to immunoglobulins in the blood to form immune complexes, and the body also stressfully produces immune complexes in the glomeruli [46]. Consequently, HBV and various immune complexes collectively stimulate neutrophils to generate a large amount of NETs. Existing epidemiological data also indicate that HBV-associated MN ranks second among the etiologies of secondary MN in China [47]. Therefore, the pathogenesis of HBV-GN can promote the release of NETs by exacerbating the accumulation of immune complexes. Hence, during the treatment of HBV-GN patients, attention to immune complexes, their induced immune dysfunction, and the level of NETs can provide a basis for disease diagnosis and treatment to a certain extent.

2.6 Mechanism of action of NETs in the development and progression of Henoch-Schönlein purpura nephritis (HSPN)

Purpura is a systemic vasculitis, among which Henoch-Schönlein purpura is a hemorrhagic disease caused by immune abnormalities. Due to its high probability of causing kidney damage, this disease is termed HSPN [48]. One of the diagnostic criteria for HSPN is the histological features of leukocytoclastic vasculitis mainly characterized by IgA immune complex deposition or chronic glomerulonephritis [48], indicating the important role of IgA in its disease progression. Furthermore, studies have shown that leukotriene B3 and B4 can serve as prognostic markers for HSPN [49], and these inflammatory factors also have the effect of inducing NET release.

3 Clinical application of NETs in CKD treatment

In CKD, enhanced formation or impaired clearance of NETs promotes the progression of inflammation, shifts the body into a hypercoagulable state, and exacerbates renal endothelial injury. In in vitro studies, key targets such as NADPH oxidase, ROS, MPO, DNase 1, as well as various inflammatory factors and chemokines, have been used to investigate the relationship between the disease and NETosis. However, these mechanisms have not been translated into clinical treatments. In clinical studies, NET levels are currently detected using methods such as microscopy, enzyme-linked immunosorbent assay (ELISA), Western blotting, and flow cytometry [50]. Due to the lack of unified standards, the assessment of NET formation varies in specificity depending on the method used [51]. Future research on the role of NETs as biomarkers in CKD progression will likely focus on the identification of specific NET-related molecules, and the development of proteomics has made this possible [52]. Additionally, the new technology of high content screening (HCS) will also enhance the potential clinical utility of NETs [53]. Therefore, further investigation into the correlation between NETs and CKD progression, their mechanisms of action, and the potential value of NETs in early diagnosis and prediction of CKD progression may provide new insights and strategies for CKD, which is difficult to diagnose and has a poor prognosis.

4 Conclusion

Accumulating evidence indicates that excessive formation or impaired clearance of NETs has high clinical relevance to the pathogenesis of CKD. Starting from the formation and clearance mechanisms of NETs, this article reviews potential targets for regulating NET levels. In summary, this article reviews NETs and their mechanisms of action in CKD, and discusses their clinical application prospects in CKD. The potential value of NETs in early diagnosis and prediction of disease progression is foreseeable, and they hold distinct diagnostic and therapeutic significance especially for CKD, which is difficult to diagnose, refractory to treatment, and has a poor prognosis.

Conflict of interest None

Reference

[1] Chen XT, Bao M, Huyan YR, et al. Expression of USP7 and autophagy-related protein in renal tissue of chronic kidney disease patients and its relationship with renal interstitial fibrosis[J]. Chin J Clin Res, 2023, 36(7): 1027-1032. **[In Chinese]**

[2] GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017[J]. Lancet, 2020, 395(10225): 709-733.**[In Chinese]**

[3] Cao WJ, Xu M, Yu HF, et al. The role of neutrophil extracellular traps in kidney diseases[J]. Acta Med Univ Sci Technol Huazhong, 2023, 52(2): 276-282. **[In Chinese]**

[4] Bellasi A, Di Micco L, Russo D, et al. Fractional excretion of phosphate (FeP) is associated with end-stage renal disease patients with CKD 3b and 5[J]. J Clin Med, 2019, 8(7): 1026.

[5] Peruzzo S, Ottaviani S, Tagliafico L, et al. Renal function assessment in older people: comparative analysis of estimation equation with serum creatinine[J]. Front Med, 2024, 31(12) 2085-2095.

[6] Ono M, Toyomoto M, Yamauchi M, et al. Platelets accelerate lipid peroxidation and induce pathogenic neutrophil extracellular trap release[J]. Cell Chem Biol, 2024: S2451-S9456(24)00461-6.

[7] Malamud M, Whitehead L, McIntosh A, et al. Recognition and control of neutrophil extracellular trap formation by MICL[J]. Nature, 2024, 633(8029): 442-450.

[8] Baratchi S, Danish H, Chheang C, et al. Piezo1 expression in neutrophils regulates shear-induced NETosis[J]. Nat Commun, 2024, 15(1): 7023.

[9] Gupta S, Kaplan MJ. The role of neutrophils and NETosis in autoimmune and renal diseases[J]. Nat Rev Nephrol, 2016, 12(7): 402-413.

[10] Okamoto M, Mizuno R, Kawada K, et al. Neutrophil extracellular traps promote metastases of colorectal cancers through activation of ERK signaling by releasing neutrophil elastase[J]. Int J Mol Sci, 2023, 24(2): 1118.

[11] Wang YJ, Du CJ, Zhang Y, et al. Composition and function of neutrophil extracellular traps[J]. Biomolecules, 2024, 14(4): 416.

[12] Chen F, Chu CN, Wang XY, et al. Hesperetin attenuates sepsis-induced intestinal barrier injury by regulating neutrophil extracellular trap formation via the ROS/autophagy signaling pathway[J]. Food Funct, 2023, 14(9): 4213-4227.

[13] Metzler KD, Goosmann C, Lubojemska A, et al. A myeloperoxidase-containing complex regulates neutrophil elastase release and actin dynamics during NETosis[J]. Cell Rep, 2014, 8(3): 883-896.

[14] Vorobjeva NV. Neutrophil extracellular traps: new aspects[J]. Moscow Univ Biol Sci Bull, 2020, 75(4): 173-188.

