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Research progress on zinc finger protein A20 in sepsis-associated acute kidney injury

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Abstract: Sepsis-associated acute kidney injury (SA-AKI) is a frequently encountered critical-care syndrome that complicates 40% 50% of sepsis cases and carries a markedly higher mortality than sepsis alone, representing a major threat to human health. Zinc finger protein A20, also known as tumor necrosis factor alpha-induced protein 3 (TNFAIP3), is an important ubiquitin-editing enzyme. It was originally identified as a gene induced by tumor necrosis factor alpha and can negatively regulate the nuclear factor-κB (NF-κB) signaling pathway, serving as a key "brake" molecule in cell death and inflammatory responses. A20 encoded by the *TNFAIP*3 gene is a key negative regulator of inflammation, which is essential for regulating cell apoptosis and suppressing inflammatory cascades. Its protective role in SA-AKI is increasingly recognized. This review delineates the structural features, and biological functions, expression regulation of A20, summarizes current mechanistic insights into its renoprotective actions in SA-AKI, and outlines emerging A20-targeted therapeutic strategies together with their prospects for clinical translation, aiming to provide novel therapeutic avenues for SA-AKI.

Keywords: Zinc finger protein A20/ tumor necrosis factor alpha-induced protein3; Sepsis-associated acute kidney injury; NLRP3 inflammasome; Nuclear factor -κB; Inflammatory response
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Sepsis-associated acute kidney injury (SA-AKI) is a common and critical complication in clinical practice. Among the stages of acute kidney injury (risk, injury, failure), SA-AKI is associated with significantly higher mortality and longer hospital stays compared with AKI from other causes [1]. The pathogenesis of SA-AKI is complex and involves multiple factors, such as renal hypoperfusion, immune inflammation, microcirculatory dysfunction, renal tubular cell apoptosis, and coagulation abnormalities. Its hallmark is a sudden decline in kidney function, leading to electrolyte imbalances, waste accumulation, and fluid overload [2]. In intensive care unit (ICU) patients, approximately 40%–50% of AKI patients have concomitant sepsis. A prospective study conducted in 198 ICUs across 24 European countries including 1,177 septic patients reported an AKI incidence of 51%. A retrospective study including 146,148 Chinese patients showed that 47.1% of sepsis cases were complicated by AKI [3]. Therefore, it is of great significance to conduct in-depth research on the pathogenesis of SA-AKI and seek effective therapeutic targets.

Zinc finger protein A20 (A20), also known as tumour necrosis factor alpha-induced protein 3 (TNFAIP3), is an important negative regulator of innate and adaptive immunity and plays a significant role in acute infection [4]. Increasing evidence indicates that A20 is involved in the pathophysiology of SA-AKI, influencing its development and progression by regulating inflammation, apoptosis, and other mechanisms, and thus holds promise as a novel therapeutic target for SA-AKI [5]. This article reviews the structural characteristics, biological functions, expression regulation, and mechanisms of action of A20 in SA-AKI, and discusses novel A20-targeted therapeutic strategies and their clinical translation prospects.

1 Structure and function of A20

1.1 Structural features of A20

The A20 protein is encoded by the TNFAIP3 gene, located on the short arm of human chromosome 6 (6q23.3). Its DNA sequence spans 10.5 kb and consists of 10 exons and 9 introns. The molecular weight of A20 is 89,613.9, with an isoelectric point of 8.61 and a molecular formula of $C_{3897}H_{6108}N_{1152}O_{1162}S_{60}$. It contains 87 acidic residues (aspartic acid, glutamic acid) and 102 basic residues (arginine, lysine) [6]. The full-length A20 cDNA is 4,440 bp, of which the coding region accounts for 2,370 bp, translating into a polypeptide chain of 790 amino acids with an apparent molecular weight of approximately 90,000 [7]. The A20 protein contains multiple functional domains that enable it to participate in complex ubiquitin-related regulatory processes. Its N-terminus has an ovarian tumour-related protease (OTU) deubiquitinase domain responsible for removing lysine (K) 63-linked ubiquitin chains. Its C-terminus contains zinc finger domains; the fourth zinc finger domain (ZnF_4) at the C-terminus possesses E3 ubiquitin ligase activity, primarily adding K48-linked ubiquitin chains to target proteins for proteasomal degradation, while the seventh zinc finger domain (ZnF_7) is known for its affinity for methionine 1 (M1)-linked chains, playing a non-catalytic but essential role in ubiquitin binding and significantly contributing to the downregulation of nuclear factor kappa-B (NF-κB) signalling [8-9]. This unique structure enables A20 to precisely regulate the activity and duration of signalling pathways by "editing" ubiquitin chains.

