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中性粒细胞胞外诱捕网在动脉粥样硬化血栓中的研究进展

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摘 要:动脉粥样硬化(atherosclerosis,AS)是心血管疾病死亡的主要病理基础,与炎症反应密切相关。中性粒细胞通过释放中性粒细胞胞外诱捕网(neutrophil extracellular traps,NETs)在AS全过程中发挥着多种效应:(1)在疾病的起始阶段加重内皮细胞损伤、促进脂质沉积和炎症持续放大;(2)进展期驱动血管平滑肌细胞表型转化和斑块坏死核心扩大;(3)并发症阶段通过介导血管钙化及促炎微环境直接参与斑块破裂事件,并通过激活血小板、触发凝血级联反应及抑制纤溶系统加剧血栓形成风险。本文系统综述NETs的组成、形成机制及其在AS中的作用,并探讨靶向NETs的治疗潜力。

关键词:动脉粥样硬化;中性粒细胞胞外诱捕网;血栓形成
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Neutrophil extracellular traps in atherothrombosis

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Abstract: Atherosclerosis, the primary pathological foundation of cardiovascular mortality worldwide, is deeply intertwined with chronic inflammatory processes. In recent years, neutrophils have been recognized as pivotal contributors to all stages of atherosclerotic cardiovascular disease (ASCVD), largely through the release of neutrophil extracellular traps (NETs). These web-like structures, composed of decondensed chromatin, citrullinated histones (e.g., H3), and granular proteins such as neutrophil elastase (NE) and myeloperoxidase (MPO), are generated via a regulated form of cell death termed NETosis. This review aims to systematically synthesize contemporary understanding of the molecular composition and regulatory mechanisms governing NET formation. Furthermore, it seeks to elucidate the multifaceted and stage-specific pathogenic roles of NETs throughout the initiation, progression, and thrombotic complications of atherosclerosis. Finally, the review critically assesses the emerging diagnostic and therapeutic potential of targeting NETs in atherothrombosis. NET formation is driven by multiple synergistic pathways. Central mechanisms include activation of the NADPH oxidase/reactive oxygen species (ROS) axis, engagement of pattern recognition receptors (e.g., TLR2/4) by oxidized low-density lipoprotein (oxLDL), NLRP3 inflammasome activation, and mitochondrial dysfunction involving mitochondrial DNA (mtDNA) release and subsequent cGAS-STING pathway stimulation. External cues, such as low shear stress sensed via the Piezo1 mechanoreceptor and extracellular vesicles carrying oxidative epitopes (e.g., malondialdehyde) from ruptured plaques, further potentiate NETosis. Several cardiovascular risk factors—including dyslipidemia, hyperglycemia, specific genetic variants, and environmental exposures—have been shown to upregulate NET formation, thereby accelerating atherosclerotic pathogenesis. During plaque initiation, NETs exacerbate endothelial injury through the release of cytotoxic histones and proteases, promoting LDL oxidation to pro-inflammatory oxLDL and amplifying early inflammatory cascades. This is achieved partly by activating interferon responses in plasmacytoid dendritic cells and the NLRP3 inflammasome in macrophages, thereby facilitating monocyte recruitment and foam cell formation. In the progression phase, NETs contribute to plaque growth

