脓毒症与中性粒细胞的移行异常

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摘要 脓毒症是危重病人死亡的主要原因, 近年来发病率仍在上升。脓毒症的病理机制是免疫系统功能失调。中性粒细胞是机体重要的免疫细胞, 许多研究表明, 在脓毒症时中性粒细胞的功能异常会影响患者预后。该文将探讨脓毒症时中性粒细胞的移行异常。

关键词 脓毒症; 中性粒细胞; 滚动; 黏附; 迁移; 募集

Sepsis and Neutrophil Abnormal Migration

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Abstract Sepsis is one of the top leading causes of death in intense care unit patients, which is becoming more prevalent in recent years. It is well known that the pathological mechanism under sepsis is the impaired immunological function, and neutrophils are the important immune cells in the body. Recently, more and more studies showed that the dysfunctional neutrophils might affect prognosis in sepsis patients. This review focus on exploring abnormal migration capacity of neutrophils in sepsis.

Keywords sepsis; neutrophil; rolling; adhesion; migration; recruitment

脓毒症的最新定义为机体对感染的反应失调而导致危及生命的器官功能障碍[1]。虽然很早就认识到这种疾病, 但是由于病理过程的复杂性, 目前的治疗措施主要是控制感染源、使用抗生素以及其他的支持治疗, 没有针对脓毒症的特异性治疗方案。近年来随着诊疗技术和护理技术的进步, 脓毒症的死亡率有所下降, 但发生率仍在增加。德国自2007年至2013年脓毒症的发病率每年平均增加5.7%[2]。研究证实, 免疫系统的功能紊乱是脓毒症最主要的特点, 即过度的炎症反应以及免疫细胞功能的异常[3-4]。

中性粒细胞的迁移对于病原体的清除和脓毒症病人的预后十分重要。中性粒细胞从外周血到达炎症部位需要经过在内皮细胞腔面滚动、黏附、跨内皮迁移、募集这几个步骤。在脓毒症早期, 过多的中性粒细胞移行可能导致炎症的加剧; 在脓毒症后期, 中性粒细胞移行异常以及数量的下降导致机体免疫功能异常, 不能控制病原体。

1 脓毒症时中性粒细胞滚动减少

机体感染时, 细菌的LPS(lipopolysaccharide)、fMLP(formyl-methionyl-leucyl-phenylalanine)及机体释放的细胞因子[如TNF-α(tumour necrosis factor-α)、IL-1β(interleukin)、IL-17]促进炎症部位内皮细胞表达P-选择素、E-选择素以及整合素超家

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族ICAM(intercellular adhesion molecule)等黏附分子的表达[5]。中性粒细胞微绒毛表达的P-选择素糖蛋白受体-1(P-selectin glycoprotein ligand-1, PSGL-1)、L-选择素[6-7]与内皮细胞表面P-选择素和E-选择素相互作用, 中性粒细胞开始在血管壁上滚动。中性粒细胞在血管壁上的滚动是迁移至炎症部位的始动阶段[5]。脓毒症时, 促炎因子和细菌产物可导致中性粒细胞的僵化[8], 僵化的中性粒细胞可变性发生了改变, 在血管内皮上滚动的中性粒细胞数量减少, 中性粒细胞更易聚集于某一部位导致血管闭塞引起局部缺血以及器官功能紊乱[9-10]。脓毒症时, 中性粒细胞滚动减少(图1)。

2 脓毒症时中性粒细胞与内皮细胞黏附改变

中性粒细胞在内皮上滚动, 选择素促进中性粒细胞表面的β2整合素LFA-1(lymphocyte function-associated antigen 1)和MAC-1(macrophage-1 antigen)活化聚集[11-12], 与内皮细胞表面免疫球蛋白超家族ICAM-1、ICAM-2结合, 中性粒细胞滚动停止, 牢固黏附于内皮细胞表面。脓毒症时, 中性粒细胞和内皮细胞表面的黏附分子的表达发生了变化。盲肠结扎穿孔(cecal ligation puncture, CLP)小鼠肺部、胸腺和脾脏*ICAM-1* mRNA的表达量明显上升。使用ICAM-1特异性抗体后中性粒细胞渗透入非炎症器官例如肺脏、胸腺、脾脏的数量减少, 进入腹腔的数量有明显增加, 肺部损伤明显减轻, 机体清除细菌的能力增加, 脓毒症的死亡率下降。ICAM-1在非特异性器官内皮细胞的过度表达, 可能是导致脓毒症引起的器官功能紊乱的主要原因[13]。脓毒症活化乙酰肝素酶, 肺部微血管内皮表面的多糖–蛋白质复合物被降解, 黏附分子ICAM-1和VCAM(vascular cell adhesion molecule)暴露, 促进中性粒细胞黏附在内皮上, 引起肺部损伤[14]。脓毒症时肺脏血管内中性粒细胞增多(图2)。