1.2 Expression and regulation of A20

A20 is a key immunoregulatory protein whose expression is highly regulated. Studies have shown that under physiological conditions, A20 protein levels are low in normal tissues. When the body is stimulated by inflammatory factors such as tumour necrosis factor (TNF)-α or oxidized self-DNA (ox-self-DNA), the NF-κB signalling pathway is activated. The activated NF-κB RelA/p50 complex directly binds to the dual κB sites in the A20 promoter, leading to a rapid increase in A20 expression. A20 then inhibits the NF-κB signalling pathway through its deubiquitinase activity and zinc finger domains, forming a negative feedback loop [10-14]. In addition, A20 is regulated by epigenetic mechanisms such as promoter methylation and histone methylation, as well as fine negative regulation by microRNAs (miR-125a/b, miR-29, miR-19, miR-221, let-7), forming multifaceted negative feedback networks that suppress excessive inflammatory responses [5].

1.3 Immune homeostasis function of A20

A20 plays a critical role in maintaining immune homeostasis. It not only reduces the release of pro-inflammatory cytokines (such as TNF-α, interleukin (IL)-1β, and IL-6) by inhibiting the NF-κB signalling pathway, but also directly regulates the assembly and activation of the NLRP3 inflammasome, inhibiting caspase-1-dependent pyroptosis [14]. A20 can also inhibit apoptosis by modulating apoptosis-related signalling pathways. Won et al. [15] demonstrated that A20, through its ZnF4 domain, directly binds to apoptosis signal-regulating kinase 1 (ASK1) and adds K48-linked polyubiquitin chains, promoting ASK1 proteasomal degradation, thereby blocking TNF-induced c-Jun N-terminal kinase/p38 mitogen-activated protein kinase (JNK/p38 MAPK) activation and ultimately inhibiting apoptosis. Thus, A20 is an important anti-apoptotic protein that protects cells from TNF-induced apoptosis by inhibiting multiple downstream pathways such as NF-κB and JNK/p38. At the same time, as an important ubiquitin-editing enzyme, A20 can regulate the activity of stimulator of interferon genes (STING), negatively modulating the STING-mediated type I interferon (IFN-I) production pathway, thereby suppressing inflammatory responses [16-17]. Furthermore, A20 removes K63 ubiquitin chains from the autophagy-related protein Beclin-1 via its deubiquitinase activity, thereby inhibiting excessive autophagy induced by inflammatory signals and protecting renal cells from severe injury and dysfunction caused by sepsis [18-19].

2 Protective mechanism of A20 in SA-AKI

2.1 Inhibition of NLRP3 inflammasome-mediated pyroptosis

The NLRP3 inflammasome is a cytosolic sensor of cellular stress and environmental stimuli. As a key node integrating multiple signals and sensing cellular homeostasis, the NLRP3 inflammasome can be activated by various microbial or sterile stimuli, such as bacterial toxins, extracellular ATP, and oxidized dsDNA (ox-dsDNA) [20-24]. The NLRP3 inflammasome is composed of the receptor protein NLRP3, the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), and pro-caspase-1 effector protein. It is mainly present in the cytoplasm of immune and inflammatory cells and mediates the maturation and release of cytokines as well as pyroptosis [25]. Its activation is roughly divided into two stages: priming and activation. The priming stage is marked by the upregulation of NLRP3 and pro-IL-1β expression, driven by activation of the NF-κB signalling pathway. In turn, NLRP3 activation is promoted by potassium efflux and/or mitochondrial changes, enabling subsequent signal transduction [26-27]. Subsequently, the serine/threonine kinase NEK7 (never in mitosis gene a-related kinase 7) directly binds to NLRP3 and regulates its oligomerisation and activation [28]. Therefore, NEK7 is a potential intervention target for NLRP3 inflammasome-related diseases [29]. Database analyses indicate that NEK7 is significantly increased in cells associated with sepsis progression, and NEK7 expression levels are elevated in myeloid cells of septic patients. Thus, NEK7 expression has crucial clinical significance in sepsis [30].

In patients with sepsis, overactivated immune cells together with tissue ischemia-reperfusion injury lead to a surge in reactive oxygen species (ROS) levels. These excessive ROS cause oxidative DNA damage, generating large amounts of ox-dsDNA [31-32]. Studies have shown that upon ox-dsDNA stimulation, the binding between A20 and NEK7 is significantly enhanced. A20 directly binds to NEK7 and mediates its K48-linked ubiquitination, thereby targeting NEK7 for proteasomal degradation [33]. 8-Hydroxydeoxyguanosine, a component of ox-dsDNA, can activate the NLRP3 inflammasome, identifying ox-dsDNA as one of the endogenous ligands of NLRP3 [23,31]. This activation ultimately leads to inflammasome assembly with ASC, promoting self-cleavage and maturation of caspase-1. This process subsequently causes cleavage of gasdermin D (GSDMD), inducing pyroptosis [34-35]. A20 disrupts the binding of NEK7 to the NLRP3 complex through the synergistic effect of its OTU domain and/or ZnF4 and ZnF7 motifs, thereby inhibiting the assembly and activation of the NLRP3 inflammasome [14]. Inhibition of NLRP3 reduces caspase-1-mediated GSDMD cleavage, suppresses pyroptosis, and alleviates renal tissue inflammation and injury [27]. Furthermore, A20 not only removes K63-linked ubiquitin chains from the ubiquitin ligases TRAF6 and RIPK1 via its OTU deubiquitinase activity, but also catalyses K48-linked ubiquitination via its E3 ubiquitin ligase activity, promoting the degradation of these signalling molecules, inhibiting NF-κB activation, and consequently suppressing NLRP3 inflammasome activation and attenuating inflammatory responses [16]. A20 also inhibits spontaneous NLRP3 activation by restricting K63-linked ubiquitination of the pro-IL-1β pre-complex [36]. Yu et al.