[15] Rivera-Concha R, León M, Prado-Sanhueza A, et al. Cytotoxic oxidative stress effects of neutrophil extracellular traps' components on cattle spermatozoa[J]. Antioxidants, 2024, 13(6): 733.

[16] Morita S, Nakamaru Y, Fukuda A, et al. Neutrophil extracellular trap formation and deoxyribonuclease I activity in patients with otitis media with antineutrophil cytoplasmic antibody-associated vasculitis[J]. Int Arch Allergy Immunol, 2024, 185(8): 810-819.

[17] Thakur M, Junho CVC, Bernhard SM, et al. NETs-induced thrombosis impacts on cardiovascular and chronic kidney disease[J]. Circ Res, 2023, 132(8): 933-949.

[18] Yu CY, Guan YQ, He YJ, et al. Role of neutrophil extracellular traps in diabetic nephropathy[J]. J Harbin Med Univ, 2022, 56(5): 483-487. **[In Chinese]**

[19] Xiang L, Cai XS, Zhao XS, et al. Uncovering the mechanism of Qidan Dihuang Granule in the treatment of diabetic kidney disease combined network pharmacology, UHPLC-MS/MS with experimental validation[J]. Heliyon, 2023, 9(11): e21714.

[20] Cohen Tervaert TW, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy[J]. J Am Soc Nephrol, 2010, 21(4): 556-563.

[21] Juha M, Molnár A, Jakus Z, et al. NETosis: an emerging therapeutic target in renal diseases[J]. Front Immunol, 2023, 14: 1253667.

[22] Vago JP, Zaidan I, Perucci LO, et al. Plasmin and plasminogen prevent sepsis severity by reducing neutrophil extracellular traps and systemic

inflammation[J]. JCI Insight, 2023, 8(8): e166044.
[23] Kim JH, Lee HS, Kwon MJ, et al. Role of neutrophil extracellular traps in vascular access thrombosis in hemodialysis patients[J]. Thromb Res, 2023, 231: 121-127.
[24] Berbudi A, Rahmadika N, Tjahjadi AI, et al. Type 2 diabetes and its impact on the immune system[J]. Curr Diabetes Rev, 2020, 16(5): 442-449.
[25] Nakazawa D, Shida H, Kusunoki Y, et al. The responses of macrophages in interaction with neutrophils that undergo NETosis[J]. J Autoimmun, 2016, 67: 19-28.
[26] Li X. Research on the Role and Mechanism of NETs Induced by High Glucose in Diabetic Nephropathy. Chongqing: Chongqing Medical University, 2017. **[In Chinese]**
[27] Liu J, Fan JH, Zhang Q, et al. The evaluation value of serum neutrophil extracellular trapping net level in patients with diabetic foot infection for disease condition and prognosis[J]. J Trop Med, 2023, 23(6): 789-792. **[In Chinese]**
[28] Zhang XT, Ma LL, Zhi Y, et al. Rituximab in the treatment of immunoglobulin-mediated membranoproliferative glomerulonephritis[J]. Chin J Clin Res, 2024, 37(3): 442-446. **[In Chinese]**
[29] Jorch SK, Kubes P. An emerging role for neutrophil extracellular traps in noninfectious disease[J]. Nat Med, 2017, 23(3): 279-287.
[30] Campbell AM, Kashgarian M, Shlomchik MJ. NADPH oxidase inhibits the pathogenesis of systemic lupus erythematosus[J]. Sci Transl Med, 2012, 4(157): 157ra141.
[31] Hakkim A, Fürnrohr BG, Amann K, et al. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis[J]. Proc Natl Acad Sci U S A, 2010, 107(21): 9813-9818.
[32] Abou-Raya A, Abou-Raya S. Inflammation: a pivotal link between autoimmune diseases and atherosclerosis[J]. Autoimmun Rev, 2006, 5(5): 331-337.
[33] Tektonidou MG, Laskari K, Panagiotakos DB, et al. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies[J]. Arthritis Rheum, 2009, 61(1): 29-36.
[34] Denny MF, Yalavarthi S, Zhao WP, et al. A distinct subset of proinflammatory neutrophils isolated from patients with systemic lupus erythematosus induces vascular damage and synthesizes type I IFNs[J]. J Immunol, 2010, 184(6): 3284-3297.
[35] Garcia-Romo GS, Caielli S, Vega B, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus[J]. Sci Transl Med, 2011, 3(73): 73ra20.
[36] Villanueva E, Yalavarthi S, Berthier CC, et al. Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus[J]. J Immunol, 2011, 187(1): 538-552.
[37] Subiela JERC, Talavera AC, Wang YC, et al. #1337 Evolution of ANCA-associated vasculitis in a population with confirmed renal involvement. Myeloperoxidase and proteinase 3 antibodies, which is worse?[J]. Nephrol Dial Transplant, 2024, 39(Supplement_1): gfae069-1302-1337.
[38] Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease[J]. Nat Rev Rheumatol, 2014, 10(8): 463-473.
[39] Wei Y, Huang MD, Jiang LG. Advancements in serine protease inhibitors: from mechanistic insights to clinical applications[J]. Catalysts, 2024, 14(11): 787.
[40] Söderberg D, Kurz T, Motamedi A, et al. Increased levels of neutrophil extracellular trap remnants in the circulation of patients with small vessel vasculitis, but an inverse correlation to anti-neutrophil cytoplasmic antibodies during remission[J]. Rheumatology, 2015, 54(11): 2085-2094.
[41] Kessenbrock K, Krumbholz M, Schönermarck U, et al. Netting neutrophils in autoimmune small-vessel vasculitis[J]. Nat Med, 2009, 15(6): 623-625.
[42] Sethi S, Fervenza FC. Membranous nephropathy-diagnosis and identification of target antigens[J]. Nephrol Dial Transplant, 2024, 39(4): 600-606.
[43] Ismail G, Mircescu G, Ditoiu AV, et al. Risk factors for predicting venous thromboembolism in patients with nephrotic syndrome: focus on haemostasis-related parameters[J]. Int Urol Nephrol, 2014, 46(4): 787-792.
[44] Gao CY, Xie R, Yu CY, et al. Procoagulant activity of erythrocytes and platelets through phosphatidylserine exposure and microparticles release in patients with nephrotic syndrome[J]. Thromb Haemost, 2012, 107(4): 681-689.
[45] Liu SY, Li ZP, Zheng X. Research progress of hepatitis B kidney[J]. Heilongjiang J Tradit Chin Med, 2016, 45(6): 70-72. [In Chinese][46] Liu HF, Guo (B/Y), Hong T. Current situation and research progress of hepatitis B infection and prevention and treatment of renal diseases[J]. Chin J Integr Tradit West Nephrol, 2024, 25(1): 1-3. [In Chinese]
[46] Liu HF, Guo (B/Y), Hong T. Current situation and research progress of hepatitis B infection and prevention and treatment of renal diseases[J]. Chin J Integr Tradit West Nephrol, 2024, 25(1): 1-3. **[In Chinese]**
[47] Wang RS, Liu ZH, Chen Y, et al. Etiology and epidemiology of membranous nephropathy[J]. Chin J Nephrol Dial &transplantation, 2006, 15(5): 416-421, 437. **[In Chinese]**
[48] Monova DV, Todorov T, Monov S. Risk factors associated with outcomes in patients with henoch - schönlein purpura nephritis[J]. Nephrol Dial Transplant, 2023, 38(Supplement_1): gfad063c_2777.
[49] Song JY. Establishment of a primary prediction nomogram for children with purpura nephritis[D]. Jinan: Shandong University of Traditional Chinese Medicine, 2020. **[In Chinese]**
[50] Wen J, Du SJ, Wang XM, et al. Diagnostic value of combined detection of serum leukotriene B4 and leukotriene E4 in allergic Purpura nephritis and its prognosis[J]. J Clin Res, 2018, 35(2): 314-316. **[In Chinese]**
[51] Li JH, Tong DX, Wang Y, et al. Neutrophil extracellular traps exacerbate coagulation and endothelial damage in patients with essential hypertension and hyperhomocysteinemia[J]. Thromb Res, 2021, 197: 36-43.
[52] Konig MF, Andrade F. A critical reappraisal of neutrophil extracellular traps and NETosis mimics based on differential requirements for protein citrullination[J]. Front Immunol, 2016, 7: 461.
[53] van Dam LS, Rabelink TJ, van Kooten C, et al. Clinical implications of excessive neutrophil extracellular trap formation in renal autoimmune diseases[J]. Kidney Int Rep, 2019, 4(2): 196-211.

