

脓毒症相关免疫性血栓形成的相关机制及治疗研究进展

马宇昊¹, 牛亚军¹, 王 义^{2*}

¹西安医学院研究生工作部, 陕西 西安

²西安交通大学附属儿童医院儿童重症医学科, 陕西 西安

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摘 要

脓毒症仍是目前重要的全球健康问题, 其特征为因机体感染后引起的免疫失调而引起的危及生命的器官功能障碍。免疫性血栓是在免疫系统激活和机体凝血途径的双重影响下形成的, 虽然其作为为机体正常生理条件下的防御机制, 但其在脓毒症中的异常激活会促使微血管血栓形成, 引起器官缺血, 最终引起弥散性血管内凝血的发生。本文通过对现有相关文献的综述, 总结了脓毒症发生免疫性血栓形成的相关机制及治疗研究进展。

关键词

免疫血栓形成, 脓毒症, 信号级联反应, 中性粒细胞外诱捕网, 弥散性血管内凝血

Research Progress on the Related Mechanisms and Treatments of Immune Thrombosis in Sepsis

Yuhao Ma¹, Yajun Niu¹, Yi Wang^{2*}

¹Graduate Work Department, Xi'an Medical University, Xi'an Shaanxi

²Department of Pediatric Critical Care Medicine, Children's Hospital Affiliated to Xi'an Jiaotong University, Xi'an Shaanxi

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*通讯作者。

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Abstract

Sepsis remains a major global health concern at present, characterized by life-threatening organ dysfunction caused by immune dysregulation secondary to infection in the body. Immune thrombosis is formed under the dual influence of immune system activation and the body's coagulation pathways. Although it acts as a defensive mechanism under normal physiological conditions, its abnormal activation during sepsis can promote the formation of microvascular thrombosis, induce organ ischemia, and ultimately lead to the development of disseminated intravascular coagulation (DIC). By reviewing the existing relevant literature, this paper summarizes the research progress on the related mechanisms and treatments of immune thrombosis in sepsis.

Keywords

Immune Thrombosis, Sepsis, Signal Cascade, Neutrophil Extracellular Traps, Disseminated Intravascular Coagulation

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1. 引言

脓毒症作为目前重要的全球健康问题，是重症监护病房中的主要死亡原因，据估计在世界范围内，每年有超过 3000 万人感染脓毒症，死亡率高达 20% [1]。脓毒症的特征是机体对感染的免疫反应严重失调，进而引发可危及生命的器官功能障碍[2]。脓毒症引起的过度免疫反应可激活凝血级联，这种过度激活会产生大量细胞因子，从而触发机体凝血系统，促进促凝因子合成并抑制抗凝因子，凝血系统激活失调可导致血管系统内持续形成血栓，这种现象称为免疫性血栓形成[3]。这一过程涉及通过先天免疫细胞、血小板和凝血因子之间的协调相互作用。在这种病理状态下，过度活化的血小板、单核细胞及中性粒细胞相互作用，诱导细胞因子的大量分泌，促使较大血栓形成，从而引起弥散性血管内凝血(Disseminated Intravascular Coagulation, DIC)，最终阻塞不同器官的血管，导致多器官功能障碍综合征(multiple organs dysfunction syndrome, MODS)，导致死亡风险大幅上升[4]。本文综述了脓毒症发生免疫性血栓形成的相关机制及治疗研究进展，旨在通过现有证据，为脓毒症相关的凝血功能异常的治疗提供一定参考。

2. 脓毒症诱导免疫性血栓形成的病理生理学机制

免疫性血栓形成是机体针对外源性及内源性刺激的先天防御机制的重要组成部分，但在机体急性损伤及各类危重疾病等病理状态下，可引起血栓的过度形成。脓毒症相关的免疫反应与凝血系统之间存在复杂的相互作用，适度的炎症反应和血栓形成可抑制病原微生物增殖并促进机体清除病原微生物，但过度的炎症反应和持续的凝血系统激活会促使组织损伤，引起 MODS。

2.1. 脓毒症引起的炎症反应

机体在感染病原微生物后，先天性免疫细胞通过模式识别受体，如 toll 样受体(Toll-like Receptor, TLR)，核苷酸结合寡聚化结构域样受体(NOD-like Receptor, NLR)等，识别病原体相关分子(Pathogen-Associated Molecular Patterns, PAMPs)，促使细胞因子与趋化因子释放，并激活机体补体系统，此过程中产生的促炎