[33] demonstrated that an A20-derived peptide (P-II peptide) significantly improved the survival of lipopolysaccharide-treated mice. These data indicate that NEK7 is a promising target for the treatment of NLRP3-mediated diseases such as sepsis. Interfering with NEK7 function in macrophages using A20-derived peptides and genetic approaches can significantly inhibit pyroptosis and delay the progression of sepsis.

2.2 Inhibition of the cyclic GMP-AMP synthase (cGAS)-STING pathway- mediated inflammatory response

The cGAS-STING signalling pathway is a pivotal axis of innate immunity that senses cytosolic DNA, responsible for recognising double-stranded DNA released by pathogens or self-damage and triggering the expression of type I IFN and pro-inflammatory cytokines [37-39]. Studies have shown that activation of the STING pathway in patients is associated with exacerbated renal tubular inflammation and the progression of SA-AKI [40]. In SA-AKI patients, due to factors such as ischemia, hypoxia, endotoxin, and inflammatory cytokines, ox-dsDNA accumulates in the body. After being recognized by cGAS, ox-dsDNA catalyzes the generation of 2′3′-cGAMP, which binds to and induces STING translocation, activating the cGAS-STING pathway. This rapidly increases the levels of phosphorylated TBK1, phosphorylated IRF3, phosphorylated STAT1 (p-STAT1), as well as the mRNA and protein levels of IFN-β, TNF-α, and IL-6, driving a storm of type I IFN and pro-inflammatory cytokines [41-45]. Moreover, oxidative modification makes self-DNA resistant to exonuclease degradation and enhances STING-dependent immune sensing, thereby amplifying the inflammatory response [46].

A20, through its OTU deubiquitinase domain, selectively removes K63-linked ubiquitin chains from STING and its adaptor proteins TRAF3/6, blocking the recruitment and phosphorylation activation of TBK1, thereby preventing excessive activation of the STING pathway and limiting the damage caused by the cytokine storm [47]. Studies have shown that A20 deficiency significantly enhances STING pathway activity, whereas A20 overexpression or exogenous supplementation (e.g., with P-II peptide) can reverse this process [5].

2.3 Inhibition of NF-κB pathway activation

NF-κB is a dimeric transcription factor composed of Rel family subunits. NF-κB can be activated by lipopolysaccharide, TNF, IL-1, IL-17, etc. It is a well-known signalling pathway that plays an important role in inducing many cytokines involved in inflammatory responses, such as IL-1, IL-6, and TNF [48]. Upon receptor triggering, NF-κB released through a series of signalling pathways rapidly translocate to the nucleus, binds to κB sites, and initiates the transcription of pro-inflammatory genes such as TNF-α and IL-6, completing the cascade amplification of the classical NF-κB signalling pathway [49]. Therefore, inhibition of NF-κB activation is considered a potential therapeutic approach because it reduces pro-inflammatory cytokines.

A20, as one of the important endogenous anti-inflammatory proteins, has a core function of blocking the NF-κB signalling pathway. It achieves this through two complementary mechanisms: first, in the TNF signalling pathway, the deubiquitinase domain of A20 selectively removes K63-linked polyubiquitin chains from RIPK1, thereby blocking the recruitment of NEMO (NF-κB essential modulator) by RIPK1, preventing the activation of downstream kinases [49]. Second, the ZnF4 domain of A20 possesses E3 ubiquitin ligase activity, enabling the addition of K48-linked ubiquitin tags to RIPK1, NEMO, and other signalling intermediates. These tags direct the above proteins to the proteasome for degradation, irreversibly blocking the NF-κB signalling process [50-51]. In addition, in the Toll-like receptor (TLR)-induced NF-κB pathway (stimulated by lipopolysaccharide and IL-1β), A20 removes K63 ubiquitin chains from TRAF6 and then impairs IκB kinase complex activity to block NF-κB activation [18,52]. Moreover, after ox-dsDNA stimulation, multiple signalling pathways, including NOD-like receptor, TNF-α, and IL-17 pathways, are upregulated, which can further activate the downstream NF-κB signalling pathway [31,53]. Studies have shown that when the NF-κB signalling pathway is inhibited by BAY11-7082 (a specific inhibitor of the NF-κB pathway), the increase in A20 expression upon ox-dsDNA stimulation is abolished [52]. During the early hyperinflammatory phase of sepsis, A20 senses ox-dsDNA stimulation and is rapidly upregulated, blocking downstream inflammatory cascades, thereby protecting the kidneys from acute injury caused by oxidative stress and excessive inflammation.