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and destabilization. They promote phenotypic switching of vascular smooth muscle cells toward a pro-inflammatory, migratory state. Additionally, NET components, particularly citrullinated histone H3, induce macrophage pyroptosis via both caspase-1/GSDMD and caspase-3/GSDME pathways. This highly inflammatory form of cell death expands the necrotic core and sustains a vicious cycle of inflammation within the evolving plaque. At the complication stage, NETs directly precipitate plaque rupture and acute thrombosis. They degrade the extracellular matrix and thin the fibrous cap by secreting matrix metalloproteinases and inducing vascular smooth muscle cell death. Furthermore, NETs establish a potent prothrombotic milieu: their DNA and histones activate platelets, provide a scaffold for trapping circulating blood cells, concurrently activate the intrinsic and extrinsic coagulation pathways, and impair endogenous fibrinolysis. The clinical relevance of NETs is underscored by their promise as biomarkers. Circulating components such as dsDNA, MPO-DNA complexes, and citrullinated histone H3 correlate with disease severity, plaque vulnerability, and thrombotic risk. Therapeutically, strategies are evolving along two fronts: inhibiting NET formation and clearing existing NETs. Promising approaches include PAD4 inhibitors, NLRP3 inflammasome blockers, DNase I to digest NET scaffolds, and histone-neutralizing antibodies. Notably, several compounds derived from traditional Chinese medicine—such as Paeonol and Guizhi Tongluo Tablets—have demonstrated efficacy in inhibiting NETosis and mitigating atherosclerosis in preclinical models, offering novel multi-target interventional perspectives. In conclusion, NETs represent a critical effector mechanism linking innate immunity, chronic inflammation, and thrombosis in atherosclerosis. Their dynamic involvement across the disease continuum highlights their dual utility as promising biomarkers and therapeutic targets. Future research should prioritize several key areas: elucidating the crosstalk between NETs and other immune cells within the plaque microenvironment; developing selective NETosis inhibitors that preserve essential host-defense functions; validating NET-based biomarker panels in large-scale clinical cohorts for improved risk stratification; exploring combinatorial regimens that integrate NET-targeted therapies with established pharmacological agents; and investigating the specific role of NETs in distinct clinical phenotypes of atherosclerosis to pave the way for personalized treatment strategies in ASCVD.

Key words: atherosclerosis; neutrophil extracellular traps; thrombosis

动脉粥样硬化性心血管疾病(atherosclerotic cardiovascular disease,ASCVD)是世界范围内导致死亡的主要原因,严重危害人类的健康[1]。动脉粥样硬化(atherosclerosis,AS)是一种以动脉内膜脂质沉积、慢性炎症反应为核心机制的慢性进展性血管病变。炎症反应在动脉粥样硬化发展进程中发挥关键的作用。CANTOS试验首次证实独立于血脂的抗炎治疗可降低心血管风险[2],秋水仙碱在冠心病二级预防中可降低20%~25%的心血管事件风险,已被欧美的临床指南推荐[3,4]。目前对炎症在动脉粥样硬化中的机制研究正逐渐转向特异性免疫细胞,这为开发新型治疗策略铺平了道路。

在过去的研究中,巨噬细胞的作用和机制在动脉粥样硬化中受到了广泛关注[5],而巨噬细胞往往需要与中性粒细胞协同发挥作用。直到如今,人们对中性粒细胞的研究要少得多[2]。哥本哈根人群和英国生物银行的研究发现,循环中性粒细胞是ASCVD的因果危险因素,中性粒细胞计数可作为心血管疾病可靠的预测指标[6,7]。动物研究显示,中性粒细胞除了通过分泌趋化因子如CCL2,调节单核-巨噬细胞的募集和分化、激活巨噬细胞外[8],还能够通过释放中性粒细胞胞外诱捕网(neutrophil extracellular traps,NETs)促进斑块不稳定、加重血管炎症、促进血栓形成等深度参与ASCVD的病理过程。本文回顾了NETs在动脉粥样硬化中的研究进展,并探讨针对NETs治疗动脉粥样硬化的潜在措施。

1 中性粒细胞胞外诱捕网

NETs的核心成分主要包括DNA、组蛋白、颗粒蛋白以及其他调节蛋白等。这些成分相互协作,共同赋予了NETs独特的结构和功能。NETs骨架由解聚后的染色质构成,组蛋白如H2A、H2B、H3、H4作为核小体的核心组分,与DNA 紧密结合形成网状纤维结构[9]。肽基精氨酸脱亚胺酶4(peptide arginine deaminase 4,PAD4)催化组蛋白H3的瓜氨酸化,在绝大多数NETs的形成中起重要作用[10]。中性粒细胞弹性蛋白酶(neutrophil elastase,NE)作为颗粒蛋白在NETs形成过程中参与染色质解聚和抗菌作用;髓过氧化物酶(myeloperoxidase,MPO)与NE协同作用,促进DNA释放并增强NETs的杀菌能力。此外,其他调节蛋白如高迁移率族蛋白B1(high mobility group box 1 protein,HMGB1)可促进炎症反应和维持NETs的稳定性[11];基质金属蛋