Submission Received: 2024-07-19/**Revised:** 2024-12-08

·研究进展·

中性粒细胞胞外诱捕网在慢性肾脏病发生发展中的作用

吴彩[1]，许俊[2]，彭红英[3]，张小莉[1]，安科[1]

1. 贵州医科大学临床医学院，贵州 贵阳 550000；2. 贵州医科大学附属医院肾内科，贵州 贵阳 550000；
3. 贵州医科大学附属白云医院，贵州 贵阳 550000

摘要：中性粒细胞胞外诱捕网（NETs）是中性粒细胞受到机体自身或者外界的病原刺激，释放出的以DNA和组蛋白、颗粒蛋白为组分的网状结构。NETs与慢性肾脏病（CKD）发生发展的相关性已被关注和研究，过量的NETs可能可以提示CKD病程的进展。因此，本文对NETs的形成与清除机制及其在CKD的发病中作用机制和临床应用作一综述，以期为NETs在CKD早期诊断、疾病进展预测及治疗中的应用提供新的思路。

关键词：中性粒细胞胞外诱捕网；慢性肾脏病；糖尿病肾病；狼疮性肾炎；肾小球肾炎；自身免疫性肾病；膜性肾病

中图分类号：R692　**文献标识码**：A　**文章编号**：1674-8182(2025)09-1310-05

Role of neutrophil extracellular traps in the development and progression of chronic kidney disease

WU Cai*, XU Jun, PENG Hongying, ZHANG Xiaoli, AN Ke

*School of Clinical Medicine, Guizhou Medical University, Guiyang, Guizhou 550000, China

Corresponding author: XU Jun, E-mail: carryxu@163.com

Abstract: Neutrophil extracellular traps (NETs) is a network structure composed of DNA, histone and granular protein released by neutrophils stimulated by their own or external pathogens. The correlation between NETs and the development and progression of chronic kidney disease (CKD) has been concerned and studied, and an excess of NETs may indicate the progression of CKD. Therefore, this article reviews the formation and clearance mechanism of NETs, as well as their mechanism and clinical application in the pathogenesis of CKD, in order to provide new ideas for the application of NETs in early diagnosis, disease progression prediction and treatment of CKD.

Keywords: Neutrophil extracellular traps; Chronic kidney disease; Diabetic kidney disease; Lupus nephritis; Glomerulonephritis; Autoimmune kidney disease; Membranous nephropathy

Fund program: Science and Technology Fund Project of Guizhou Provincial Health Commission (gzwkj2021-129)

慢性肾脏病（chronic kidney disease，CKD）是一种多种原发性或继发性的病因导致的，症状表现为肾功能受损并伴随病情逐渐加重，症状持续3个月以上的慢性疾病[1]。在2017年，全球有6.975亿例CKD患者，患病率达到9.1%，并且逐年增高[2]。CKD初期难以诊断，知晓率仅在10%左右，并且在其发展过程中难以治愈，预后不佳，合并症数量多。CKD主要分为糖尿病肾病（diabetic kidneydisease，DKD）、狼疮性肾炎（lupus nephritis，LN）、膜性肾病（membranous nephropathy，MN）等类型，表现为肾小球滤过率下降，还会出现蛋白尿、高血压、水肿、贫血、低血糖等症状，临床目前使用血肌酐作为肾功能的评估指标[2-5]。