2.4 Inhibition of apoptosis and necroptosis

Renal tubular epithelial cell apoptosis is one of the important pathological mechanisms in the development and progression of SA-AKI. A20 protects renal tubular epithelial cells and thus preserves kidney function by interfering with multiple programmed cell death pathways [54]. In death receptor-mediated (e.g., Fas receptor, TNFR1) apoptotic pathways, A20 can inhibit apoptotic signalling by interfering with the formation of the death-inducing signalling complex, which is the activation platform for downstream FADD and caspase-8 [52,55]. Necroptosis is an important form of programmed necrosis in AKI. A20 can deubiquitinate RIPK1 and RIPK3 (the core kinases of necroptosis), removing their K63-linked ubiquitin chains, thereby disrupting the formation of the necrosome (RIPK1-RIPK3 complex) and preventing the phosphorylation and oligomerisation of downstream MLKL, effectively inhibiting necroptosis [9]. As mentioned earlier, A20 also inhibits TNF-induced JNK/p38 MAPK activation, ultimately inhibiting apoptosis. Furthermore, A20 can inhibit ox-dsDNA-induced pyroptosis and STING pathway activation, thereby delaying AKI progression [5].

A20, as a direct inhibitor of multiple inflammation-

and cell death-related signalling pathways, may be a key anti-inflammatory factor in the pathogenesis of SA-AKI, effectively suppressing the immune injury and cytokine storm induced by sepsis. However, there is still a lack of therapeutic methods that can precisely control A20 expression. Therefore, further in-depth research on A20 and potential therapeutic approaches is warranted.

3 Therapeutic strategies targeting A20

Therapeutic strategies targeting A20 represent a field full of potential, and their development is highly dependent on the development of biomarkers. Li et al. [5] developed a P-II peptide, which is currently one of the most promising A20 derivatives. In a mouse model of AKI, the P-II peptide significantly attenuated renal injury and improved mouse survival. This suggests that A20-derived peptides have the potential to be developed into novel anti-inflammatory drugs, but they are still at the preclinical stage. NEK7 is also a promising target; its pro-inflammatory pathway can be inhibited using genetic tools or small molecules that block the NEK7-NLRP3 interaction [5,56]. In addition, there are some natural A20 activators, such as curcumin and resveratrol. These are not derivatives of A20 but have been found to upregulate or activate endogenous A20 expression or function [57]. Currently, these compounds are mainly used as research tools to study A20 function and related biological processes such as inflammation and immunity. Some of them (e.g., curcumin, resveratrol) also exist as dietary supplements, but their specific efficacy in humans and the mechanisms by which they act through A20 require further exploration. Translating basic research findings on A20 into clinical practice should be regarded as a key pathway with greater breakthrough potential and practical significance in future research.

4 Summary and perspectives

At present, although some progress has been made in research on A20 and SA-AKI, unresolved issues remain: translating research findings on A20 into clinical therapeutics and developing A20-related treatment methods while overcoming technical and safety challenges. Furthermore, tailoring personalized treatment strategies based on individual patient differences also merits further consideration and research.

The following aspects can serve as future research directions for A20: developing small-molecule compounds, peptides, or gene therapy drugs that specifically regulate A20 expression or activity, and conducting preclinical and clinical trials to evaluate their efficacy and safety in treating SA-AKI; integrating clinical data and precision medicine concepts to study the relationship between A20 and the severity and prognosis of SA-AKI, thereby providing new therapeutic targets for early diagnosis, risk assessment, and personalised treatment of SA-AKI. It is believed that with continued in-depth research into the relationship between A20 and SA-AKI, new breakthroughs in the clinical treatment of SA-AKI are expected, improving the prognosis of SA-AKI patients.

Conflict of Interest None

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·脓毒症专题·研究进展·

锌指蛋白A20与脓毒症相关急性肾损伤的研究进展

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摘要：脓毒症相关急性肾损伤(SA-AKI)是一种临床常见的危重症，在脓毒症患者中的发病率为40%~50%，且SA-AKI患者的死亡率较单纯的脓毒症患者显著升高，对人类健康构成严重威胁。锌指蛋白A20，亦称肿瘤坏死因子α诱导蛋白3(TNFAIP3)，是一种重要的泛素编辑酶，最初被发现为肿瘤坏死因子α诱导表达的基因，能够负向调控核因子-κB(NF-κB)信号通路，是细胞死亡和炎症反应的关键“刹车”分子。A20是机体重要的内源性抗炎蛋白之一，在炎症反应的调控与细胞存活等方面起着关键作用。A20(由*TNFAIP3*基因编码)作为炎症反应的关键负调控因子，在调控细胞凋亡、抑制炎症级联反应等方面起着不可或缺的作用。同时，A20在SA-AKI中的保护作用逐渐被揭示。本文讨论A20的结构特征、生物学功能、表达调控及其在SA-AKI中的肾脏保护作用机制，并展望了以A20为靶点的新型治疗策略及其临床转化前景，以期为SA-AKI的临床治疗提供新思路。

