主动脉瘤的细胞生物学机制与药物治疗策略

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摘要: 主动脉瘤 (aortic aneurysm, AA) 是主动脉病理性扩张超正常血管直径50%的不可逆性疾病, 会大大增加主动脉夹层及破裂猝死的风险, 全球每年约20万人死于相关疾病。AA可发病于主动脉全程的不同节段, 主要分为胸主动脉瘤和腹主动脉瘤, 前者发病率低但预后差, 两者病因与分子机制不同, 但均与炎症反应和多种蛋白酶激活密切相关, 本综述将重点介绍可适用于两者的一般细胞和分子事件。AA通常无症状, 即使超声检查发现, 也多因未达手术标准而纳入监测。鉴于目前无有效药物阻止其生长或降低破裂风险, 本综述将简要回顾动物及临床药物试验, 以期提供治疗策略。

关键词: 主动脉瘤; 风险因素; 细胞生物学机制; 免疫反应; 药物治疗策略

中图分类号: R966 **文献标识码**: A **文章编号**: 0513-4870(2026)06-1913-11

Cellular biology mechanisms and pharmacological strategies of aortic aneurysm

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Abstract: Aortic aneurysm (AA), an irreversible pathological dilation of the aorta exceeding 50% of its normal diameter, significantly increases the risk of aortic dissection and rupture-related sudden death, causing approximately 200 000 global deaths annually. AA can occur in various aortic segments and is primarily categorized into thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm. TAA, though less common, has a worse prognosis. While the etiology and molecular mechanisms differ between the two types, both are closely linked to inflammatory responses and the activation of various proteases. This review will focus on the general cellular and molecular events applicable to both conditions. AA is usually asymptomatic, and even when detected *via* ultrasonography, it is usually monitored due to not meeting surgical criteria. As no effective medication currently exists to halt its growth or reduce rupture risk, this review will briefly cover animal and clinical drug trials to explore potential therapeutic strategies.

Key words: aortic aneurysm; risk factor; cellular biology mechanism; immune response; pharmacological strategy

主动脉瘤 (aortic aneurysm, AA) 严重威胁人类健康, 流行病学显示, 全球范围内AA的死亡负担在下降了20年后开始反弹, 在未来10年可能继续上升[1]。AA因无明显症状, 真实患病率可能更高。AA的早期检查主要包括超声、CT血管造影、核磁共振显像和动脉造影, 其中超声可精确评估瘤体结构及腔内血栓, 且无创、便捷、无辐射, 故为筛查随访首选。

目前尚无经临床验证并纳入指南的AA诊断或预后生物标志物, 但研究发现生长/分化因子15和胱抑素B组合具诊断潜力, 髓过氧化物酶与预后相关。腹主

收稿日期: 2025-08-18; 修回日期: 2025-11-24.
基金项目: 上海市“科技创新行动计划”扬帆计划 (24YF2733300).
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DOI: 10.16438/j.0513-4870.2025-0983

动脉瘤 (abdominal aortic aneurysm, AAA) 患者体内，与蛋白水解、氧化应激、脂质代谢和炎症相关的21种蛋白质水平显著升高，而与高密度脂蛋白代谢相关的对氧磷酶3水平降低，这些蛋白质有望成为新型生物标志物[2]。此外，miRNA也被认为是AAA诊断及预后标志物的潜在候选[3]。循环GMP-AMP合成酶−干扰素基因刺激因子的异常信号与多种无菌性炎症疾病密切相关，包括心力衰竭、非酒精性脂肪肝病、AA与主动脉夹层 (aortic dissection, AD) 等[4]。AA生物标志物的发现与鉴定在近3年来取得的进展如下：2023年的1项研究聚焦阻塞性睡眠呼吸暂停促发的AAA，鉴定出*Homer2*、*Robo2*、*Ehf*和*Asic1*这4个在慢性间歇性缺氧模型中表达异常的基因作为新型生物标志物，可能通过调控血管重塑途径影响AAA进展。鉴定方法包括转录组分析和生物信息学预测，临床潜力在于早期筛查高风险AAA患者，特别是伴随阻塞性睡眠呼吸暂停者，但面临样本异质性和功能验证不足的挑战[5]。2023年的1项综述总结了急性AD中的新型标志物，如炎症相关蛋白 [白介素6 (interleukin-6, IL-6)、C-反应蛋白]、*D*-二聚体、平滑肌肌球蛋白重链 (smooth muscle myosin heavy chain, SMMHC) 以及基质金属蛋白酶-9 (matrix metalloproteinase-9, MMP-9)。这些标志物在AD快速诊断中显示潜力，如*D*-二聚体的高灵敏性可通过阴性结果有效排除急性胸痛由AD引起的可能性，减少不必要的影像学检查，IL-6和C-反应蛋白反映炎症级联激活，而SMMHC和MMP-9与血管壁损伤和重塑相关。然而，临床应用受限于生物标志物的稳定性差 (如*D*-二聚体在其他急性事件中非特异性增高)、检测时间窗狭窄以及缺乏大规模多中心验证[6]。2024年研究发现，核蛋白1作为AAA中与$CD4^+$ T细胞浸润负相关的关键生物标志物，其表达下调可增强AAA的诊断准确性，并为靶向免疫炎症的治疗提供了潜在靶点[7]。这些发现凸显了多组学整合在生物标志物鉴定中的价值，但AA标志物的临床转化仍面临敏感性/特异性不足、患者队列规模小，以及缺乏标准化协议将标志物与影像学整合用于动态监测的挑战，需通过大规模前瞻性试验进一步优化。