细胞因子会引起机体出现广泛的炎症反应及细胞功能障碍[5]。一般情况下,免疫系统和凝血系统可通过机体自身调节而恢复到正常状态,当机体因严重感染出现脓毒症时,病原微生物难以从体内清除,机体始终暴露于损伤相关分子(Damage-Associated Molecular Patterns, DAMPs)中,促使中性粒细胞、单核细胞等大量募集及激活,释放大促炎细胞因子,如肿瘤坏死因子(Tumor Necrosis Factor, TNF)和白细胞介素- 1β 等,使机体出现细胞因子风暴,产生高炎症反应,极大促进了凝血级联的激活[6][7]。

2.2. 脓毒症诱导的免疫性血栓形成

脓毒症引起的高炎症反应会导致细胞组织损伤,破坏机体正常的凝血及纤溶平衡,促使全身微血管内血栓形成,并消耗大量凝血因子和血小板,同时继发纤溶亢进,出现 DIC [8]。其中凝血因子、血小板和机体免疫细胞的协同活化以及血管内皮损伤在脓毒症诱导的凝血功能障碍和 DIC 中起着重要作用。凝血过程中,纤维蛋白原被凝血酶转化为纤维蛋白,形成稳定血凝块和诱捕病原微生物的结构网。正常生理条件下,机体可通过纤溶系统抑制过量的纤维蛋白形成[9],但在机体出现脓毒症时,组织循环系统中纤维蛋白原及炎症因子水平升高,可损害机体纤溶系统,导致过度凝血和纤维蛋白溶解减少。因此,在凝血因子活性升高、血管内皮功能障碍及凝血-纤溶平衡被破坏的相互作用下,促使循环系统内的血栓过度形成[10]。

2.3. 炎症反应与凝血系统的相互作用

机体炎症反应与凝血系统存在双向作用,炎症反应可激活凝血系统,凝血系统又进一步放大炎症反应[11]。免疫细胞所释放的促炎细胞因子及趋化因子可放大促凝活性,同时抑制机体抗凝活性。组织因子(Tissue Factor, TF)广泛分布于组织及内皮细胞(Endothelial Cell, ECs)中,在脓毒症的条件下,ECs遭到破坏后会释放组织因子,且促炎细胞因子可诱导 TF 的表达,并与凝血酶共同激活凝血级联反应[12, 13]。此外,促炎细胞因子会抑制 ECs 的蛋白 C 受体合成的抗凝蛋白 C,凝血系统会因抗凝活性降低而进一步放大,共同驱动了脓毒症期间微血管血栓的形成[14][15]。

除了细胞因子和趋化因子外,其他炎症分子,如基质金属蛋白酶、肝素酶、透明质酸酶、活性氧(Reactive Oxygen Species, ROS)等也会损害 ECs 的内皮糖萼,从而改变组织细胞表面受体及因子的表达,如 TF、粘附分子和血管性血友病因子(von Willebrand Factor, VWF)。粘附分子可促进单核细胞、中性粒细胞和血小板附着到血管内皮细胞表面,促进微血栓形成[16]。此外,内皮糖萼的破坏会促进免疫细胞粘附并聚集于内皮细胞上,并激活凝血因子,加剧凝血反应[14]。

3. 免疫性血栓形成期间的细胞活化

在脓毒症条件下,单核细胞、巨噬细胞及中性粒细胞等免疫细胞,因 TF 表达增加、可形成中性粒细胞外陷阱(Neutrophil Extracellular Traps, NETs)等,并激活信号通路及因凝血因子驱动的正常蛋白酶激活受体,引起高炎症反应[17]。同时血小板和内皮细胞也在脓毒症中的微血栓形成中起着重要作用[18]。

3.1. 单核细胞的活化

单核细胞和巨噬细胞作为免疫系统的第一道防线,感染病原微生物后,活化的单核细胞可表达多种表面受体,并分泌 TF 和趋化因子招募更多的免疫细胞[19],同时, PAMPs (如脂多糖等)和 DAMPs 可激活 TLR 等,触发蛋白酶级联反应,促进 DIC 的发生,当单核细胞通过 TLRs 识别脂多糖时,会释放组织因子,并启动凝血级联反应,导致微血栓形成[20]。此外,单核细胞可通过核因子- κ B 等信号传导,极化为促炎性巨噬细胞 M1,并促进细胞因子的产生和细胞间的相互作用,包括与血小板和内皮细胞间的相互作用[21]。