关键词：锌指蛋白A20/肿瘤坏死因子α诱导蛋白3；脓毒症相关急性肾损伤；NLRP3炎症小体；核因子-κB；炎症反应

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Research progress on zinc finger protein A20 in sepsis-associated acute kidney injury

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Abstract: Sepsis-associated acute kidney injury (SA-AKI) is a frequently encountered critical-care syndrome that complicates 40%-50% of sepsis cases and carries a markedly higher mortality than sepsis alone, representing a major threat to human health. Zinc finger protein A20, also known as tumor necrosis factor alpha-induced protein 3 (TNFAIP3), is an important ubiquitin-editing enzyme. It was originally identified as a gene induced by tumor necrosis factor alpha and can negatively regulate the nuclear factor-κB(NF-κB) signaling pathway, serving as a key "brake" molecule in cell death and inflammatory responses. A20 encoded by the *TNFAIP3* gene is a key negative regulator of inflammation, which is essential for regulating cell apoptosis and suppressing inflammatory cascades. Its protective role in SA-AKI is increasingly recognized. This review delineates the structural features, and biological functions, expression regulation of A20, summarizes current mechanistic insights into its renoprotective actions in SA-AKI, and outlines emerging A20-targeted therapeutic strategies together with their prospects for clinical translation, aiming to provide novel therapeutic avenues for SA-AKI.

Keywords: Zinc finger protein A20/ tumor necrosis factor alpha-induced protein 3; Sepsis-associated acute kidney injury; NLRP3 inflammasome; Nuclear factor -κB; Inflammatory response

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脓毒症相关急性肾损伤(sepsis-associated acute kidney injury，SA-AKI)是临床上常见且凶险的并发症，在急性肾损伤的分期(风险期、损伤期、衰竭期)中，相较于由其他病因导致的急性肾损伤(acute kidney injury，AKI)，SA-AKI的死亡率显著升高，且住院时间更长[1]。SA-AKI的发病机制复杂多样，涉及多种因素，比如肾灌注不足、免疫炎症反应、微循环障碍、肾

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小管细胞凋亡和凝血异常等，其特征是肾功能骤然下降，致使电解质失衡、废物堆积及体液超负荷[2]。在重症监护室（intensive care unit，ICU）患者中，约40%~50%的AKI患者合并脓毒症。一项在24个欧洲国家针对198个ICU的1 177名脓毒症患者开展的前瞻性研究报告显示，AKI的发生率为51%。一项包括146 148名中国患者的回顾性研究表明，有47.1%的脓毒症病例并发了AKI[3]。因此，深入研究SA-AKI的发病机制并寻找有效的治疗靶点具有重要意义。

锌指蛋白A20（zinc finger protein A20，A20），又称肿瘤坏死因子α诱导蛋白3（tumor necrosis factor alpha-induced protein 3，TNFAIP3），是天然免疫和获得性免疫的重要负调控因子，在急性感染中发挥重要作用[4]。越来越多的证据表明，A20参与了SA-AKI的病理生理过程，通过调节炎症反应、细胞凋亡等机制影响SA-AKI的发生发展，有望成为SA-AKI治疗的新靶点[5]。本文综述A20的结构特征、生物学功能、表达调控及其在SA-AKI中的作用机制，展望以A20为靶点的新型治疗策略及其临床转化前景。

1 A20的结构与功能

1.1 A20的结构特征 A20蛋白由*TNFAIP3*基因编码，该基因位于人类6号染色体短臂（6q23.3），其DNA序列总长10.5 kb，由10段外显子与9段内含子交替构成。A20的分子量是89 613.9，等电点8.61，分子式为$C_{3897}H_{6108}N_{1152}O_{1162}S_{60}$，其中酸性残基（天冬氨酸、谷氨酸）共87个，碱性残基（精氨酸、赖氨酸）共102个[6]。A20的cDNA全长4 440 bp，其中编码区占2 370 bp，可翻译出一条含790个氨基酸、表观分子量约90 000的多肽链[7]。A20蛋白包含多个功能结构域，使其能够参与复杂的泛素相关调控过程。其N末端具有卵巢肿瘤相关蛋白酶（ovarian tumor-related proteases，OTU）去泛素化酶结构域，负责去除赖氨酸（lysine，K）63连接的泛素链；C末端含有锌指结构域，其C端第四个锌指结构域（ZnF_4）具有E3泛素连接酶活性，主要添加K48连接的泛素链标记目标蛋白用于蛋白酶体降解，而C端第七个锌指结构域（ZnF_7）基序以其对蛋氨酸1（M1）链的亲和力而闻名，在泛素结合中起非催化但至关重要的作用，显著促进核因子-κB（nuclear factor kappa-B，NF-κB）信号通路的下调[8-9]。这种独特的结构使A20能够通过“编辑”泛素链的方式精密调控信号通路的活性和持续时间。