1 AA的风险因素

AA的传统风险因素包括男性、高龄、吸烟、动脉瘤家族史、冠心病、外周动脉疾病、血脂异常、高血压和慢性阻塞性肺疾病。针对中国患者，年龄 ≥ 65岁、吸烟、高血压和主动脉根部直径 > 30 mm是AAA的独立预测因子，其数量与患病率成正比。男性AAA发病率高于女性，可能原因包括：首先，女性体型较小，现有的腹主动脉直径 > 30 mm统一诊断标准可能导致漏诊；其次，雌激素在绝经前女性中发挥保护作用 (有趣的是，在男性内部风险分层中，较低的睾酮水平及较高的雌二醇、孕酮水平反而与AAA风险增加相关[8])；最后，男性吸烟率显著高于女性。戒烟是针对以上风险因素最易行的干预措施，孟德尔随机化分析显示吸烟显著增加AAA风险，与胸主动脉瘤 (thoracic aortic aneurysm, TAA) 则关系不大[9]。吸烟使女性AAA风险高15倍，男性高7倍[10]，电子烟同样有害[11]。戒烟与AAA的预后也密切相关，长期戒烟会显著降低开放手术修复 (open surgical repair, OSR) 后肺部并发症，短期则不能，建议至少在术前8周戒烟。与直觉相悖的是，适度饮用啤酒和葡萄酒可以降低AA的发病风险[12]；糖尿病可能因二甲双胍的脱靶效应延缓AA进展。

遗传风险因素上，基因位点如20q13.12区域的突变会增加AAA风险，可能是因为其携带*MMP9*基因[13]。Klarin等[14]在百万退伍军人计划中探究了AAA风险位点突变与下肢、大脑和髂动脉床动脉瘤的关联，构建了全基因组多基因风险评分以识别高遗传风险人群，同时确定了14个新的风险位点，使AAA的高遗传风险位点总数达到24个，包括*LRP1*、*LDLR*、*PLTP*、*APOE*、*LPA*和*PCSK9*等。他们随后也对TAA和AD进行了全基因组关联研究 (genome-wide association study, GWAS)，确定了21个风险位点，这些位点与动脉粥样硬化几乎不重叠，表明TAA和AD是非动脉粥样硬化性疾病，与脂质斑块相关的AAA有很大区别[15]。AA的风险因素与类型示意详见图1。

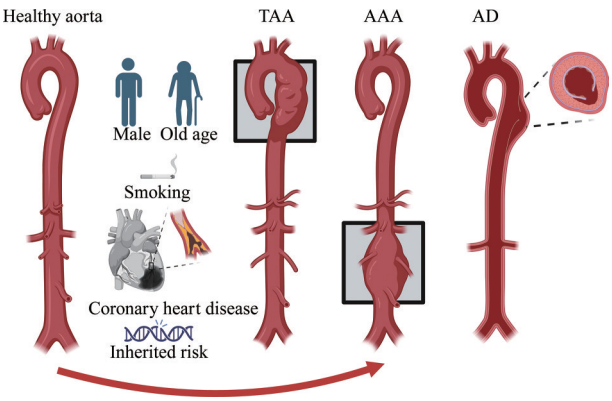


Figure 1 Risk factors and types of aortic aneurysm (AA). TAA: Thoracic aortic aneurysm; AAA: Abdominal aortic aneurysm; AD: Aortic dissection

2 AA的细胞生物学机制

主动脉壁由三层组成：内膜由主动脉腔的内皮细胞 (endothelial cells, EC) 组成，中膜含血管平滑肌细胞 (vascular smooth muscle cells, VSMC) 和弹性蛋白纤维，外膜是胶原蛋白、基质蛋白和成纤维细胞组成的

网络。AA依据结构可分为真性和假性, 前者是动脉管壁病变、弹性降低、结构薄弱形成的局限性扩张, 各层结构完整保留。后者是外膜撕裂、血液流出并被周围组织包裹形成的血肿, 瘤壁并非完整的动脉壁结构。此外, 内膜撕裂使血液侵入中膜并逐渐延伸剥离时会形成AD。AA的核心病理特征是细胞外基质(extracellular matrix, ECM)降解和VSMC损失, 伴随外膜和中膜的炎性细胞浸润。AA的关键病理过程为炎症与氧化应激刺激VSMC表型与数量变化、MMP表达升高、MMP继而消化并破坏管壁, 导致主动脉壁退变。本篇综述将重点从细胞层面介绍AA病理学过程。

2.1　免疫细胞

AA中存在大量免疫细胞浸润, 单核细胞、巨噬细胞、树突状细胞、肥大细胞、T细胞和B细胞等通过分泌趋化因子、炎性因子、活性氧, 加剧炎症与氧化应激, 推动病情发展。