中性粒细胞在受到刺激的情况下，选择释放出一种含有DNA、组蛋白和中性粒细胞颗粒蛋白等成分的网状结构来捕获病原体等物质，这种网状结构称为中性粒细胞胞外诱捕网（neutrophil extracellular traps，NETs）[6]。NETs形成过多或者清除异常会引发机体功能障碍，导致肾脏损伤，炎症加剧，以及造成凝血功能上调和疾病的发生，如自身免疫性疾病、恶性肿瘤、血栓形成、炎症等。在部分疾病中，过量的NETs可能可以指示疾病的发生发展。本文讨论NETs的形成与消除机制，以及CKD的发病作用机制，综述NETs在CKD发生发展过

DOI：10.13429/j.cnki.cjcr.2025.09.003

基金项目：贵州省卫生健康委科技基金项目（gzwkj2021-129）

通信作者：许俊，E-mail：carryxu@163.com

出版日期：2025-09-20

QR code for English version

程中的作用，以及其在CKD早期诊断和疾病进展预测中的潜在临床应用价值，旨在为CKD的治疗提供新策略。

1　NETs的形成及作用机制

受到各种不同的生理刺激后，NETs开始形成。抗体、免疫复合物、趋化因子[白细胞介素(interleukin，IL)-8、细胞坏死因子(tumor necrosis factor，TNF)-α、干扰素(interferon，IFN)-γ]以及钙、钾离子等可以诱导中性粒细胞释放NETs的过程[7]。NETs的骨架是由去浓缩和扩散后的染色质DNA形成的，中性粒细胞因为释放出的染色质DNA而死亡，这一过程称为NETosis[8-9]。NETs的骨架上黏附着瓜氨酸化的组蛋白和初级、次级的颗粒蛋白，如髓过氧化物酶(myeloperoxidase，MPO)、中性粒细胞弹性蛋白酶(neutrophil elastase，NE)、组织蛋白酶G、乳铁蛋白等[10-11]。

有研究表明，还原型烟酰胺腺嘌呤二核苷酸磷酸(reduced nicotinamide adenine dinucleotide phosphate，NADPH)氧化酶诱导活性氧(reactive oxygen species，ROS)生成是NETs的骨架形成过程的源头。因此，抑制NADPH氧化酶或者中和ROS可抑制NETs的形成。NADPH氧化酶的激活导致氧分子转化为活性氧的一种——超氧阴离子自由基，加剧了ROS的产生。这种活性氧首先转化为过氧化氢，然后在MPO的催化下转化为卤化物酸[12]。MPO，与上文提到的颗粒蛋白NE、组织蛋白酶G，以及其他几种蛋白质共同组成偶氮体。其中NE和组织蛋白酶G同属于丝氨酸蛋白酶。过氧化氢可以导致偶氮体的解离，丝氨酸蛋白酶随着解离释放出来[13]。丝氨酸蛋白酶转运进入细胞核后，可以切割组蛋白，促进细胞核中的染色质去浓缩，进一步促进NETs的形成[13]。MPO对丝氨酸蛋白酶促进染色质去浓缩的过程也有协同的作用[14]。因此，减少过氧化氢的产生、抑制MPO以及抑制丝氨酸蛋白酶如NE、组织蛋白酶G，都可以抑制NETs的形成。在NET形成的过程中，大量组蛋白被释放到组织中，不仅对病原体有毒性，同时也对组织有很大损伤[15]。NETs中大量的双链DNA可以被DNA酶降解，之后再被巨噬细胞内吞，再在溶酶体介导下进一步裂解[16]。NETs的消除出现异常时，也会导致NETs大量存在，进一步造成炎症状态或是机体损伤。NETs的形成与清除机制如图1所示，本图由笔者使用Figdraw绘制。

机体内存在大量NETs，其中组蛋白等成分由于其细胞毒性，会造成组织损伤，而存在的大量蛋白会激活机体自身的免疫应答，导致免疫失调，进一步造成自身免疫性疾病的发病。此外，还有研究表明，NETs其中的DNA可以提高蛋白酶的促凝活性，而组蛋白可以抑制血栓调节蛋白和抑制血浆抗凝血活性，从而导致血小板聚集，进一步导致体内微血栓形成、纤维蛋白和血小板沉积[16-17]。NETs通过诱导炎症反应，释放大量的IL-4、IL-6及TNF-α，这些炎症因子具有纤维蛋白溶解(纤溶)抵抗的作用[18]。

2　NETs在慢性肾病发生发展中的作用机制

CKD的主要表现是肾小球滤过率下降，还有蛋白尿、高血压、水肿、贫血、低血糖等，临床目前使用血肌酐作为指标评估肾功能[3-5]。NETs形成过多或者清除异常会引发机体功能障碍，导致肾脏损伤，炎症加剧，以及造成凝血功能上调和CKD的发生。NETs的水平有望作为辅助的指标评价CKD的发展阶段。