1.2 A20的表达与调控 A20是关键免疫调节蛋白，其表达呈现高度可调控的特征。研究表明在生理状态下，正常机体A20蛋白的表达水平较低，当炎症因子如肿瘤坏死因子（tumor necrosis factor，TNF）-α、氧化自身DNA（oxidized self-DNA，ox-self-DNA）等刺激机体时，激活NF-κB信号通路，活化后的NF-κB RelA/p50复合物直接结合A20启动子双κB位点，使得A20的表达水平迅速升高，A20借助其去泛素化酶活性与锌指结构抑制NF-κB信号通路，从而形成负反馈调节环路[10-14]。此外，A20还受到启动子甲基化、组蛋白甲基化等表观遗传机制的调控，以及微小RNA（microRNA，miR）-125a/b、miR-29、miR-19、miR-221、let-7等的精细负调控，组成多方面负反馈网络，抑制过度的炎症反应[5]。

1.3 A20的免疫平衡功能 A20在免疫稳态的维持中发挥着关键作用。它不仅能通过抑制NF-κB信号通路，减少促炎细胞因子[如TNF-α、白细胞介素（interleukin，IL）-1β、IL-6]的释放，还能直接调控核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体3（nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3，NLRP3）炎症小体的组装和激活，抑制胱天蛋白酶-1（caspase-1）依赖的细胞焦亡[14]。A20也可以通过调节凋亡相关信号通路，抑制细胞凋亡。Won等[15]的研究表明，A20通过其ZnF_4结构域直接结合并给凋亡信号调节激酶1（apoptosis signal-regulating kinase 1，ASK1）添加K48连接的多聚泛素链，促使ASK1经蛋白酶体降解，从而阻断TNF诱导的Jun氨基末端激酶/p38丝裂原活化蛋白激酶（c-Jun N-terminal kinase/p38 mitogen activated protein kinase，JNK/p38 MAPK）激活，最终抑制细胞凋亡。因此，A20是一种重要的抗细胞凋亡蛋白，通过抑制NF-κB、JNK/p38等多条下游通路保护细胞免受TNF诱导的凋亡。同时，A20作为一种重要的泛素编辑酶，可调节干扰素基因刺激因子（stimulator of interferon gene，STING）的活性，负向调节STING介导的Ⅰ型干扰素（type Ⅰ interferon，IFN-Ⅰ）产生通路，从而抑制炎症反应[16-17]。此外，A20还通过其去泛素化酶活性去除自噬相关蛋白Beclin-1上的K63泛素链，从而抑制炎症信号诱导的自噬过度激活，保护肾脏细胞免于脓毒症引发的严重损伤和功能障碍[18-19]。

2 A20在SA-AKI中的保护作用机制

2.1 抑制NLRP3炎症小体介导的细胞焦亡 NLRP3炎症小体是细胞应激与环境刺激的胞质感受器，作为整合多种信号、感知细胞失衡状态的关键节点，NLRP3炎症小体可被多种微生物或无菌刺激激活，如细菌毒素、胞外ATP及氧化DNA（oxidized dsDNA，ox-dsDNA）[20-24]。NLRP3炎症小体是由受体蛋白NLRP3蛋白、含有caspase募集结构域的凋亡相关斑点样蛋白（apoptosis-associated speck-like protein containing a CARD，ASC）和效应蛋白caspase-1前体构成，主要存在于免疫和炎症细胞的细胞质，介导细胞因子的成熟、释放及细胞焦亡[25]。它的激活大致分为两个阶段：启动和激活。启动阶段的标志是NLRP3和IL-1β前体表达的上调，由NF-κB信号通路的激活驱动。反过来，NLRP3的激活由钾外排和/或线粒体变化促进，从而实现随后的信号传导[26-27]。随后，丝/苏氨酸激酶—永离有丝分裂基因A相关激酶7（never in mitosis gene A-related kinase 7，NEK7）直接与NLRP3结合，调控其寡聚与活化[28]。因此，NLRP3炎症小体相关疾病的潜在干预靶点是NEK7[29]。对数据库的分析表明，与脓毒症进展相关的细胞中NEK7显著增加，脓毒症患者的髓系细胞中NEK7的表达水平升高。因此，NEK7的表达在脓毒症中具有至关重要的临床意义[30]。

在脓毒症患者中，过度活化的免疫细胞以及组织缺血再灌注损伤，共同导致体内活性氧（reactive oxygen species，ROS）水平激增。这些过量的ROS会造成DNA氧化损伤，从而生成大量的ox-dsDNA[31-32]。研究表明，在ox-dsDNA的刺激下，A20