白酶（matrix metalloproteinases，MMPs）可参与组织重塑和炎症扩散[12]。

2 NETs在动脉粥样硬化中的动态调控与病理效应

2.1 NETs的形成机制

NETs的形成是一个多途径协同作用的过程。（1）在中性粒细胞内部，NADPH氧化酶/活性氧（reactive oxygen species，ROS）通路通过ROS激活PAD4，诱导组蛋白瓜氨酸化并驱动染色质解聚，启动NETosis[13]；在Toll样受体（Toll-like receptor，TLR）信号通路中，氧化低密度脂蛋白（oxidized low density lipoprotein，oxLDL）等损伤相关分子模式经TLR2/4激活MyD88-NF-κB轴，促进IL-8、IL-1β等促炎因子释放，从而触发NETs形成[14]；NLRP3炎症小体被胆固醇结晶激活后，通过Caspase-1切割IL-1β前体生成活性IL-1β，进一步募集中性粒细胞并增强NETs生成[15]。此外，组蛋白去乙酰化酶抑制剂可剂量依赖性调控组蛋白乙酰化水平，低浓度促进NETosis，高浓度抑制NETosis并诱导凋亡[16]。（2）线粒体相关机制：自噬缺陷导致的线粒体ROS积累可通过激活PAD4加剧NETosis[17]；补体C5a通过结合C5aR1受体抑制线粒体STAT3活性，诱导线粒体ROS积累并促进NETs释放[18]；而线粒体DNA（mitochondrial DNA，mtDNA）释放至胞质后，通过激活cGAS-STING通路，触发NF-κB和I型干扰素（type I interferons，IFN-I）信号，协同促进中性粒细胞活化与NETosis[19]。（3）细胞内外的调控：血管平滑肌细胞通过PI3K/Akt通路介导的巨胞饮和吞噬作用摄取胆固醇晶体，分泌IL-33以增强中性粒细胞ROS生成及NETs形成[20]；而细胞外囊泡（extracellular vesicles，EVs）与传统NETs形成不同，在急性心肌梗死的病理过程中，冠状动脉斑块破裂会释放大量携带氧化特异性表位如丙二醛（malondialdehyde，MDA）的EVs，在斑块破裂部位显著富集，通过激活TLR4-PAD4通路驱动中性粒细胞NETosis，并形成动态的NETs调控网络，显著加速动脉粥样硬化的病理进程[21,22]。目前，NETs与T细胞、肥大细胞之间的交互作用已在银屑病、黑色素瘤等多种疾病的研究中得到报道，并可能参与AS的进展，但其具体分子机制尚未完全阐明，仍需进一步深入探究。

2.2 危险因素促进动脉粥样硬化中NETs的形成

在AS中，NETs含量的增加与AS病变进展有关，这一过程受代谢、基因、环境等多种复杂因素共同影响。

在代谢性因素中，脂质代谢异常可调控中性粒细胞重编程，促进AS疾病的进展。近期在*Nature*发表的一项研究表明，交替高脂饮食通过IL-1β依赖性中性粒细胞重编程，导致循环中性粒细胞增多并释放NETs，与持续性高脂饮食相比显著增加动脉粥样硬化斑块中NETs含量，同时促进斑块内炎症因子的产生[23]。此外，在糖尿病相关的AS中，高血糖通过激活固有免疫系统促进中性粒细胞活化及NETs释放，加速AS的早期病变[11]。NETs与糖基化终末产物相互作用，通过激活巨噬细胞炎症小体和促进糖酵解途径，加剧斑块炎症反应，进一步削弱斑块的稳定性[24]，深度参与了AS的发生发展过程。