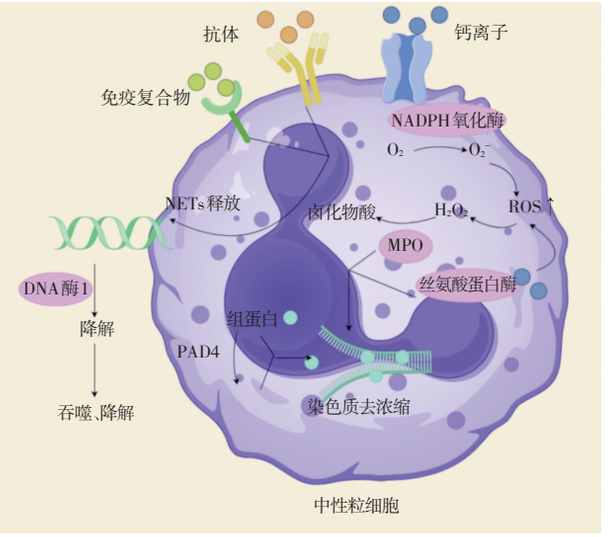

图1　NETs的形成与清除机制

Fig.1　Formation and clearance mechanism of NETs

2.1　NETs在DKD发生发展中的作用机制　DKD是最常见的糖尿病的微血管并发症[19]。它的病理特征为肾小球系膜扩张、肾小球硬化和Kimmelstiel-Wilson结节[20]，临床表现为大量的蛋白尿。DKD发病的主要特征是葡萄糖水平升高。研究表明，高水平的葡萄糖可上调蛋白激酶C(protein kinase C，PKC)活性，进一步诱导NADPH氧化酶水平上调，从而大量产生NETs[21]。这一过程诱导了氧化应激，同时激活了凝血途径，以及产生纤溶抵抗作用[22-23]。虽然并没有直接证据表明DKD是通过NETs实现纤溶抵抗作用的，但这与NETs的作用效果高度一致。此外，还有研究表明，在DKD中，炎症信号通路和胰岛素信号通路被激活，进而产生了大量炎症因子，促进了NETs的释放[24]。研究表明，高浓度葡萄糖条件下，糖酵解可以促使巨噬细胞极化为促炎的M1表型，炎症反应加剧并释放细胞外DNA，加剧了DNA聚集，从而加剧疾病进展[25]。对糖尿病患者进行随访发现，NETs的主要成分DNA浓度与患者发展成为DKD的风险成正比，这说明NETs水平或许可以预测DKD发病情况[26-27]。

2.2　NETs在慢性肾小球肾炎(chronic glomerulonephritis，CGN)发生发展中的作用机制　CGN的发病机制因为主要与免疫炎症损伤有关，所以其在NETs形成中的作用主要是靠炎症因子等物质实现的。如IL-2、IL-6等炎症因子，可以刺激中性粒细胞释放NETs到炎症环境中[28-29]。因此，在CGN中，NETs的水平可以一定程度上指示肾脏损伤的情况。

2.3　NETs在自身免疫性肾病发生发展中的作用机制　自身免疫性肾病的往往临床表现为免疫失调。DNA和抗双链DNA IgG抗体的免疫复合物沉积于肾脏也是导致肾炎的重要原因。

NET形成过程中，DNA被ROS氧化，而氧化DNA比未氧化的DNA更不易被核酸酶降解。大量存在的氧化DNA激活了cGAS/STING信号通路，增加IFN-Ⅰ合成以及导致免疫失调[30-31]。同时，自身免疫性疾病出现冠状动脉粥样硬化性疾病和血栓栓塞并发症的风险很高，研究表明，这可能是由中性粒细胞和NETs的诱导体内微血栓形成、纤维蛋白和血小板沉积、以及抑制纤溶的作用导致的[30]。常见的自身免疫性肾病包括LN和抗中性粒细胞胞浆抗体相关性血管炎（anti-neutrophil cytoplasmic antibodies associated vasculitis，AAV）。

2.3.1　NETs在LN发生发展中的作用机制　NETs与LN的发病机制通过ROS、DNA酶1、NADPH氧化酶等起作用。研究表明，LN的典型特征是患者体内有明显的低密度中性粒细胞（low-density granulocyte，LDGs）群，这一现象显著区别于健康人群[32]。LDGs中，线粒体ROS产生诱导NETs大量形成。并且，LN患者比健康人中性粒细胞的NETs含有更多的致病性自身抗原，这也导致了严重的组织损伤和浆细胞样树突状细胞的活化，进而诱导IFN的释放[33-34]。另外，在一些LN患者中发现，由于DNA酶1的作用被抑制，NETs的清除被抑制，导致NETs的堆积[28]。另外，LN患者组织病理切片中，可明显观察到靠近肾小球囊的小管间质室有NETs的形成，表明NETs可能参与了LN患者体内包膜破裂和新月体形成[35]。

2.3.2　NETs在AAV发生发展中的作用机制　AAV是一类影响中小血管的，与ANCA有关的血管炎，这种血管炎常累及肾脏，因此是一种CKD[9]。在AAV患者体内，MPO作为AAV的血清标志物，可以激活中性粒细胞，导致ROS的产生以及NET形成，最终破坏血管，并导致血管外炎症的发展[36-37]。AAV常伴有血栓形成，并且血栓组织富含NETs及其相关分子[38]。NETs在其中起到重要的作用，组蛋白以血小板依赖的方式进一步增加血栓形成。丝氨酸蛋白酶如NE，则通过促进凝血来促进血栓形成[39]。免疫染色实验显示，在AAV患者肾活检标本中，炎症区域、坏死性肾小球肾炎肾脏纤维蛋白样坏死区域周围以及小叶动脉壁，存在有NETs和NETs相关分子[40-41]，这充分说明NETs参与了AAV发病进程。

2.4　NETs在MN发生发展中的作用机制　MN是一种免疫复合物相关的肾小球疾病，临床表现多为不同程度的蛋白尿、低蛋白血症、高度水肿、高脂血症。病理特征表现为肾小球毛细血管袢上皮下免疫复合物沉积以及肾小球基底膜（glomerular basement membrane，GBM）弥漫性增厚，免疫球蛋白IgG和补体膜攻击复合物和抗原抗体免疫复合物沿肾小球毛细血管袢颗粒样沉积，上皮下可见到电子致密物[42]。同时，研究表明特发性MN也可能由于凝血功能增强、抗凝作用减弱，微粒表达增加等，导致血栓[43]。研究证明了特发性MN患者外周血中高表达的NETs可反映肾脏内皮损伤程度，NETs的高表达导致内皮损伤，因此呈现出大量蛋白尿以及高凝的表现，这说明NETs对内皮细胞和肾小管上皮细胞的损伤可能加重特发性MN的发展[44]。同时研究表明，NETs升高越明显，血栓发生概率越大，这在一定程度上指出了NETs能够及时监测MN患者高凝状态的形成[44]。

2.5　NETs在乙型肝炎病毒相关性肾炎（hepatitis B virus associated glomerulonephritis，HBV-GN）发生发展中的作用机制　HBV-GN是由于乙型肝炎病毒（hepatitis B virus，HBV）感染导致的、出现在机体除肝脏以外部位的一种疾病[45]，主要临床表现为肾损伤。当HBV进入机体内，而没能被及时清除，HBV会与血液中的免疫球蛋白结合形成免疫复合物，同时机体也会应激性地在肾小球产生免疫复合物[46]。于是，HBV和各类免疫复合物在共同作用下，刺激中性粒细胞产生了大量的NETs。在现有的流行病学数据中，也指出我国HBV相关性MN是在继发性MN的发病原因中居第二位[47]。因此，HBV-GN的发病可以通过加剧免疫复合物的沉积而促进NETs的释放。因而，在HBV-GN患者的治疗过程中，关注免疫复合物及其带来的免疫功能紊乱，以及关注NETs的水平，都可以为疾病的诊断和治疗提供一定程度的依据。