2.1.1　单核细胞　人类循环单核细胞可分为经典型($CD14^{++}CD16^{-}$)、非经典型($CD14^{+}CD16^{++}$)、中间型($CD14^{++}CD16^{+}$)三个亚群。经典型占比约90%, 主要分泌IL-1促进炎症; 非经典型分泌IL-10发挥抗炎作用; 中间型分泌肿瘤坏死因子(tumor necrosis factor, TNF)和IL-1, 兼具促炎和吞噬特性。AA中单核细胞发生了显著的扩增和活化, 亚群比例也发生改变, 经典型减少而中间型增加[16]。单核细胞可通过自身效应参与AA进展: 在小鼠的血管紧张素II输注模型中观察到经典型$CCR2^{+}$单核细胞增加并趋化到炎症组织; $LY6C^{high}$经典单核细胞可表达髓样细胞表达触发受体-1 (triggering receptor expressed on myeloid cells-1, TREM-1)以加重AAA。单核细胞也可分化为巨噬细胞, 主动脉壁中的大多数巨噬细胞来自循环单核细胞。使用含氯膦酸盐的脂质体消耗小鼠的单核细胞后, 主动脉壁中巨噬细胞的积聚也会被限制, 抑制了AAA进展。单核细胞的特定亚群还可产生功能不同的巨噬细胞亚群, 如$LY6C^{high}$单核细胞亚群可基于PU.1表达水平分化为一氧化氮合酶2阳性(nitric oxide synthase 2 positive, $NOS2^{+}$)巨噬细胞。

2.1.2　巨噬细胞　巨噬细胞在AA中具有双重作用, 分为促炎的M1型和抗炎的M2型: M1分泌蛋白水解酶和炎性因子如TNF、IL-6、IL-12、IL-1β、NOS2或CC趋化因子配体(CC chemokine ligand, CCL), 其中CCL2招募单核细胞, CCL5促进T细胞浸润。而M2型则分泌IL-10、转化生长因子-β (transforming growth factor-beta, TGF-β)、CCL17、CCL18等因子参与组织重塑及炎症组织修复。在AA样本中, 巨噬细胞多聚集于外膜和腔内血栓, 早期以M1型为主导, 维持高M1/M2比例, 加剧炎症反应。

巨噬细胞通过分泌蛋白酶如组织蛋白酶S (cathepsin S, CTSS)、膜型1基质金属蛋白酶(membrane-type 1 matrix metalloproteinase, MT1-MMP)和MMP-9, 破坏主动脉弹性蛋白, 促进AA形成。研究发现, 将MT1-MMP缺失的骨髓移植至野生型小鼠后, 氯化钙无法诱导其形成AA, 而MT1-MMP过表达的巨噬细胞可恢复小鼠模型对AA的易感性, 表明其关键作用。*MMP9*过表达的巨噬细胞也可以恢复*Mmp9*缺陷型小鼠对AA的易感性, 且M1和M2型巨噬细胞中MMP-9表达水平存在差异, 表明巨噬细胞能根据其表型和活化特征调节ECM降解[17]。AAA中巨噬细胞的Krüppel样因子5 (Krüppel-like factor 5, KLF5)表达水平上升, 通过增强肌球蛋白9b (myosin 9b, Myo9b)表达、抑制Ras同源基因家族成员A (Ras homolog family member A, RHOA)信号通路, 提升巨噬细胞运动与侵袭迁移能力, 进而加剧ECM降解[18]。

巨噬细胞既能释放炎症介质, 又能被炎症信号激活: 其分泌CXC趋化因子配体1吸引高表达IL-6的中性粒细胞向炎症部位迁移[19], IL-6可促进单核细胞分化为活化巨噬细胞, 并促使其分泌CCL2, 进而招募更多单核细胞至AA部位, 形成持续放大的炎症级联反应, 加重AA进展。不过, 巨噬细胞也有保护作用, 如清除AAA病变处的细胞外血红蛋白以助组织修复, 且特定亚群如HA-mac型巨噬细胞可促进抗炎因子IL-10分泌[16]。

2.1.3　树突状细胞　树突状细胞是重要的抗原提呈细胞, 其耗竭可显著抑制AA血管扩张[20]。不同亚型的树突状细胞通过多种机制参与AA进程: 浆细胞样树突状细胞(plasmacytoid dendritic cells, pDCs)通过产生I型干扰素(interferon, IFN)如IFN-α和IFN-β, 激活效应T细胞、细胞毒性T细胞和自然杀伤细胞来加强炎症反应。传统1型树突状细胞(conventional dendritic cell 1, cDC1)通过MHC I类分子交叉呈递抗原激活$CD8^{+}$ T细胞, 并依赖IL-12间接促进Th1极化及自然杀伤反应[21]。传统2型树突状细胞(conventional dendritic cell 2, cDC2)通过MHC II类分子直接激活$CD4^{+}$ T细胞, 诱导其分化为Th1效应细胞, 进而协同cDC1增强抗肿瘤免疫[22]。两者在肿瘤微环境中形成"cDC2→$CD4^{+}$ T→cDC1→$CD8^{+}$ T"级联, 但在AA炎症中的作用机制仍需进一步验证。

2.1.4　肥大细胞　肥大细胞富含肝素、组胺、5-羟色胺, 在细胞崩解时释放这些内容物引起速发型过敏反应。肥大细胞聚集在AA血管外膜, 数量与瘤体最大直径呈正相关。肥大细胞通过释放蛋白酶直接促进血