在相关基因突变中，*LNK*造血调控基因的功能缺失可通过氧化磷脂依赖的方式促进NETosis和动脉血栓形成，升高携带突变个体的冠心病风险[25]。近期研究发现，不明原因克隆造血*JAK2 V617F*基因突变携带者的中性粒细胞表达更高水平的CD44和CD177，中性粒细胞在受损血管壁表现出更强的黏附、迁移和NETs形成能力，加剧了AS局部炎症反应[26]。另一项研究表明，*PTAFR*基因编码的血小板活化因子受体通过激活PKC信号通路驱动中性粒细胞NETosis，增强AS炎症微环境氧化应激及斑块基质降解[27]。

当血管发生炎症反应或狭窄时，血流剪切应力变化可促进中性粒细胞形成NETs。低剪切应力可通过Piezo1-HDAC2-ROS轴促进NETs形成，进而加剧AS[28]。另一项研究表明，短期低剂量电离辐射可减少NETs释放，对AS有一定的保护作用。低剂量电离辐射的*ApoE*基因敲除小鼠血浆中NETs的浓度较非辐射组显著降低。在高脂饮食诱导的动脉粥样硬化小鼠模型中，电离辐射使主动脉斑块面积较对照组减少34.2%，表明低剂量辐射通过抑制NETs释放发挥抗AS的作用[29]。此外，健康个体在臭氧暴露量升高时，体内NETs水平显著上升，同时伴随D-二聚体、凝血酶-抗凝血酶复合物等与AS密切相关的促血栓形成生物标志物水平升高，这意味着臭氧暴露极有可能通过提升体内NETs水平，进而激活免疫性血栓形成，参与AS的进展[30]。

2.3 NETs在动脉粥样硬化起始阶段

在AS起始阶段，多种刺激激活内皮细胞启动

白细胞募集。单核细胞迁移至动脉管壁并分化为巨噬细胞，吞噬修饰脂蛋白形成泡沫细胞，其增殖与炎症因子分泌形成正反馈，促进斑块进展及慢性炎症[31]。中性粒细胞则通过释放NETs加重内皮细胞损伤、促进脂质沉积和炎症持续放大参与AS进程(图 1A)。

在内皮细胞损伤的机制中，NETs通过释放瓜氨酸化组蛋白H3和蛋白酶MPO、NE等成分直接对内皮细胞造成损伤[2,32]，促进黏附分子的表达进而招募炎性细胞，形成“NETs形成-内皮损伤-炎症细胞募集”的正反馈循环。

在脂质沉积过程中，NETs可通过核心成分中的MPO催化LDL氧化修饰，产生具有促炎作用的oxLDL[33]，使得巨噬细胞对脂质的摄取能力增强，形成泡沫细胞。与此同时，oxLDL也可通过降低中性粒细胞中囊性纤维化跨膜电导调节因子的表达，导致胞内氯离子浓度升高，进而激活氯离子敏感的SGK1信号通路，增强NETs的形成[34]。由此，oxLDL与NETs两者之间形成恶性循环，促进AS的不断进展。除此之外，oxLDL可通过激活中性粒细胞内的NLRP3炎症小体，促进NETs释放，加剧动脉壁炎症和斑块进展[35]。

在炎症持续放大的机制中，NETs或死亡细胞产生的DNA与中性粒细胞产生的颗粒蛋白共同激活血管壁中的浆细胞样树突状细胞，引发强烈的IFN-I反应，通过JAK/STAT通路增强巨噬细胞对oxLDL的摄取，上调清道夫受体表达，加速泡沫细胞的形成[14,36]。此外，NETs中的mtDNA激活巨噬细胞的NLRP3炎症小体，释放IL-1β和IL-18，驱动慢性炎症[37]。这些促炎因子大量释放，进一步加剧炎症反应，为后续病变持续进展提供可能。