2.6　NETs在过敏性紫癜肾炎（Henoch-Schönlein purpura nephritis，HSPN）发生发展中的作用机制　紫癜是一种系统性血管炎，其中过敏性紫癜则是免疫异常引起的一种出血性疾病。因具有很高的概率引起肾脏损伤，这一疾病被称为HSPN[48]。HSPN的诊断标准之一为具有以IgA免疫复合物沉积为主的白细胞碎裂性血管炎或慢性肾小球肾炎的组织学特征[48]，由此可见IgA在其疾病发展中的重要作用。更有研究表明，白三烯B3、B4可作为HSPN预后的标志物[49]。这类炎症因子也具有诱导NETs释放的作用。

3　NETs在CKD临床治疗中的应用

在CKD中，NETs的形成被增强或者清除被抑制，具备促进机体炎症发展、转变机体为高凝状态、加重肾脏内皮损伤的作用。在体外研究中，重要靶点如NADPH氧化酶、ROS、MPO、DNA酶1，以及各类涉及到的炎症因子、趋化因子都被用来探究疾病与NETosis的过程，但临床上从未应用这些机制进行治疗。而临床研究中，目前NETs的水平主要是通过显微镜观察、酶联免疫吸附法、蛋白质印迹法、流式细胞术等方法来检测[50]。因为缺乏统一的标准，如何统一评定NETs的形成情况因方法不同存在特异性[51]。未来对NETs作为生物标记物在CKD发展中的作用，应当会聚焦在特异性NETs相关分子的鉴定，其中，蛋白质组学的发展就为这一点提供了可能[52]。此外，新技术高内涵筛选（high content screening，HCS）也将提高NETs临床使用的潜在价值[53]。因此，进一步探究NETs与CKD病程的相关性及其作用机制，以及NETs在CKD早期诊断和疾病进展预测中的潜在价值，可能有望为难以诊断、预后不佳的CKD提供新的思路和策略。

4　结　语

越来越多的证据表明，NETs的形成过多或者清除障碍，与CKD的发病具备相当高的临床相关性。本文从NETs的形成与清除机制出发，综述了调控NETs水平的潜在靶点。总的来说，本文综述了NETs及其在CKD中的作用机制，并对其在CKD中的临床应用前景进行了讨论，其早期诊断和疾病进展

预测中的潜在价值可以预见，尤其对于难以诊断、难以治愈、预后不佳的CKD具备不同的诊断、治疗意义。

利益冲突　无

参考文献

[1] 陈新田，鲍苗，呼延逸然，等. 慢性肾脏病患者肾组织USP7和自噬相关蛋白的表达及其与肾间质纤维化的关系[J]. 中国临床研究，2023，36(7)：1027-1032.

[2] GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017[J]. Lancet, 2020, 395(10225): 709-733.

[3] 曹文洁，许毛，余惠凡，等. 中性粒细胞胞外诱捕网在肾脏疾病中的作用[J]. 华中科技大学学报(医学版)，2023，52(2)：276-282

[4] Bellasi A, Di Micco L, Russo D, et al. Fractional excretion of phosphate (FeP) is associated with end-stage renal disease patients with CKD 3b and 5[J]. J Clin Med, 2019, 8(7): 1026.

[5] Peruzzo S, Ottaviani S, Tagliafico L, et al. Renal function assessment in older people: comparative analysis of estimation equation with serum creatinine[J]. Front Med, 2024, 11: 1477500.

[6] Ono M, Toyomoto M, Yamauchi M, et al. Platelets accelerate lipid peroxidation and induce pathogenic neutrophil extracellular trap release[J]. Cell Chem Biol, 2024,31(12):2085-2095.

[7] Malamud M, Whitehead L, McIntosh A, et al. Recognition and control of neutrophil extracellular trap formation by MICL[J]. Nature, 2024, 633(8029): 442-450.

[8] Baratchi S, Danish H, Chheang C, et al. Piezo1 expression in neutrophils regulates shear-induced NETosis[J]. Nat Commun, 2024, 15(1): 7023.

[9] Gupta S, Kaplan MJ. The role of neutrophils and NETosis in autoimmune and renal diseases[J]. Nat Rev Nephrol, 2016, 12(7): 402-413.

[10] Okamoto M, Mizuno R, Kawada K, et al. Neutrophil extracellular traps promote metastases of colorectal cancers through activation of ERK signaling by releasing neutrophil elastase[J]. Int J Mol Sci, 2023, 24(2): 1118.

[11] Wang YJ, Du CJ, Zhang Y, et al. Composition and function of neutrophil extracellular traps[J]. Biomolecules, 2024, 14(4): 416.

[12] Chen F, Chu CN, Wang XY, et al. Hesperetin attenuates sepsis-induced intestinal barrier injury by regulating neutrophil extracellular trap formation via the ROS/autophagy signaling pathway [J]. Food Funct, 2023, 14(9): 4213-4227.

[13] Metzler KD, Goosmann C, Lubojemska A, et al. A myeloperoxidase-containing complex regulates neutrophil elastase release and actin dynamics during NETosis[J]. Cell Rep, 2014, 8(3): 883-896.

[14] Vorobjeva NV. Neutrophil extracellular traps: new aspects[J]. Moscow Univ Biol Sci Bull, 2020, 75(4): 173-188.

[15] Rivera-Concha R, León M, Prado-Sanhueza A, et al. Cytotoxic oxidative stress effects of neutrophil extracellular traps' components on cattle spermatozoa[J]. Antioxidants, 2024, 13(6): 733.

[16] Morita S, Nakamaru Y, Fukuda A, et al. Neutrophil extracellular trap formation and deoxyribonuclease I activity in patients with otitis media with antineutrophil cytoplasmic antibody-associated vasculitis[J]. Int Arch Allergy Immunol, 2024, 185(8): 810-819.