3.2. 中性粒细胞的活化

中性粒细胞或多形核细胞作为一线免疫细胞。当其表面的趋化因子受体(CXC Chemokine Receptors, CXCRs)与趋化因子结合,启动下游信号通路,并定向迁移至炎症区域[22]。同时,中性粒细胞可释放 NETs,其主要由组蛋白、游离的 DNA 和弹性蛋白酶组成,这些成分可通过与凝血相关分子相互作用,促进免疫性血栓的形成[17]。组蛋白可激活血小板并诱导凝血酶生成,且游离的 DNA 可激活凝血因子XII,而弹性蛋白酶则会降解凝血抑制物,共同促进血凝块的形成[23][24]。NETs 受到肽精氨酸脱亚胺酶 4、脂多糖、白细胞介素-8 等多种物质调节,并在脓毒症相关的免疫性血栓形成期间中发挥作用[25]。NET 可激活凝血因子并促进血栓形成,且动物实验中发现 NET 中存在大量 TF,可放大炎症反应及促使内皮细胞转变为促凝表型,同时 NET 有助于血小板驱动凝血反应发生,进一步加剧脓毒症中的血管内皮功能障碍和凝血功能障碍[26]。此外,核因子- κ B 等可驱动细胞因子如白细胞介素-1 和白细胞介素-12 等产生,促进炎症反应[24]。

3.3. 血小板的活化

血小板作为凝血及血栓形成过程中的一环,其会参与免疫调节及免疫性血栓形成过程。血小板可表达 TLR、补体受体、Fc 受体等,合成并释放调控机体免疫应答的调节分子[27]。机体感染后,病原微生物可激活血小板,诱发病理性血栓形成及 DIC,导致多器官功能障碍,最终导致患者死亡[28]。同时,血小板对炎症反应及促凝因子很敏感,血小板活化后可通过其表面的 δ 颗粒合成血栓素 A_2 (Thromboxane A_2 , TXA_2)与二磷酸腺苷(Adenosine Diphosphate, ADP),促进血小板的聚集;同时,其膜表面的 α 颗粒会释放富含 ADP 的颗粒,并通过 G 蛋白偶联受体超家族中的 ADP 受体进一步放大血小板活化信号[29]。此外,P-选择素作为重要的炎症标志物,可与 P-选择素糖蛋白配体 1 (P-selectin glycoprotein ligand 1, PSGL-1)结合,介导血小板与单核细胞、中性粒细胞及血管内皮细胞的黏附,且脓毒症状态下的高炎症反应会促进血小板-单核细胞聚集体(Platelet-Monocyte Aggregate, PMA)及血小板-中性粒细胞聚集体(Platelet-Neutrophil Aggregate, PNA)的形成,并通过 P-选择素及其他分子保持稳定状态[18][30]。TLR4 介导的血小板与中性粒细胞间的相互作用会影响 NET 的正常生存,进而引发组织损伤及免疫血栓形成[31]。血小板中的凝血酶可促进后续凝血反应及组织因子表达,进一步放大凝血级联反应及促进 NET 形成[32]。

3.4. ECs 的激活

正常生理状态下,ECs 可表达抗炎及抗血栓分子维持血管稳态[33]。在病原微生物感染后,作为接触病原微生物及炎性介质的第一批细胞,其可被病原微生物的 PAMPs 直接激活,也可被 NETs 及白细胞介素-6、白细胞介素-1 等细胞因子间接激活[34]。与免疫细胞类似,ECs 通过 TLR 检测 PAMPs,表达粘附分子、e-选择素、p-选择素和 VWF 等,促进机体炎症反应,并与脓毒症的严重程度相关[35]。