管损伤: 在氯化钙诱导的AAA模型中, 肥大细胞缺陷型大鼠的血管扩张、T细胞浸润及MMP-9激活显著减轻, 肥大细胞脱颗粒抑制剂曲尼司特可抑制AAA进展。此外, 体外实验证实肥大细胞能增强单核/巨噬细胞MMP-9的活性。临床观察发现, AA患者中肥大细胞来源的糜蛋白酶和类胰蛋白酶水平升高, 这些蛋白酶会促进白细胞黏附迁移、诱导VSMC凋亡、加速泡沫细胞形成并上调MMP和组织蛋白酶的表达[23]。值得注意的是, 组织蛋白酶C (cathepsin S, CTSC) 可通过剪切类胰蛋白酶和糜蛋白酶酶原的N端前肽对它们进行反向激活, *Ctsc*缺陷型小鼠对弹性蛋白酶诱导的AAA具有抗性, 炎性细胞浸润也较少[24]。

2.1.5 T细胞 T细胞是AA中最主要的炎性细胞, 大多为$CD4^+$ T细胞, 可分化为Th1细胞、Th2细胞、Th17细胞和Treg等亚群。Th1分泌IFN-γ、IL-2和TNF-β, 抑制胶原蛋白合成, 加剧AA破裂; Th2通过FasL促进VSMC凋亡, 阻碍胶原和弹性蛋白合成; Th17分泌IL-17, 促进中性粒细胞募集和氧化应激, *Il17a*缺陷型小鼠对AAA形成具有抗性[25]。Treg细胞通过叉头框P3蛋白 (forkhead box P3 protein, FOXP3) 的乙酰化水平调控其抑制局部炎症的能力, 该功能受损可能会加重AAA的进展[26]。在功能上, Treg细胞可以分泌IL-10来抑制炎性细胞趋化、动脉壁重塑和病理性血管生成。临床观察显示, AAA患者外周血单核细胞中Treg细胞的比例显著降低, 凸显其保护作用[27]。$CD8^+$ T细胞具有双重作用, 既能释放IFN-γ促进VSMC凋亡并募集分泌MMP的巨噬细胞, 又可促进抗原提呈细胞的凋亡, 抑制$CD4^+$ T细胞的功能从而抑制动脉粥样硬化[28]。

2.1.6 B细胞 B细胞主要通过分泌抗体参与病理过程, 其亚群包括B1、B2和调节性B细胞。动物模型显示, 抗CD20抗体消耗B1和B2细胞可抑制AAA进展[29]。小鼠AAA中存在免疫球蛋白的广泛沉积, 如抗β2糖蛋白I抗体、抗磷脂抗体和抗肺炎衣原体外膜蛋白 (outer membrane protein, OMP) 抗体, 这些自身抗体不仅可以诱导T细胞和巨噬细胞分泌IL-6和MMP-9, 还可以直接破坏主动脉壁[30]。值得注意的是, OMP抗体的存在证明了肺炎衣原体与AAA之间的相关性。此外, 一些免疫球蛋白亚型可以与其他免疫细胞相互作用, 如IgE可影响巨噬细胞极化并激活肥大细胞以合成各种弹性蛋白酶[31]。

2.2 血管平滑肌细胞

VSMC是动脉壁的主要细胞, 其数量减少是AA的关键病理特征。在AA样本中检测到凋亡标志物上调, 并证实大多数凋亡细胞为VSMC[32]; VSMC凋亡显著削弱血管产生结缔组织和修复弹性蛋白断裂的能力。应激介质蛋白激酶Cδ (protein kinase C δ, PKCδ) 在AA中显著升高, 通过激活促凋亡蛋白如Bax、Caspase-3诱导VSMC凋亡, 并激活NF-κB信号加剧炎症, *Pkcδ*缺陷型小鼠中VSMC凋亡和AAA形成显著减少。抗吞噬信号CD47在AAA中上调, 导致凋亡细胞清除障碍, 加剧疾病进展; 而抗CD47抗体治疗可在小鼠模型中抑制AAA形成[33]。

除凋亡外, VSMC的表型转换也参与AA的形成。正常情况下, VSMC多为收缩型, 调节血管张力和直径以控制血压和血流分布。在易患AD的小鼠模型中, 药物诱导的收缩型VSMC可以保护主动脉壁的分层, 维持主动脉结构完整[34]。但VSMC具有高度可塑性, 在炎症或氧化应激下可转化为合成型[35], 表现为收缩蛋白如α-SMA、SMMHC、SM22α表达下调, 并引发以下病理改变: 弹性蛋白层缺失促使VSMC向前弹性蛋白溶解表型转化, MMP等弹性蛋白酶分泌增加, 加速ECM降解; 此外, 促炎性细胞外囊泡分泌增加, 加剧局部炎症和血管钙化[36]。钙化是主动脉壁中层磷酸钙晶体沉积的过程, 与动脉硬化有关。VSMC从收缩型向成骨/软骨的表型转换时, 伴随着调节ECM矿化的骨特异性蛋白表达[37]。VSMC是血管钙化的关键参与者, 其机制包括细胞凋亡增加、细胞外囊泡释放和天然钙化抑制剂 (如MGP) 丧失。细胞凋亡产生的凋亡小体若未被清除, 会刺激钙化, 而钙沉积又会加重炎症和机械应力。研究证实, 二氢杨梅素可使VSMC中血红素氧合酶-1蛋白的表达显著增加, 从而抑制其炎症和氧化应激, 维持其收缩表型[38]。