[17] Thakur M, Junho CVC, Bernhard SM, et al. NETs-induced thrombosis impacts on cardiovascular and chronic kidney disease [J]. Circ Res, 2023, 132(8): 933-949.

[18] 禹程远，关雨晴，何育婧，等. 中性粒细胞胞外诱捕网在糖尿病肾病中的作用[J]. 哈尔滨医科大学学报，2022，56(5)：483-487.

[19] Xiang L, Cai XS, Zhao XS, et al. Uncovering the mechanism of *Qidan Dihuang* Granule in the treatment of diabetic kidney disease combined network pharmacology, UHPLC-MS/MS with experimental validation[J]. Heliyon, 2023, 9(11): e21714.

[20] Cohen Tervaert TW, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy [J]. J Am Soc Nephrol, 2010, 21(4): 556-563.

[21] Juha M, Molnár A, Jakus Z, et al. NETosis: an emerging therapeutic target in renal diseases [J]. Front Immunol, 2023, 14: 1253667.

[22] Vago JP, Zaidan I, Perucci LO, et al. Plasmin and plasminogen prevent sepsis severity by reducing neutrophil extracellular traps and systemic inflammation[J]. JCI Insight, 2023, 8(8): e166044.

[23] Kim JH, Lee HS, Kwon MJ, et al. Role of neutrophil extracellular traps in vascular access thrombosis in hemodialysis patients [J]. Thromb Res, 2023, 231: 121-127.

[24] Berbudi A, Rahmadika N, Tjahjadi AI, et al. Type 2 diabetes and its impact on the immune system[J]. Curr Diabetes Rev, 2020, 16 (5): 442-449.

[25] Nakazawa D, Shida H, Kusunoki Y, et al. The responses of macrophages in interaction with neutrophils that undergo NETosis [J]. J Autoimmun, 2016, 67: 19-28.

[26] 李璇. 高糖诱导的NETs在糖尿病肾病中的作用及机制研究[D]. 重庆：重庆医科大学，2017.

[27] 刘军，范金虎，张青，等. 糖尿病足感染患者血清中性粒细胞胞外诱捕网水平对病情和预后的评估价值[J]. 热带医学杂志，2023，23(6)：789-792.

[28] 张笑恬，马雷雷，支勇，等. 利妥昔单抗治疗免疫球蛋白介导的膜增生性肾小球肾炎的研究进展[J]. 中国临床研究，2024，37 (3)：442-446.

[29] Jorch SK, Kubes P. An emerging role for neutrophil extracellular traps in noninfectious disease[J]. Nat Med, 2017, 23(3): 279-287.

[30] Campbell AM, Kashgarian M, Shlomchik MJ. NADPH oxidase inhibits the pathogenesis of systemic lupus erythematosus [J]. Sci Transl Med, 2012, 4(157): 157ra141.

[31] Hakkim A, Fürnrohr BG, Amann K, et al. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis [J]. Proc Natl Acad Sci U S A, 2010, 107(21): 9813-9818.

[32] Abou-Raya A, Abou-Raya S. Inflammation: a pivotal link between autoimmune diseases and atherosclerosis [J]. Autoimmun Rev, 2006, 5(5): 331-337.

[33] Tektonidou MG, Laskari K, Panagiotakos DB, et al. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies[J]. Arthritis Rheum, 2009, 61(1): 29-36.

[34] Denny MF, Yalavarthi S, Zhao WP, et al. A distinct subset of proinflammatory neutrophils isolated from patients with systemic lupus erythematosus induces vascular damage and synthesizes type I IFNs [J]. J Immunol, 2010, 184(6): 3284-3297.

[35] Garcia-Romo GS, Caielli S, Vega B, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus[J]. Sci Transl Med, 2011, 3(73): 73ra20.

[36] Villanueva E, Yalavarthi S, Berthier CC, et al. Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus[J]. J Immunol, 2011, 187(1): 538-552.

[37] Subiela JERC, Talavera AC, Wang YC, et al. Evolution of ANCA-associated vasculitis in a population with confirmed renal involvement. Myeloperoxidase and proteinase 3 antibodies, which is worse?[J]. Nephrol Dial Transplant, 2024, 39(Supplement_1): gfae069-1302-1337.

[38] Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease[J]. Nat Rev Rheumatol, 2014, 10 (8): 463-473.

[39] Wei Y, Huang MD, Jiang LG. Advancements in serine protease inhibitors: from mechanistic insights to clinical applications[J]. Catalysts, 2024, 14(11): 787.