ECs 表面的内皮糖萼是维持血管表面完整性和调节物质运输的重要结构,其主要由硫酸乙酰肝素组成。在脓毒症状态下,持续炎症及氧化应激反应促使内皮糖萼降解,且在内皮细胞损伤和细胞间连接破坏的相互作用下,使血管通透性增加及组织间隙液体蓄积,从而导致组织水肿,并促进白细胞和血小板的粘连,为细胞聚集体的形成及血管内血栓的形成创造条件。内皮细胞受损后释放的 VWF 会促进血小板黏附并产生微血栓串,且粘附因子的表达可促进白细胞向炎症中心区域聚集,细胞因子和细胞聚集体释放的 TF 又可进一步放大凝血反应,加剧血栓形成[36]。此外,组织细胞产生的 ROS、促凋亡介质等可进一步损伤内皮细胞,使凋亡的内皮细胞数量增加,而凋亡的内皮细胞中 TF 含量较高,而血栓调节蛋白及组织因子途径抑制物(Tissue Factor Pathway Inhibitor, TFPI)含量低,进一步加剧凝血反应,推动血栓炎症和免疫血栓形成,最终导致血管内皮功能障碍[37]。

4. 免疫性血栓形成中的细胞信号通路

免疫细胞和内皮细胞之间存在复杂的细胞相互作用和信号转导, 病原微生物引起的高炎症反应, 会导致多器官功能障碍及衰竭, 其主要由炎症相关信号通路介导, 包括结节样受体蛋白 3 受体通路(NOD-like receptor protein 3, NLRP3)、Janus 激酶信号转导与转录激活因子通路(Janus kinase-signal transducer and activator of transcription, JAK-STAT)、核因子- κ B、环磷酸鸟苷-腺苷合成酶-干扰素基因刺激蛋白通路(Cyclic GMP-AMP synthase-Stimulator of interferon genes, cGAS-STING)等, 共同参与介导脓毒症期间的炎症反应[38]。

4.1. NLRP3 通路

NLRP3 通路在血栓形成中起着重要作用, 其对 PAMPs 及 DAMPs 很敏感, 可通过激活半胱氨酸天冬氨酸特异性蛋白酶-1 (Cysteine-dependent aspartate-specific protease-1, caspase-1)及随后释放白细胞介素-1 β 和白细胞介素-18 引发促炎级联反应, 并分别通过 caspase-1 和 caspase-11 的激活, 促进 TF 的释放, 从而激活凝血因子 II, 启动凝血级联反应, 随后激活凝血因子 X, 进而经相同的凝血途径, 生成血栓形成所需的凝血酶[39][40]。根据现有的研究发现, NLRP3 通路也可以被其他信号通路进一步放大, 包括 cGAS-STING 通路和核因子- κ B 等。核因子- κ B 可被多种信号激活, 如 PAMPs、细胞因子及各种物理性刺激等, 该通路能将炎症反应与凝血激活过程相联系, 进而促进免疫性血栓的形成[41]。

4.2. cGAS-STING 通路

cGAS-STING 通路可被细胞内的 DNA 异常激活[42], 在脓毒症中, cGAS-STING 通路中的干扰素基因刺激蛋白被激活会同时引起炎症信号传导和凝血功能紊乱[43]。该通路可诱导穿孔素 D 生成, 其作为一种通过在细胞膜上形成孔道从而介导细胞凋亡的蛋白, 可促进组织因子的释放, 进而启动凝血级联反应[40, 44]。在脓毒症发生时, STING-IRF3-NF- κ B 信号轴被激活, 其作为固有免疫与炎症调控的核心信号通路, 可使循环中游离 DNA 水平显著升高, 并与干扰素基因刺激蛋白相互作用, 进一步加剧炎症反应[45]。此外, 干扰素调节因子 3(Interferon regulatory factor 3, IRF3)、核因子- κ B 和干扰素基因刺激蛋白可与 TANK 结合激酶 1 形成复合物, 可对下游转录因子进行磷酸化修饰, 增强其转录活性[46]。

4.3. 其他信号传导途径

参与血小板活化和血栓形成的另一个关键途径是磷脂酰肌醇 3-激酶/蛋白激酶 B 信号轴(Phosphatidylinositol 3-kinase/protein kinase B axis, PI3K/Akt axis), 该通路在血小板整合素相关的信号传导中起着重要作用。血小板整合素可通过介导细胞内及细胞间的相互作用, 在凝血和血栓形成过程中发挥重要作用[47]。此外, PI3K/Akt 通路产生的复合物可与中性粒细胞上的缺氧诱导因子-1 α 协同作用, 调控细胞糖酵解过程, 从而调节中性粒细胞活性, 加剧凝血反应[48]。