2.4 NETs在动脉粥样硬化的进展阶段

在AS的发展过程中，大量的泡沫细胞不断积累，逐渐融合形成脂质核心。在此过程中，泡沫细胞在氧化应激与炎症微环境的作用下，可通过凋亡、坏死等多种细胞死亡方式，进一步促进细胞内脂质的释放与累积。而斑块内平滑肌表型转化、斑块坏死核心扩大与动脉粥样硬化斑块进展密切相关，其中NETs作为独特的炎症介质和细胞外结构，参与AS的进展(图 1B)。

NETs释放的NE可通过降解血管平滑肌细胞(vascular smooth muscle cells，VSMCs)表面TLR4的胞外域，使游离的TIR结构域激活下游促炎基因表达，进而增强VSMCs的迁移能力，促进其向血管内膜下异常迁移。与此同时，NETs中的NE与DNA/组蛋白等成分协同作用，激活VSMCs分泌炎症因子如IL-6等，形成促迁移的炎症微环境[38]。

NETs中的抗菌肽和蛋白酶吸引单核细胞和巨噬细胞至斑块部位，促进炎症浸润[39]。NETs通过释放瓜氨酸化组蛋白H3与泡沫细胞表面的NLRP3直接结合，激活下游的caspase-1依赖的炎症通路，促进泡沫细胞分泌TNF-α、IL-1β等炎症介质，加剧斑块内炎症，推动AS的进展[40]。除此之外，NETs通过诱导巨噬细胞焦亡促进斑块内坏死核心形成。NETs释放的瓜氨酸化组蛋白H3和DNA可激活巨噬细胞内的模式识别受体，触发NLRP3炎症小体组装，进而激活caspase-1，切割GSDMD形成膜孔，导致细胞焦亡[41,42]。此外，NETs中的MPO和ROS可通过氧化应激途径激活STAT3，促进GSDME转录。GSDME被caspase-3剪切后形成膜孔，将凋亡信号转化为焦亡，释放IL-1β、IL-18等促炎因子，加剧炎症和坏死核心扩张[41]。

2.5 NETs在动脉粥样硬化并发症阶段

多种因素如血流动力学的改变、炎症反应的加剧以及血管痉挛等，可成为斑块破裂的触发因素，会限制细胞间质胶原蛋白的产生，并升高胶原溶解酶的活性，使原本薄弱的纤维帽发生破裂，引发血栓形成。在此过程中，NETs可通过促进血管钙化和炎症微环境等机制参与斑块破裂，进而引发血小板活化、凝血级联反应激活以及纤溶抑制等一系列反应(图 1C)。

2.5.1 斑块破裂

既往研究中证实NETs可通过释放钙结合蛋白，如钙卫蛋白S100A8/A9，促进血管钙化，降低斑块机械稳定性[43]。此外，NETs通过NE和MMPs降解细胞外基质(extracellular matrix，ECM)，抑制平滑肌细胞的收缩表型，促进收缩型平滑肌细胞向合成型平滑肌细胞转化，导致纤维帽变薄[44]。在此过程中，NETs分泌的MMPs降解纤维帽中的胶原，削弱斑块稳定性，增加破裂风险[45]。2024年，在Nature上发表的研究表明，在动脉粥样硬化小鼠模型中，卒中后中性粒细胞NETosis显著增加，其释放的NET-DNA通过激活斑块内巨噬细胞的AIM2炎症小体，诱导IL-1β分泌并上调MMP-2和MMP-9的表达。进一步研究证实，卒中后MMPs活性增强导致斑块