和NEK7之间的结合作用会显著增强，A20可直接与NEK7结合，介导其K48连接的泛素化，从而通过靶向NEK7进行蛋白酶体的降解[33]。ox-dsDNA的组成部分8-羟基脱氧鸟苷可以激活NLRP3炎性小体，将ox-dsDNA视为NLRP3的内源性配体之一[23,31]。这种激活最终导致具有ASC的炎症小体组装，促进半胱天冬氨酸蛋白酶-1的自我裂解和成熟。这个过程随后导致焦亡蛋白D(gasdermin D，GSDMD)的裂解，诱导细胞焦亡[34-35]。A20通过OTU结构域和/或ZnF_4和ZnF_7基序的协同效应破坏NEK7与NLRP3复合物的结合，从而抑制NLRP3炎症小体的组装与激活[14]。抑制NLRP3后，减少半胱天冬氨酸蛋白酶-1介导的GSDMD裂解，抑制细胞焦亡，减轻肾组织炎症和损伤[27]。此外，A20不仅通过其OTU去泛素化酶活性移除泛素连接酶—TNF受体相关因子(TNF receptor-associated factors，TRAF)6/受体相互作用蛋白激酶1(receptor-interacting protein kinase 1，RIPK1)的K63泛素链，并且以E3泛素连接酶活性催化K48泛素化促使这些信号分子降解，抑制NF-κB激活，进而抑制NLRP3炎症小体活化，减轻炎症反应[16]；A20还通过限制IL-1β前复合物的K63连接泛素化来抑制NLRP3的自发激活[36]。Yu等[33]研究表明A20衍生肽(P-Ⅱ肽)显著提高了脂多糖处理的小鼠的存活率。这些数据表明NEK7是治疗NLRP3介导的疾病(如脓毒症)的有希望的靶点。利用A20衍生肽和遗传方法干扰巨噬细胞中的NEK7功能，可以显著抑制细胞焦亡并延缓脓毒症的进程。

2.2　*抑制环鸟苷酸-腺苷酸合成酶(cyclic GMP-AMP synthase，cGAS)-STING通路介导的炎症反应*　cGAS-STING信号通路是先天免疫轴心感知细胞质DNA的关键，负责识别病原体或自身损伤释放的双链DNA，并触发IFN-Ⅰ及促炎因子的表达[37-39]。研究表明患者体内STING通路的激活与肾小管炎症加剧和SA-AKI进展有关[40]。在SA-AKI患者中，由于缺血、缺氧、内毒素及炎症因子等因素的影响，ox-dsDNA在体内积聚，ox-dsDNA被cGAS识别后催化生成2′3′-cGAMP，结合并诱导STING转位，激活cGAS-STING通路，迅速提升磷酸化TANK结合激酶1(TANK binding kinase 1，TBK1)、磷酸化干扰素调节因子3(interferon regulatory factor 3，IRF3)、磷酸化信号转导和转录激活蛋白1(phosphorylate signal transducer and activator of transcription，p-STAT1)及IFN-β、TNF-α、IL-6的mRNA与蛋白水平，驱动IFN-Ⅰ与促炎因子风暴的发生[41-45]。此外，氧化修饰使自身DNA抵抗核酸外切酶降解，并增强STING依赖性免疫传感，从而放大了炎症反应[46]。

A20可通过其OTU去泛素化酶结构域选择性地切除STING及其适配蛋白TRAF3/6上的K63连接泛素链，阻断TBK1的招募与磷酸化激活，从而防止STING通路过度激活，限制炎症因子风暴对机体造成的损害[47]。研究表明，A20缺失会显著增强STING通路活性，而A20过表达或外源性补充(如P-Ⅱ肽)可逆转这一过程[5]。

2.3　*抑制NF-κB通路的激活*　NF-κB是一种由Rel家族亚基构成的二聚体转录因子。NF-κB可被脂多糖、TNF、IL-1、IL-17等激活，是一种众所周知的信号通路，在诱导许多参与炎症反应的细胞因子(如IL-1、IL-6和TNF)中起着重要作用[48]。在受体触发后，通过一系列的信号通路释放的NF-κB迅速核转位，结合κB位点启动TNF-α、IL-6等促炎基因转录，完成经典NF-κB信号通路的级联放大[49]。因此，抑制NF-κB激活被认为是一种潜在的治疗方法，因为它能够减少促炎细胞因子。