2.3 成纤维细胞

成纤维细胞是外膜的主要细胞, 负责分泌ECM, 尤其是I型和III型胶原。成纤维细胞通过活化、增殖和迁移到损伤部位, 沉积ECM分子和胶原蛋白, 为其他细胞的黏附生长提供支架, 促进伤口愈合, 还可通过分泌细胞因子、趋化因子和生长因子改变主动脉壁的表型[39], 如与巨噬细胞相互作用加强IL-6/单核细胞趋化蛋白-1 (monocyte chemoattractant protein-1, MCP-1) 正反馈通路, 加速血管炎症。马凡综合征患者AA中成纤维细胞存在TGF-β过度表达。在小鼠的血管紧张素II输注模型中, 成纤维细胞特异性NADPH氧化酶2 (NADPH oxidase 2, Nox2) 缺陷显著降低了血管重塑和高血压, 可能与其通过生长分化因子6 (growth differentiation factor 6, GDF6) 调节中膜VSMC的旁分泌信号有关, 这也是血管紧张素II诱导血管重塑的病理基础[40]。然而, 成纤维细胞的体外研究较为复杂, 当其从外膜移除后会发生转化, 且目前还没有用于鉴定

的特异性标志物[41]。研究表明成纤维细胞具有显著异质性, 可分为两个亚群, 一个高表达胶原蛋白, 另一个高表达增殖和炎症基因, 后者更易参与炎症放大与病理重塑[42]。

在应对刺激时, 成纤维细胞可活化为肌成纤维细胞, 标志是α-SMA表达, 其收缩活性、迁移和增殖能力、细胞因子和趋化因子的分泌均增强, 并伴有纤维化和ECM重塑。这种转化在伤口愈合和组织修复中是必要的, 但过度活化和表型转换会导致胶原沉积增加, 主动脉壁硬化, 肌成纤维细胞迁移到中膜和内膜分泌炎性因子增强炎症反应, 最终导致血管重塑[43]。在AA小鼠模型中, 利用热休克蛋白90抑制剂减少线粒体分裂可抑制成纤维细胞活化, 延缓AA进展[44]。

2.4　内皮细胞

EC负责调节血管张力, 维持血液–组织界面及抗炎、抗血栓的局部环境, 从而维持血管稳态。单细胞测序显示EC存在异质性, 可分为与脂代谢和与基质重塑相关的亚群[42]。

剪切应力是EC在新血管发育中的重要驱动力, 低壁剪切应力和异常血流会上调血管内皮生长因子(vascular endothelial growth factor, VEGF)和细胞黏附分子VCAM-1和ICAM-1, 导致EC的形态由线性矩形变为圆形, 细胞间连接减弱, 通透性增强, 从而促进炎性细胞与EC和VSMC的结合, 加重炎症反应, 促进AA形成[45]。EC通过内皮型一氧化氮合酶(endothelial nitric oxide synthase, eNOS)生成NO扩张血管, 但四氢生物蝶呤不足时, eNOS解偶联产生超氧化物, 引发内皮功能障碍。四氢生物蝶呤水平受GTP环化水解酶1及二氢叶酸还原酶(dihydrofolate reductase, DHFR)调控, 血管紧张素II降低eNOS和DHFR表达, 加剧氧化应激, 升高AAA风险, 而补充DHFR可缓解[46]。腔内血栓是AAA的一个普遍特征, 由血小板、中性粒细胞和巨噬细胞组成, 破坏邻近内皮。抗凝剂如依诺肝素可减少血栓形成, 抑制AAA扩张[47]。在层流和高剪切应力条件下, 健康EC可产生多种抗凝和抗血小板物质。然而在湍流、低剪切应力和内皮损伤条件下, EC由抗凝转为促凝, 加剧腔内血栓生成。EC治疗通过旁分泌途径驱动内皮稳定因子上调和天然血管细胞募集, 恢复内皮, 减少炎症和血栓, 从而改善AAA[48]。AA的细胞生物学机制总结详见表1[16-48]。