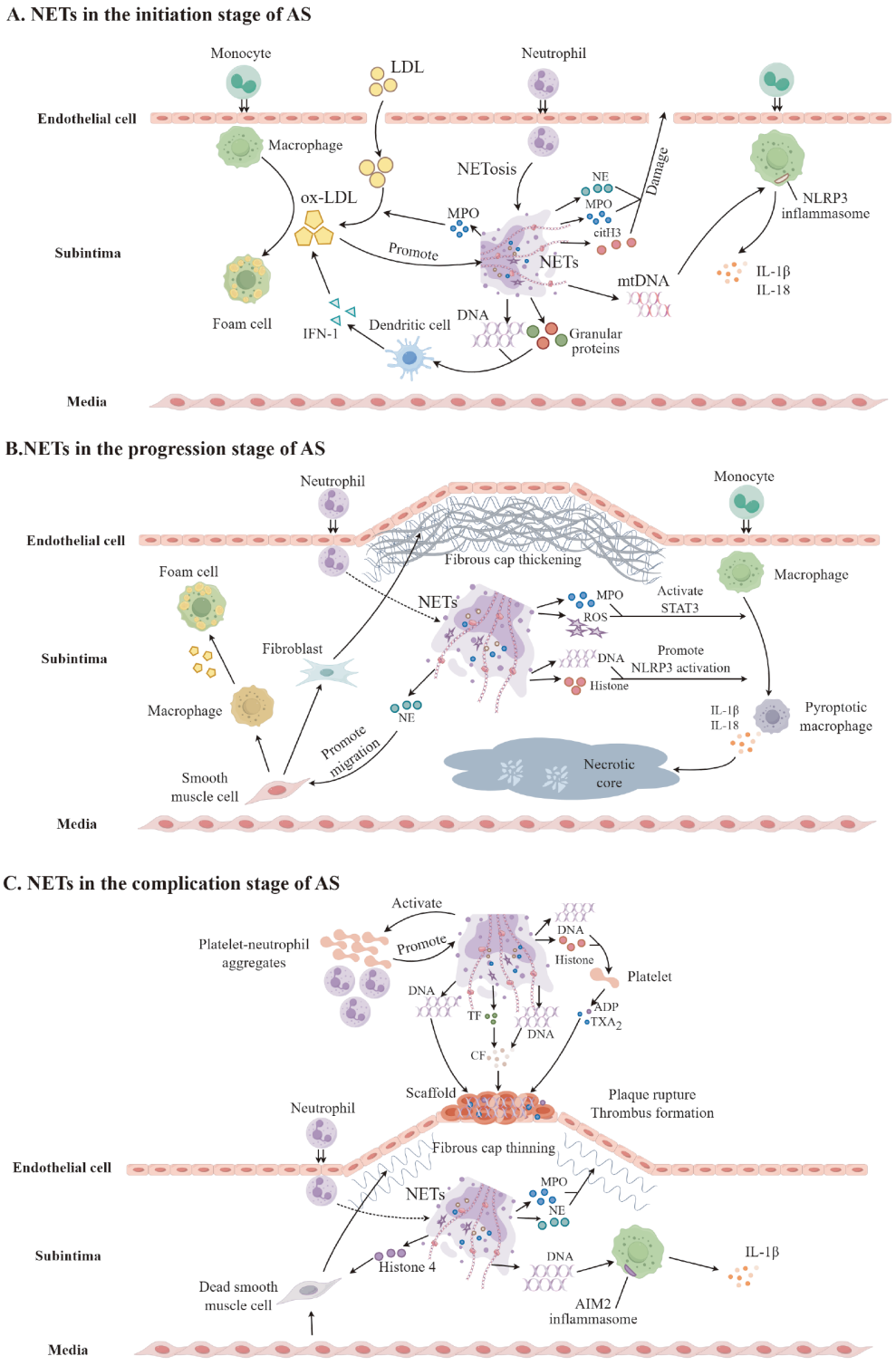

图 1　NETs在动脉粥样硬化中的作用

（A）NETs在AS起始阶段；（B）NETs在AS进展阶段；（C）NETs在AS并发症阶段。citH3，citrullinated histone H3，瓜氨酸化组蛋白H3；NE，neutrophil elastase，中性粒细胞弹性蛋白酶；MPO，myeloperoxidase，髓过氧化物酶；MMP，matrix metalloproteinase，基质金属蛋白酶；TXA_2，thromboxane A_2，血栓素A_2；TF，tissue factor，组织因子；CF，coagulation factor，凝血因子。（本图由Figdraw绘制）

Figure 1 Role of NETs in atherosclerosis

(A) Initiation: NETs promote endothelial injury, LDL oxidation, and early inflammation. (B) Progression: NETs drive VSMC phenotypic switching and macrophage pyroptosis, expanding the necrotic core. (C) Complication: NETs facilitate plaque rupture by matrix degradation and trigger atherothrombosis via platelet activation and coagulation.