3 脓毒症时中性粒细胞迁移紊乱

牢固黏附于内皮细胞后, 中性粒细胞需要穿过血管内皮细胞和基质层到达感染部位。脓毒症时中性粒细胞迁移有利于细菌的消除, 但也会导致器官功能紊乱。脓毒症病情的发展主要是由于中性粒细胞不能到达感染部位清除病原微生物, 同时有过多的中性粒细胞募集到非炎症部位引起器官损伤。

3.1 CXCR2的表达异常影响中性粒细胞迁移

脓毒症时细菌刺激中性粒细胞TLRs(Toll-like receptors), 上调G蛋白偶联受体激酶2(G protein-coupled receptor kinase 2, GRK2), 中性粒细胞CXCR2(C-X-C chemokine receptor 2)内化, 表达减少, 迁移能力下降[15]。死于脓毒症的病人中性粒细胞CXCR2表达量下降, 并且依赖CXCR2途径的趋化能力下降[16]。研究表明, TLR2缺失的脓毒症小鼠中性粒细胞CXCR2表达正常, TLR2的激动剂上调GRK2, 抑制中性粒细胞表面CXCR2的表达[17]。类凝集素氧化型低密度脂蛋白受体-1(lectin-type oxidized LDL receptor-1, LOX-1)是表达于内皮细胞的膜蛋白, 研究发现, LOX-1也表达于中性粒细胞的表面, 脓毒症

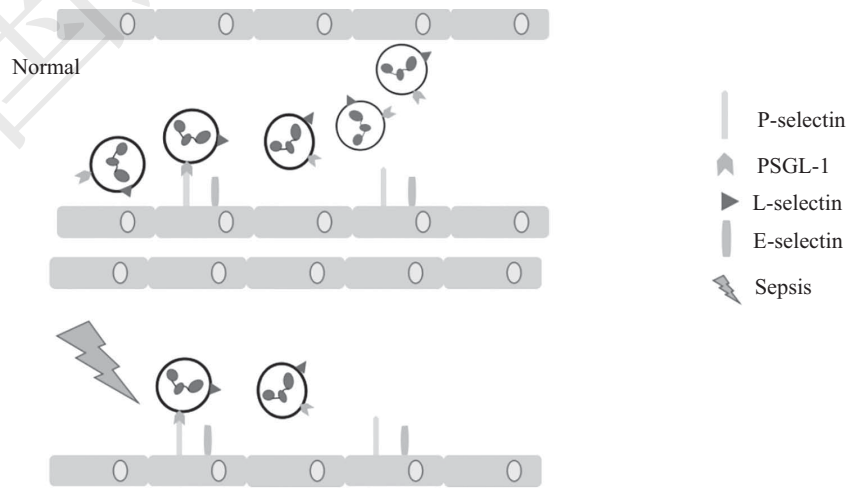

图1 脓毒症时中性粒细胞滚动减少

Fig.1 The number of rolling neutrophil decreases in sepsis

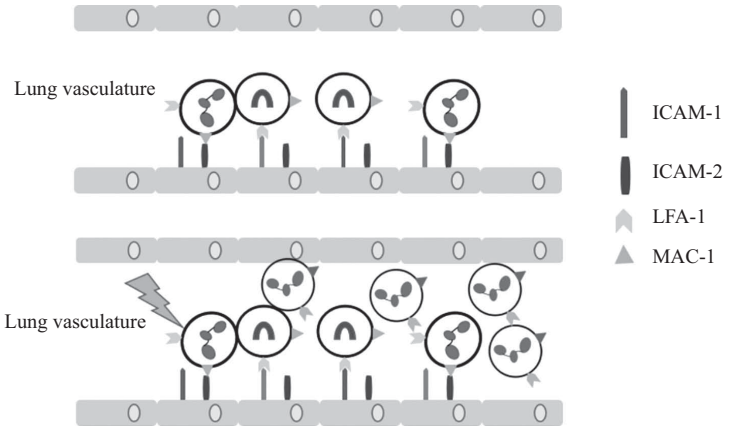

图2　脓毒症时肺脏血管中性粒细胞增多

Fig.2　The number of neutrophil in lung vasculature increases during sepsis

时, LOX-1的表达升高。*LOX-1*缺失的小鼠CLP处理后中性粒细胞表面CXCR2下调被抑制, 表明在脓毒症时中性粒细胞表面LOX-1表达增加, 抑制CXCR2的表达, 导致中性粒细胞的迁移能力下降[18]。