（下转第1318页）

Int J Mol Sci, 2021, 22(3): 1229.
[35] Steinberg GR, Hardie DG. New insights into activation and function of the AMPK[J]. Nat Rev Mol Cell Biol, 2023, 24(4): 255-272.
[36] Barbhuiya PA, Yoshitomi R, Pathak MP. Understanding the link between sterol regulatory element binding protein (SREBPs) and metabolic dysfunction associated steatoticliver disease (MASLD)[J]. Curr Obes Rep, 2025, 14(1): 36.
[37] Libby AE, Jones B, Lopez-Santiago I, et al. Nuclear receptors in the kidney during health and disease[J]. Mol Aspects Med, 2021, 78: 100935.
[38] Li JZ, Yang YJ, Li QM, et al. STAT6 contributes to renal fibrosis by modulating PPARα-mediated tubular fatty acid oxidation[J]. Cell Death Dis, 2022, 13(1): 66.
[39] Jin L, Hua H, Ji Y, et al. Anti-inflammatory role of fenofibrate in treating diseases[J]. Biomol Biomed, 2023, 23(3): 376-391.
[40] Li SY, Mariappan N, Megyesi J, et al. Proximal tubule PPARα attenuates renal fibrosis and inflammation caused by unilateral ureteral obstruction[J]. Am J Physiol Renal Physiol, 2013, 305(5): F618-F627.
[41] Tan HWS, Anjum B, Shen HM, et al. Lysosomal inhibition attenuates peroxisomal gene transcription via suppression of PPARA and PPARGC1A levels[J]. Autophagy, 2019, 15(8): 1455-1459.
[42] Zhang LW, Liu J, Zhou FF, et al. PGC-1α ameliorates kidney fibrosis in mice with diabetic kidney disease through an antioxidative mechanism[J]. Mol Med Rep, 2018, 17(3): 4490-4498.
[43] Nam BY, Jhee JH, Park J, et al. PGC-1α inhibits the NLRP3 inflammasome via preserving mitochondrial viability to protect kidney fibrosis[J]. Cell Death Dis, 2022, 13(1): 31.
[44] Yang XP, Liu QH, Li YP, et al. The diabetes medication canagliflozin promotes mitochondrial remodelling of adipocyte via the AMPK-Sirt1-Pgc-1α signalling pathway[J]. Adipocyte, 2020, 9(1): 484-494.
[45] Huang QW, Chen HB, Yin K, et al. Formononetin attenuates renal tubular injury and mitochondrial damage in diabetic nephropathy partly viaregulating Sirt1/PGC-1α pathway[J]. Front Pharmacol, 2022, 13: 901234.
[46] Opazo-Ríos L, Mas S, Marín-Royo G, et al. Lipotoxicity and diabetic nephropathy: novel mechanistic insights and therapeutic opportunities[J]. Int J Mol Sci, 2020, 21(7): 2632.
[47] Giardini E, Moore D, Sadlier D, et al. The dual role of lipids in chronic kidney disease: Pathogenic culprits and therapeutic allies[J]. Atherosclerosis, 2024, 398: 118615.
[48] Lin JW, Cheng A, Cheng K, et al. Newinsights into the mechanisms of pyroptosis and implications for diabetic kidney disease[J]. Int J Mol Sci, 2020, 21(19): 7057.
[49] Luo C, Urgard E, Vooder T, et al. The role of COX-2 and Nrf2/ARE in anti-inflammation and antioxidative stress: Aging and anti-aging[J]. Med Hypotheses, 2011, 77(2): 174-178.
[50] Patel VA, Massenburg D, Vujicic S, et al. Apoptotic cells activate AMP-activated protein kinase (AMPK) and inhibit epithelial cell growth without change in intracellular energy stores[J]. J Biol Chem, 2015, 290(37): 22352-22369.
[51] Wang N, Zhang C. Oxidative stress: aculprit in the progression of diabetic kidney disease[J]. Antioxidants (Basel), 2024, 13(4): 455.
[52] Li HY, Oh YS, Choi JW, et al. Blocking lysophosphatidic acid receptor 1 signaling inhibits diabetic nephropathy in db/db mice[J]. Kidney Int, 2017, 91(6): 1362-1373.
[53] Zhang XW, Ritter JK, Li NJ. Sphingosine-1-phosphate pathway in renal fibrosis[J]. Am J Physiol Renal Physiol, 2018, 315(4): F752-F756.

收稿日期:2025-02-03 **修回日期**:2025-06-28 **编辑**:王国品

(上接第1313页)

[40] Söderberg D, Kurz T, Motamedi A, et al. Increased levels of neutrophil extracellular trap remnants in the circulation of patients with small vessel vasculitis, but an inverse correlation to anti-neutrophil cytoplasmic antibodies during remission[J]. Rheumatology, 2015, 54(11): 2085-2094.
[41] Kessenbrock K, Krumbholz M, Schönermarck U, et al. Netting neutrophils in autoimmune small-vessel vasculitis[J]. Nat Med, 2009, 15(6): 623-625.
[42] Sethi S, Fervenza FC. Membranous nephropathy-diagnosis and identification of target antigens[J]. Nephrol Dial Transplant, 2024, 39(4): 600-606.
[43] Ismail G, Mircescu G, Ditoiu AV, et al. Risk factors for predicting venous thromboembolism in patients with nephrotic syndrome: focus on haemostasis-related parameters[J]. Int Urol Nephrol, 2014, 46(4): 787-792.
[44] Gao CY, Xie R, Yu CY, et al. Procoagulant activity of erythrocytes and platelets through phosphatidylserine exposure and microparticles release in patients with nephrotic syndrome[J]. Thromb Haemost, 2012, 107(4): 681-689.
[45] 刘思远, 李志鹏, 郑心. 乙肝肾的研究进展[J]. 黑龙江中医药, 2016, 45(6): 70-72.
[46] 刘华锋, 郭赟, 洪涛. 乙肝感染与肾脏疾病防治现状及研究进展[J]. 中国中西医结合肾病杂志, 2024, 25(1): 1-3.
[47] 王瑞石, 刘志红, 陈燕, 等. 肾小球膜性病变的病因分析及流行病学特点[J]. 肾脏病与透析肾移植杂志, 2006, 15(5): 416-421, 437
[48] Monova DV, Todorov T, Monov S. Risk factors associated with outcomes in patients with Henoch-Schönlein purpura nephritis[J]. Nephrol Dial Transplant, 2023, 38(Supplement_1): gfad063c_2777.
[49] 宋均亚. 儿童紫癜性肾炎风险预测模型的初步构建及消风散治疗过敏性紫癜的机制研究[D]. 济南: 山东中医药大学, 2020.
[50] 温杰, 杜三军, 王晓美, 等. 血清白三烯B4和白三烯E4联合检测对变应性紫癜肾炎及其预后的诊断价值[J]. 医学临床研究, 2018, 35(2): 314-316.
[51] Li JH, Tong DX, Wang Y, et al. Neutrophil extracellular traps exacerbate coagulation and endothelial damage in patients with essential hypertension and hyperhomocysteinemia[J]. Thromb Res, 2021, 197: 36-43.
[52] Konig MF, Andrade F. A critical reappraisal of neutrophil extracellular traps and NETosis mimics based on differential requirements for protein citrullination[J]. Front Immunol, 2016, 7: 461.
[53] van Dam LS, Rabelink TJ, van Kooten C, et al. Clinical implications of excessive neutrophil extracellular trap formation in renal autoimmune diseases[J]. Kidney Int Rep, 2019, 4(2): 196-211.

收稿日期:2024-07-19 **修回日期**:2024-12-08 **编辑**:石嘉莹