ECM中胶原纤维的异常降解和结构紊乱，进而使纤维帽厚度减小、机械稳定性降低，最终促进斑块破裂及继发性动脉血栓形成风险升高[46]。此外，NETs通过释放组蛋白H4诱导平滑肌细胞的溶解性死亡，平滑肌细胞的减少导致纤维帽胶原含量减少、厚度降低，斑块结构被破坏，促进斑块破裂[47]。

2.5.2 血栓形成

斑块破裂后暴露促凝物质触发急性血栓形成，同时NETs激活补体系统释放IL-1β，加剧内皮损伤并促进白细胞募集[48]。随后，NETs的组蛋白和DNA结合血小板TLR4和GPVI受体，激活MAPK/ERK信号通路并释放血栓素A_2和二磷酸腺苷，驱动血小板聚集，招募更多血小板、红细胞和纤维蛋白原，导致血管堵塞[49]。与此同时，NETs的DNA网状结构可捕获红细胞、血小板和凝血因子[21]，形成血栓核心。NETs释放的组织因子与凝血因子VIIa结合启动外源性凝血，而NETs的DNA激活凝血因子XII启动内源性凝血并抑制组织因子途径抑制物，双重激活凝血级联反应[39]。此外，血小板-中性粒细胞聚集体可通过IRGM/Irgm1介导的MAPK-cPLA2通路促进NETs释放，NETs反过来进一步激活血小板和中性粒细胞，形成正反馈循环，加剧血栓形成[50]。

3 靶向NETs的动脉粥样硬化诊治策略

3.1 NETs作为生物标志物用于早期诊断

在AS的诊疗中，NETs相关生物标志物具有重要临床价值。双链DNA水平与冠状动脉狭窄程度正相关；MPO-DNA复合物升高与心肌梗死面积及30天死亡率显著相关；破裂斑块中瓜氨酸化组蛋白H3表达量较稳定斑块高2.1倍；NE活性与血栓负荷指数呈正相关，联合检测可将AS早期诊断灵敏度提升至82%[11]。值得注意的是，瓜氨酸化组蛋白虽为NETs的特征性成分，但其亦可由其他炎症细胞产生，因此需结合多指标检测以提高诊断准确性。

3.2 抑制NETs治疗动脉粥样硬化的可能性

3.2.1 抑制NETs的产生

靶向NETs形成的干预策略为AS治疗提供了新方向。核心机制聚焦于关键分子调控与表观遗传修饰：PAD4抑制剂（氯脒[51]、GSK484[52]）可通过阻断GSDME介导的钙内流，抑制组蛋白H3瓜氨酸化，显著减少NETs生成，且敲除PAD4可减轻AS[53]；以BRCC3为靶点的抑制剂霍洛霉素，可通过抑制NLRP3炎性小体激活来调控IL-1β分泌和NETosis，发挥双重作用。在Tet2基因突变模型中，该药物既能降低NETs水平，又可规避传统免疫抑制剂的全身毒性[54]。而MDA特异性IgM通过结合氧化表位抑制NETosis，显著改善心脏功能且与左心室射血分数呈正相关[21]。其他调控途径包括：miR-146a通过抑制TLR4/NF-κB通路调控中性粒细胞活化，其低表达会加剧NETs相关的血栓形成和内皮损伤[55]；抗CD11b抗体通过阻断血小板-中性粒细胞相互作用，在反复社交失败小鼠模型中有效抑制血栓性NETs生成[56]。靶向抑制NETs的形成与功能，作为干预动脉粥样硬化血栓形成的新策略，需通过进一步临床试验实现转化应用。