Table 1　The cellular biology mechanism of AA

Cell type	Cell subtype and marker	Key molecular event	Mechanism
Monocyte[16]	Classical ($CD14^{++}CD16^{-}$, IL-1 ↑); non-classical ($CD14^{+}CD16^{++}$, IL-10 ↑); intermediate ($CD14^{++}CD16^{+}$, TNF/IL-1 ↑)	$CCR2^{+}$ ↑; TREM-1 activation; differentiation into macrophages	Recruited to inflammatory sites, exacerbating inflammation/ECM degradation, promoting vascular wall degeneration
Macrophage[17-19]	M1 (TNF, IL-6, IL-12, IL-1β, NOS2, CCL2/CCL5 ↑); M2 (IL-10, TGF-β ↑)	MMP-9, CTSS, MT1-MMP ↑; KLF5/Myo9b inhibiting RHOA; IL-6, CCL2 ↑	Degrade elastin *via* proteases, enhance migration exacerbating ECM degradation/inflammation, promoting vascular wall damage
Dendritic cell[20-22]	pDCs (IFN-α/β ↑); cDC1 (MHC I); cDC2 (MHC II)	IFN-α/β ↑; MHC antigen presentation; T cell activation	Activate T cells/NK cells, enhancing inflammation, promoting vascular wall immune infiltration/damage
Mast cell[23,24]	Main features (heparin, histamine, 5-hydroxytryptamine ↑; chymase/tryptase ↑)	CTSC activates chymase/tryptase; MMP-9 activation	CTSC and chymase/tryptase activation and promote MMP-9 expression, enhancing leukocyte migration/VSMC apoptosis, exacerbating ECM degradation/foam cell formation
T cell[25-28]	$CD4^{+}$ T: Th1 (IFN-γ, IL-2, TNF-β ↑), Th2 (FasL ↑), Th17 (IL-17 ↑), Treg (FOXP3 acetylation, IL-10 ↑); $CD8^{+}$ T (IFN-γ ↑)	IFN-γ, IL-17 ↑; FasL induces VSMC apoptosis; FOXP3 dysfunction leads to IL-10 ↓; $CD8^{+}$ T promotes MMP secretion	IFN-γ/IL-17 inhibits collagen synthesis, FasL induces VSMC apoptosis, IL-10 ↓ exacerbates inflammation/neutrophil recruitment, enhancing ECM degradation/rupture risk
B cell[29-31]	B1/B2 (antibodies ↑); regulatory B (IL-10 ↑)	IgE, IgG deposition; anti-OMP antibodies induce IL-6, MMP-9; interact with mast cells	Antibodies disrupt vascular walls/activate elastases, exacerbating inflammation/ECM degradation
VSMC[32-38]	Contractile (α-SMA, SMMHC, SM22α ↑); synthetic (contractile proteins ↓, MMP ↑); osteogenic (osteopontin ↑)	PKCδ activates Bax, Caspase-3; CD47 ↑ inhibits apoptosis clearance; eNOS/phenotype switching	Apoptosis/phenotype switching accelerates ECM degradation/calcification, causing weakened vascular wall/abnormal remodeling
Fibroblast[39-44]	Myofibroblasts (α-SMA ↑); collagenic (I/III collagen ↑); inflammatory (IL-6, MCP-1 ↑)	TGF-β ↑; Nox2 ↑; differentiate into myofibroblasts	TGF-β promotes excessive fibrosis, Nox2 regulates GDF6 inducing vascular remodeling, excessive myofibroblast activation and phenotype switching lead to increased collagen deposition and aortic wall sclerosis
EC[42,45-48]	Lipid metabolism related (Gpihbp1, Fabp4, Cd36); matrix remodeling related (Mgp, Bgn, Sulf1)	VEGF, VCAM-1, ICAM-1 ↑; eNOS uncoupling produces superoxide; intraluminal thrombi	Enhanced permeability/oxidative stress/procoagulant activity exacerbates thrombus formation, leading to vascular wall damage/dilation

3 AA的治疗

目前, AA的诊断、随访和干预主要依赖于胸腹部成像和直径大小。AA破裂的风险随直径增加而上升, 40～49 mm时年破裂风险小于5%, 而超过80 mm时风险高达30%～50%。当男性AA直径达到55 mm、女性达到50 mm, 或6个月内增长超过5 mm、12个月内增长超过10 mm时, 通常需要进行OSR或腹主动脉瘤腔内修复术, 后者术后生活质量更好, 3年内破裂死亡率更低。然而, 针对40～55 mm无症状AAA的早期手术干预并不能降低死亡率[49]。由于部分患者不适合手术及手术并发症的存在, 亟需能够限制AA生长和破裂的药物。多数临床前研究基于弹性蛋白酶、氯化钙或血管紧张素II输注的啮齿动物模型。

AA的进展通常被认为由局部炎症反应和蛋白水解失衡引发。因此, 药物研发主要针对炎症反应或纠正蛋白水解失衡, 可分为抗炎药、降压药、抗血栓药、抗生素、调脂药和降血糖药等类别。

3.1 抗炎药

在动物模型和患者的AA样本中, 多种炎症途径发生上调, 抗炎药具有限制AA的潜力。针对10项小鼠研究的荟萃分析发现, 抗炎药如受体相互作用蛋白1抑制剂、选择性环氧化酶-2抑制剂塞来昔布、c-Jun N-末端激酶抑制剂、缓激肽2受体拮抗剂均可显著减小AAA的直径和破裂风险[50]。肥大细胞在AA样本中参与炎症浸润, 其缺失或活性抑制可限制啮齿动物模型中AAA的进展[51]。但AAA的抗炎口服治疗试验(AORTA)测试了3种不同剂量(20、50、80 mg·d^{-1})的新型肥大细胞抑制剂吡米司特, 12个月随访均未见明显改善[52]。此外, 临床观察显示效果不一: 在癌症与AAA并发患者中, 放疗可减缓AAA生长[53]; 而器官移植后服用免疫抑制剂的AAA患者则出现快速生长[54]。抗炎药的临床转化存在广泛激活炎症级联的问题, 下调某一组分可能引起其他组分代偿性变化, 非特异性免疫抑制还会加重癌症和感染风险, 需要探索更有针对性的抗炎药靶点。