3.2　整合素高表达引起中性粒细胞迁移增多

整合素是跨膜的异二聚体受体, 在细胞迁移中发挥重要作用。脓毒症时, 整合素的表达异常导致中性粒细胞迁移功能受损。β1/CD29介导淋巴细胞在血管周和细胞外基质中黏附和运动, 主要与富含精氨酸–甘氨酸–天冬氨酸的序列(arginylglycylaspartic acid, RGD)结合[19]。脓毒症时, 人和小鼠的中性粒细胞β1/CD29表达上调, 条件性敲除*β1*后, 中性粒细胞的迁移减少脓毒症的死亡率也下降。使用环形RGD类似物可以减少活化的中性粒细胞的外渗和迁移, 从而提高脓毒症的生存率[20]。近期研究发现, 使用人工合成的RGD多肽可以减少肺部中性粒细胞和巨噬细胞的迁移和聚集, 从而减轻肺脏的炎症损伤[21]。Yelena等[22]发现, 脓毒症患者中性粒细胞高表达α3β1, 使用抑制剂或者条件性敲除粒细胞*α3β1*可以明显减少中性粒细胞的渗出, 提高脓毒症小鼠的存活率。

3.3　TLRs信号通路参与中性粒细胞的迁移过程

脓毒症时, 细菌或者内源性配体HMGB-1(high mobility group box-1)、HSP70(heat shock proteins 70)激活TLRs[23], 活化MyD88(myeloid differentiation primary response 88), 进而激活转录因子[NF-κB(nuclear factor kappa-light-chain-enhancer of activated B cells)、AP-1(activator protein 1)]、促进促炎因子(TNF-α、IL-6、IL-1β)表达。*TLR2*(Toll-like receptor 2)、*TLR4*、*MyD88*缺失的小鼠CLP处理后迁移至肾脏的中性粒细胞明显减少[24]。*TLR4*基因敲除小鼠CLP处理后, 中性粒细胞迁移至感染部位能力正常[25], 到达腹膜腔的数量正常, 对脓毒症抵抗能力增强迁移至肺部的数量下降[26]。CCR2(C-C chemokine receptor type 2)是表达在单核细胞表面的趋化因子受体, 静息状态下人和小鼠中性粒细胞不表达。CLP小鼠中性粒细胞检测到*CCR2* mRNA的表达, 并且表现出CCL2[chemokine (C-C motif) ligand 2]的趋化迁移能力[27]。脓毒症时, 感染部位病原体或者其产物释放入血, 激活TLR信号通路[28], 通过MYD88/NF-κB上调外周血中性粒细胞CCR2的表达, 促进中性粒细胞迁移至非炎症部位引起器官损伤, *CCR2*的敲除可以提高脓毒症小鼠的存活率。脓毒症患者的中性粒细胞CCR2表达增高, 并且CCL2趋化能力增高, 病情严重程度和中性粒细胞表面CCR2的表达量正相关[29]。脓毒症时, 中性粒细胞迁移相关分子通路的改变(图3)。

3.4　中性粒细胞表面特定分子改变中性粒细胞的迁移

ADAM17(ADAM metallopeptidase domain 17)是一种表达在中性粒细胞、内皮细胞表面的金属蛋白酶[30], 主要功能是切除跨膜蛋白胞外区域。CLP小鼠和脓毒症患者中发现ADAM17活化异常。外周血中性粒细胞表面ADAM17表达的上调与脓毒症的严重程度和转归相关[31]。在CLP脓毒症模型中, 条件性敲除*ADAM17*的小鼠生存率提高, 细菌数量以及促炎因子水平都下降[32]。脓毒症引起ADAM17活化增强, 导致中性粒细胞在血管内黏附和去黏附失衡, 血