3.2.2 消除NETs及其促炎活性

清除NETs的治疗手段主要依赖DNase I，其通过降解NETs的DNA骨架改善心肌缺血再灌注损伤。临床前研究证实，静脉输注DNase I可显著降低梗死面积，其作用机制涉及抑制中性粒细胞浸润、减少血小板聚集及下调炎症因子网络[57]。使用DNase I分解NETs的DNA骨架，或阻断中性粒细胞激活通路如TLR2/IL-3信号，已在动物模型中显示出减轻病变的效果[8]。在组蛋白靶向干预策略中，PL2_3 Fab抗体通过阻断组蛋白与TLR4之间的相互作用，有效中和已释放NETs的促炎活性[58]。

3.3 中医药治疗AS的创新策略

中药干预从中国传统医学与现代分子机制结合的独特视角，为AS的治疗提供新的可能。丹皮酚可通过抑制NE活性，减少瓜氨酸化组蛋白H3的释放，并阻断NLRP3/caspase-1通路，从而减轻泡沫细胞炎症，最终抑制AS进程[40]。而改良桃红四物汤则通过多靶点作用展现独特优势，其活性成分在小鼠模型中可抑制血管细胞凋亡、调控血小板功能及中性粒细胞迁移，并通过抑制NF-κB信号通路减少NETs成分双链DNA、NE和瓜氨酸化组蛋白H3的表达，减缓AS疾病的进展[59]。桂枝通络片则通过抑制NETs生成，降低瓜氨酸化组蛋白H3和MPO水平，从而减轻炎症反应，改善AS相关病理损伤[60]（表1）。

4. 总结与展望

NETs可通过促炎、促栓及基质重塑等多重机制，参与动脉粥样硬化的起始、进展及并发症全过程。多种危险因素如高血糖、氧化应激等，对NETs

表 1　靶向NETs的药物研究

Table 1　Research on drugs targeting NETs

Drug / Compound	Target of Action	Development Stage	Potential Risks	Reference
Chloramine	PAD4	Preclinical	Not reported	[51]
GSK484	PAD4	Preclinical	Not reported	[52]
Holomycin	BRCC3 Deubiquitinase	Preclinical	Decreased immune cell count; long-term use may increase infection risk	[54]
MDA-specific IgM	MDA	Preclinical	Not reported	[21]
DNase I	dsDNA in NETs	Preclinical	Not reported	[8]
Paeonol	Not specified	Preclinical	Not reported	[40]
MTHSWD	Not specified	Preclinical	Monitoring the impact of different doses on liver and kidney function is required	[59]
Guizhi Tongluo Tablet	Not specified	Preclinical	Not reported	[60]

注:Chloramine, 氯胺;PAD4, 肽基精氨酸脱亚胺酶4;GSK484, PAD4抑制剂;Holomycin, 霍洛霉素;BRCC3 Deubiquitinase, BRCC3去泛素化酶, 间接抑制NLRP3炎症小体;MDA, 氧化特异性表位丙二醛;Paeonol, 丹皮酚;MTHSWD, 改良桃红四物汤。
Abbreviations: PAD4, peptidylarginine deiminase 4; MDA, malondialdehyde; dsDNA, double-stranded DNA; MTHSWD, Modified Tao Hong Si Wu Decoction.

形成的调控作用及其在疾病防治中的机制仍存在未知领域。此外,NETs通过持续激活免疫反应加剧血管炎症贯穿AS的始终。在治疗上,抑制NETs生成或清除的策略虽在动物实验中被证实有效,但这些方法能否安全应用于临床并治疗AS仍需进一步验证。未来研究可探索通过NETs靶向干预、中药复方免疫调节及个体化治疗策略,为ASCVD的精准防治提供新方案。

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