3.2 降压药

3项独立试验分别测试了β-受体阻滞剂普萘洛尔[55,56]、血管紧张素转换酶抑制剂(angiotensin-converting enzyme inhibitor, ACEI)培哚普利及钙通道阻滞剂氨氯地平[57]对AAA的疗效, 荟萃分析表明这些降压药并未显著改善AAA的生长、手术率或破裂风险[58]。BAV研究因招募问题提前终止, 但初步结果也证实了3年来阿替洛尔未限制TAA生长[59]。动物实验和临床研究均证实肾素−血管紧张素系统(renin-angiotensin system, RAS)与AAA的细胞生物学机制相关[60], 但RAS抑制剂对AA的生长和破裂效果不一: 病例对照研究发现RAS抑制剂可降低AAA破裂的风险, 并确定治疗效果主要源于ACEI[61]。注册研究也发现ACEI或血管紧张素II受体拮抗剂可降低AA相关死亡风险[62]。厄贝沙坦与洛沙坦可减缓马凡综合征患者的主动脉扩张, 从而降低主动脉并发症的发生率[63,64]。对7组受试者的荟萃分析发现, ACEI未能限制AAA生长[65], 替米沙坦治疗腹主动脉瘤(TEDY)试验发现, 40 mg·d^{-1}的剂量未能限制AAA生长[66]。这表明降压药可能降低AAA破裂死亡率, 但对小型AAA生长无效, 其局限性可能源于AA生长与破裂存在不同病理机制[67,68]。2023年的综述进一步指出, 尽管降压药在动物模型中显示了缓解AA形成的潜力, 但临床试验常因样本量小、随访时间短及超声测量瘤体直径的不一致性而失败, 导致其长期疗效难以评估[69]。

3.3 抗血栓药

血小板激活和腔内血栓更新是AA进展的关键驱动因素, 在心肌梗死小鼠模型及患者中, 缺血事件后循环血小板会合成并分泌活化的MMP-9[70], 增强的血小板反应性可能参与AAA的生长和破裂。2015年研究显示, 阿司匹林和氯吡格雷可抑制小鼠血管紧张素II输注模型中主动脉MMP活性, 防止AAA破裂, 临床队列研究亦进一步验证了这一结论[71]。但2016年大型研究表明, 入院前使用低剂量阿司匹林并未改变AAA破裂风险, 且可能与更差预后相关[72]。2020年对超过2.45亿例住院患者的分析发现抗血小板药可防治AA的形成、夹层和破裂, 但未区分药物类别[73]。2022年研究发现抗凝药如华法林、阿哌沙班能防治AA的生长与破裂, 但不降低心血管事件总发病率[74]。在替格瑞洛对AAA扩张的疗效试验(TicAAA)中, 替格瑞洛未延缓AAA生长。鉴于替格瑞洛也没有减少患者的腔内血栓体积, 还不能排除腔内血栓在AAA细胞生物学机制中的作用[75]。此外, 长期使用阿司匹林联合抗凝治疗可能增加主动脉囊袋未回缩及持续II型内漏的风险, 导致其临床应用受限[76]。

3.4 抗生素

有研究在AA样本中检测到肺炎支原体抗原, 并发现肺炎衣原体高IgA抗体滴度与AAA快速生长相关[77]。基于此, 4项试验探索了抗生素对小型AAA的疗效, 包括大环内酯类抗生素阿奇霉素[78]、罗红霉素[79,80]、四环素类抗生素多西环素[81]。此外, 基于多西环素降低MMP活性和限制炎症的多效性作用的大规模试验[82]发现, 给予2周的多西环素后再进行OSR, 术中取出AA样本中蛋白水解酶的表达和炎性细胞的渗透会显著降低[83]。5项抗生素试验共纳入743名患者,

但多数试验存在设计缺陷, 如持续时间短、样本量计算缺失、主要结果不明确和数据不完整。小规模试验显示短程罗红霉素或多西环素可减缓AAA生长, 而较大规模试验中阿奇霉素和长期多西环素效果不佳, 甚至可能加剧AAA第1年的生长。对这些试验的荟萃分析表明, 抗生素总体上不能改善AAA的生长或临床事件[58]。然而该荟萃分析存在显著的临床异质性, 可能导致结论无效[84]。进一步的无创治疗AAA的临床研究 (N-TA^{3}CT) 将多西环素剂量提升至200 mg·d^{-1}, 干预2年后未发现显著直径变化差异, 且多西环素组关节痛的发病率略高[85]。抗生素在AA临床转化的主要局限性在于靶点特异性不足 (如仅抑制MMP难以应对多通路病理)、难以筛选适合的患者亚群 (如炎症主导型) 以及长期不良反应 (如关节痛) 风险, 限制了其在临床实践中的推广。

3.5　调脂药

GWAS指出, 血脂异常是AAA发病的关键因素之一。1项前瞻性队列研究发现, 高强度使用他汀与AAA生长速度减缓及手术、破裂和死亡风险降低相关: 高强度他汀组AAA年生长速率显著低于低强度组 (1.5 ± 2.1 mm·y^{-1} *vs* 2.4 ± 2.3 mm·y^{-1}); 每增加1个限定日剂量 (defined daily dose, DDD) 的他汀类药物, AAA生长速率降低0.22 mm·y^{-1}; 5年随访期间, 他汀剂量每翻倍, 修复手术风险的调整后风险比为0.82, 即降低18%, 且该保护作用在2.5年后显著显现[86]。但作为非随机对照试验, 其结果可能存在偏倚。贝特类也是常用的调脂药, 可在啮齿动物模型中抑制AA的进展。非诺贝特治疗腹主动脉瘤2试验 (FAME-2) 旨在评估非诺贝特对AAA患者关键病理标志物的影响[87], 尽管非诺贝特如预期降低了血清甘油三酯水平, 却并未显著改善关键病理标志物如骨桥蛋白水平, 也未能减缓AAA生长。他汀和贝特类在AA临床转化的主要局限性在于长期使用可能增加肌肉痛或肝功能异常等不良反应的风险。