5. 脓毒症诱导免疫血栓的治疗策略

由于免疫性血栓形成的病理生理机制十分复杂, 目前仍没有针对该病症的单一、有效及安全的治疗方式。根据现有的研究方向, 由于凝血在微血管血栓形成及炎症放大中起核心驱动作用, 抗凝治疗可有助于改善微血管灌注、减轻炎症反应并维持器官功能。在目前临床实践中, 大部分抗血栓治疗方案均以采用针对促凝因子及促炎分子的抗凝药物为主。对于合并脓毒症的患者, 临床通常采用抗生素联合抗凝剂治疗, 但抗凝剂的长期应用会使出血的风险显著升高[49]。

对于凝血功能障碍的患者, 目前研究最为广泛的兼具抗凝与抗炎活性的药物为肝素类制剂(包括天然

肝素与合成肝素),被广泛用于脓毒症相关凝血功能障碍及静脉血栓栓塞的预防与治疗中。在目前的临床实践中,其主要并发症为出血及肝素引起的血小板减少症,且普通肝素出现并发症的风险更高,但根据现有研究发现,肝素在抗凝血活性之外,还具有抗炎、保护细胞内皮糖萼等作用,且可提高脓毒症患者的临床疗效[50]。同时,有研究表明,肝素还可作为吸附分子结合多种凝血相关成分,包括血小板外囊泡、血小板因子、组蛋白及高迁移率族蛋白 1 (HMGB1)等[51]。此外,活化蛋白 C、抗凝血酶、TFPI、凝血调节素等天然抗凝剂也已应用于抗凝治疗[52]。

在脂多糖诱导的脓毒症模型中,血小板 P2Y₁₂ 抑制剂,如氯吡格雷、替格瑞洛,已被证实可显著削弱 P2Y₁₂ 的促炎及促血栓效应[53]。同理,糖蛋白 IIb/IIIa (GPIIb/IIIa)抑制剂,包括前列环素、依替巴肽、替罗非班及阿司匹林,也被证实对脓毒症相关凝血并发症具有治疗效果[54]。同时,针对组织因子激活途径的抑制剂已完成相关研究并推向临床应用阶段,此类药物主要针对外源性凝血途径,作用机制与 TFPI 相似[55]。此外,有研究报道部分药物可通过抑制肽酰精氨酸脱亚胺酶 4 (PAD14)或通过拮抗 CXCRs 抑制 NETs 形成,从而减少脓毒症中 NETs 介导的血栓形成[56] [57]。

在动物实验中,针对细胞表面受体的抗体可有效抑制补体活化、减少细胞因子释放并抑制炎症反应,可提高实验动物的生存率[58]。同时,MCC950 可通过抑制 NLRP3 通路,抑制血小板的活化水平及细胞因子生成[59]。此外,抗抑郁药阿米替林可下调肿瘤坏死因子- α 表达及调控巨噬细胞极化,减轻炎症反应,进而抑制脓毒症小鼠模型的凝血功能异常[60]。目前已有大量体内外研究对脓毒症相关的凝血功能障碍的治疗药物进行评估并进行了大量临床试验,但大部分研究的结果均不尽人意,受治疗相关的并发症及改善凝血异常的效果有限等因素影响,此类药物的临床应用仍十分有限。

6. 结语与展望

脓毒症相关的免疫性血栓形成本质上是过度的炎症反应与凝血系统的交互作用,表现为促炎细胞因子与趋化因子的大量产生,破坏生理性血栓形成与纤溶的正常稳态平衡,炎症细胞的持续激活(包括单核细胞、巨噬细胞、中性粒细胞及 NETs、血小板及 ECs 等)会促进促凝物质与凝血因子的活化,最终导致微血管血栓形成。此过程依赖于多种细胞内信号通路的介导,如 NLRP3 通路、JAK-STAT 通路、cGAS-STING 通路、核因子- κ B 等通路,在脓毒症相关的凝血功能障碍的细胞信号转导中发挥核心调控作用。目前,抗炎与抗凝治疗是临床常用的治疗手段,但出血风险及治疗相关性出血仍是目前的主要问题。因此,掌握脓毒症不同阶段的动态变化,并应用精确的个体化治疗亦是未来研究的目标,未来可专注于发现能实时反映机体炎症与凝血反应的生物标记物,以精准干预炎症及凝血级联反应的关键点,同时可进一步完善如选择性 NLRP3 抑制剂及免疫调节剂等靶向治疗的临床验证,以改善脓毒症相关凝血功能障碍的临床治疗。

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