A20作为重要的内源性抗炎蛋白之一，其核心功能是阻断NF-κB信号通路。它通过两种互补机制实现这一功能：首先，在TNF信号通路中，A20的去泛素化结构域会选择性地切除RIPK1上的K63连接的多聚泛素链，可阻断RIPK1招募NF-κB必需调节蛋白(NF-κB essential modulator，NEMO)，从而使下游激酶无法被激活[49]。其次，A20的ZnF4具有E3泛素连接酶活性，能够添加K48型连接的泛素标记到RIPK1、NEMO及其他信号中间分子中，这些标记会使上述蛋白质转运至蛋白酶体降解，从而不可逆地阻断NF-κB信号传递过程[50-51]。另外，在Toll样受体(Toll-like receptor，TLR)诱导的NF-κB通路中(由于脂多糖和IL-1β刺激)，A20可以去除TRAF6上的K63泛素链，然后损害NF-κB抑制蛋白激酶复合物活性以阻断NF-κB的激活[18,52]。此外，在ox-dsDNA刺激后，包括NOD样受体、TNF-α和IL-17信号通路在内的多种信号通路被上调，这些通路可以进一步激活下游NF-κB信号通路[31,53]。研究表明，当NF-κB信号通路被BAY11-7082(NF-κB信号通路的特异性抑制剂)抑制时，ox-dsDNA刺激下A20的表达增加被消除[52]。在脓毒症早期过度炎症阶段，A20通过感知ox-dsDNA刺激并快速上调，阻断下游炎症级联反应，从而保护肾脏免受氧化应激与过度炎症导致的急性损伤。

2.4　*抑制细胞凋亡和程序性坏死*　肾小管上皮细胞凋亡是SA-AKI发生发展的重要病理机制之一。A20通过干预多种程序性死亡途径来保护肾小管上皮细胞，从而保护肾脏功能[54]。在死亡受体(如Fas受体、TNF受体1)介导的凋亡通路中，A20可以通过干扰下游Fas相关死亡结构域蛋白和caspase-8的激活平台—死亡诱导信号复合体的形成，来抑制凋亡信号传导[52,55]。坏死性凋亡是AKI中一种重要的程序性坏死形式。A20可以通过去泛素化RIPK1和RIPK3(坏死性凋亡的核心激酶)，移除其K63连接的泛素链，从而破坏坏死小体(RIPK1-RIPK3复合物)的形成，阻止下游混合谱系激酶域样蛋白的磷酸化和寡聚化，从而有效抑制细胞坏死性凋亡[9]。如前所述，A20还可通过阻断TNF诱导的JNK/p38 MAPK激活，最终抑制细胞凋亡。此外，A20可抑制ox-dsDNA诱导的细胞焦亡和STING通路激活进而延缓AKI的进展[5]。

A20作为多种炎症和细胞死亡相关信号通路的直接抑制蛋白，可能是SA-AKI发病机制的关键抗炎因子之一，能有效抑制脓毒症引起的免疫损伤和炎症风暴。然而，目前仍缺乏能够精确控制A20表达的治疗方法。因此，应进一步深入研究A20以及潜在的治疗方法。

3　靶向A20的治疗策略

靶向A20的治疗策略是充满潜力的领域，其发展高度依

赖于生物标志物的开发。Li等[5]开发了一种P-Ⅱ肽，这是目前最有前景的A20衍生物之一。在小鼠的AKI模型中，P-Ⅱ肽显著减轻了小鼠的肾脏损伤，并提高了小鼠的存活率。这表明A20衍生肽具有研发为新型抗炎药物的潜力，但目前仍处于临床前研究阶段。NEK7同样是具有前途的靶点之一，可通过遗传学工具或小分子(阻断NEK7-NLRP3相互作用)来抑制其促炎通路[5,56]。此外，还有一些天然来源的A20激活剂，如姜黄素、白藜芦醇等，它们并非是A20的衍生物，而是被研究发现能够上调或激活细胞内A20表达或功能的化合物[57]。目前，这些物质主要作为科研工具，用于研究A20的功能和相关的炎症、免疫等生物学过程。其中一些(如姜黄素、白藜芦醇)也作为膳食补充剂存在，但对人体的具体效能和通过A20起作用的机制还需进一步探索。目前，将A20的基础研究成果转化为临床实践，应被视为未来研究中更具突破潜力和实际意义的关键路径。

4 总结与展望

目前，针对A20与SA-AKI的研究虽获得了一定的进展，但仍存在未解决的问题：将A20的研究成果转变为临床治疗药物、开发A20相关的治疗方法，同时需要攻克技术与安全性方面的难题。此外，根据患者的个体化差异制定个性化的治疗方案，也值得进一步深思与研究。

下述几方面可以作为A20未来的研究方向：开发能特异性调节A20表达或活性的小分子化合物、多肽或基因治疗药物，并进行临床前和临床试验，评估其治疗SA-AKI的有效性和安全性；结合临床数据和精准医学理念，研究A20与SA-AKI病情严重程度及预后的关系，为SA-AKI的早期诊断、风险评估及个体化治疗提供新的治疗靶点。相信随着对A20与SA-AKI关系研究的不断深入，有望为SA-AKI的临床治疗带来新的突破，改善SA-AKI患者的预后。

利益冲突 无

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