3.6　降血糖药

动物实验显示, 二甲双胍通过抑制巨噬细胞的浸润和M1极化, 减轻炎症反应, 进而抑制VSMC从收缩型向合成型转化, 减缓AA的进展[88]。3项观察性研究报告了二甲双胍可以减缓糖尿病患者中AAA的生长[89-91]。大型研究发现相较于其他血糖控制疗法, 二甲双胍可以降低糖尿病患者的AAA破裂率[92]。但观察性研究存在固有偏倚, 仍不能确定这种改善源于二甲双胍还是糖尿病。1项平均随访时间长达5.5年的病例对照研究证明二甲双胍至少不会增加糖尿病患者AAA破裂的风险, 其改善血脂和炎症标志物的作用与AAA破裂风险降低无直接关联[93]。小型的随机对照试验 (MetAAA trial) 评估了二甲双胍对非糖尿病患者AAA进展的影响, 结果显示二甲双胍并未显著改变AAA生长速度, 研究因COVID-19大流行提前终止, 样本量较小, 结论的可靠性受限[94]。2023年综述指出, 二甲双胍在AA临床转化的主要局限性在于其作用机制局限于糖尿病相关炎症通路, 难以推广至非糖尿病患者, 且长期使用可能导致胃肠道不适和维生素B12缺乏等不良反应[95]。针对AA的试验测试药物总结详见表2[52,55-57,59,66,75,78-82,85,87,94]。

Table 2　Previous randomized placebo-controlled trials testing drugs. NS: Not supported

Category	Trial	Drug tested (daily dose)	Sample size	AA diameter entry criteria /mm	Method of AA measurement	Primary outcome	Follow-up /month
Anti-inflammatory drug	AORTA[52]	Pemirolast (20 mg/50 mg/80 mg)	326	39−49	Ultrasound	AA growth	12
Antihypertensive drug	Propranolol *versus* placebo trial[55]	Propranolol (80 mg)	54	30−49	Ultrasound	Not reported	NS
	Propranolol aneurysm trial[56]	Propranolol (240 mg)	552	30−50	Ultrasound	AA growth	NS
	AARDVARK[57]	Perindopril (10 mg) or amlodipine (5 mg)	227	30−54	Ultrasound	AA growth	24
	BAV[59]	Atenolol (25 mg up-titrated to 100 mg)	32	37−50	MRI	AA growth	36
	TEDY[66]	Telmisartan (40 mg)	210	35−49	Ultrasound and CT	AA growth	24
Antithrombotic drug	TicAAA[75]	Ticagrelor (180 mg)	144	35−49	MRI and ultrasound	AA growth	12
Antibiotic	Azithromycin[78]	Azithromycin (600 mg·d^{-1} for 3 days, then 600 mg once weekly for 15 weeks)	247	35−49	Ultrasound	AA growth	18
	Roxithromycin 1[79]	Roxithromycin (300 mg·d^{-1} for 28 days)	92	⩾ 30	Ultrasound	AA growth	24
	Roxithromycin 2[80]	Roxithromycin (300 mg·d^{-1} for 28 days annually)	84	30−50	Ultrasound	Not reported	NS

Continued

Category	Trial	Drug tested (daily dose)	Sample size	AA diameter entry criteria /mm	Method of AA measurement	Primary outcome	Follow-up /month
Antibiotic	Doxycycline 1[81]	Doxycycline (150 mg·d^{-1} for 3 months)	34	30−54	Ultrasound	Not reported	18
	PHAST[82]	Doxycycline (100 mg)	286	35−50 or ≥ 50 mm if unfit or declined repair	Ultrasound	AA growth	18
	N-TA^{3}CT[85]	Doxycycline (200 mg)	261	35−50 (male) or 35−45 (female)	CT	AA growth	24
Lipid-lowering drug	FAME-2[87]	Fenofibrate (145 mg)	140	35−49	Ultrasound	Difference in circulating concentrations of osteopontin and kallistatin	6
Antidiabetic drug	MetAAA trial[94]	Metformin (2 000 mg)	58	30−49	CT	AA growth	18

4 结论

AA是一种潜在致命疾病, 目前尚无明确的药物治疗方法, 许多药物如非诺贝特在动物模型上有效而临床效果不佳, 这种转化差异源于对AA细胞生物学机制的认识不足, 为此研究者需要开发出与人类AA病理过程拟合程度更高的啮齿动物模型: 如在主动脉外膜使用弹性蛋白酶并结合口服赖氨酰氧化酶抑制剂。此外, 应利用不断进步的基因组学、表型组学和蛋白质组学技术来确定新的药物靶点。目前正在测试的二甲双胍被寄予厚望, 血脂异常、IL-6信号转导和ECM的稳定也是药物开发的潜在靶向领域。以往临床试验未能找到有效药物, 这可能与试验设计的缺陷有关。未来试验若想检测出AA生长及破裂的临床相关差异, 必须加大样本量、延长随访时间, 并采用具高度重复性的成像技术来评估。

作者贡献: 尹航负责文章撰写与修改; 王培负责文章指导修改与审核。

利益冲突: 所有作者声明无利益冲突。

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