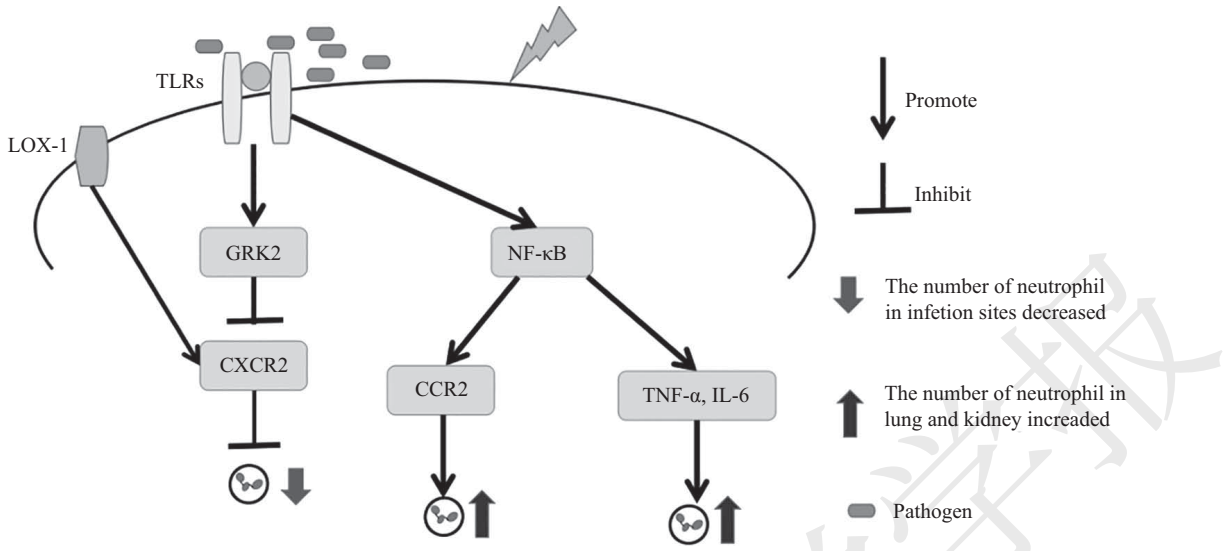

图3 脓毒症时中性粒细胞迁移相关分子通路的改变

Fig.3 Changes in molecular pathways associated with neutrophil migration in sepsis

液中ADAM17的底物TNF-α浓度增高, 中性粒细胞僵化, 整合素黏附分子表达上调, 微血管系统堵塞, 局部缺血, 细胞因子释放导致局部组织损伤[10,17,33]。

研究发现, A3腺苷受体以及P2Y2嘌呤受体在中性粒细胞的趋化过程中发挥重要作用[34]。*A3*和*P2Y2*缺乏的小鼠发生脓毒症后, 肺部中性粒细胞数量明显下降[35], 表明在脓毒症时A3和P2Y2受体促进中性粒细胞趋化迁移至肺部引起肺部损伤。胃泌素释放肽受体(gastrin releasing peptide receptor, GRPR)是七次跨膜G蛋白偶联受体, 在趋化因子活化中性粒细胞的信号通路中发挥重要作用。研究发现, 脓毒症时, GRPR拮抗剂可以下调TLR-4的表达, 并且其下游的信号通路也被抑制, 促进中性粒细胞迁移至感染部位, 清除细菌, 改善脓毒症的结局[36]。

4 脓毒症时, 中性粒细胞募集异常

活化的中性粒细胞募集至感染部位在保护机体中发挥了重要作用。CLP引起的脓毒症严重程度与腹腔内募集的中性粒细胞的数量有关。研究发现, 缺乏*CXCL1*的小鼠在CLP处理后, NF-κB的活化减少[37], 影响例如ICAM-1这样的黏附分子的表达, 导致中性粒细胞募集能力下降, 腹膜内白细胞总数和中性粒细胞的数量下降, 并且从腹膜以及其他器官中清除细菌的能力也下降, 导致生存率下降[38]。

脓毒症时, 中性粒细胞在肺部的过多募集是导致肺部损伤的主要原因。在白假丝酵母菌引起的致死脓毒症小鼠和人肺部血管循环模型中, 白假丝酵母菌依赖补体促进肺部中性粒细胞产生白三烯B4(leukotriene B4, LTB4), LTB4募集更多的中性粒细胞至肺部血管, 大量中性粒细胞聚集在血管引起血管炎症, 引起肺部损伤[39]。CLP小鼠中性粒细胞表面Mac-1的表达上调, 趋化因子表达量增加, 肺部中性粒细胞数量增加[40]。ρ蛋白激酶(Rho-associated protein kinase, ROCK)抑制剂Y-27632可以显著减少支气管肺泡中性粒细胞的数量[41]。同时, 外周血中性粒细胞表面Mac-1的表达下降, 趋化因子CXCL1和CXCL2的含量下降[40]。另外ρ-激酶促进外周血中性粒细胞表达F-肌动蛋白, 中性粒细胞的骨架蛋白改变, 导致中性粒细胞聚集于肺部[42]。研究发现, 小鼠CLP处理后, 支气管肺泡液中性粒细胞MPO(myeloperoxidase)的水平提高了10倍以上, 使用PSGL-1和P-选择素的抗体后, 脓毒症小鼠支气管肺泡液内中性粒细胞的数目明显下降, 外周中性粒细胞数量增加。研究表明, 脓毒症时, 中性粒细胞表面的PSGL-1促进了肺部中性粒细胞的募集, 过多的中性粒细胞聚集于肺部引起损伤[43]。Rac-1(Ras-related C3 botulinum toxin substrate 1)作为信号分子参与细胞黏附、趋化、血管渗透以及细胞骨架变构多种过程[44]。Rac-1在脓毒症小鼠的肺部活动增强, Rac-1的抑制剂可以明显下调中性粒细胞Mac-1的表达以及肺部CXC趋化因子的形成[45]。脓毒症时, Rac-1信号通路促进中性粒细胞募集并隔离在肺部, 引起肺组织的损伤。受体结合丝氨酸苏氨酸激酶3(receptor-interacting serine/threonine-protein kinase

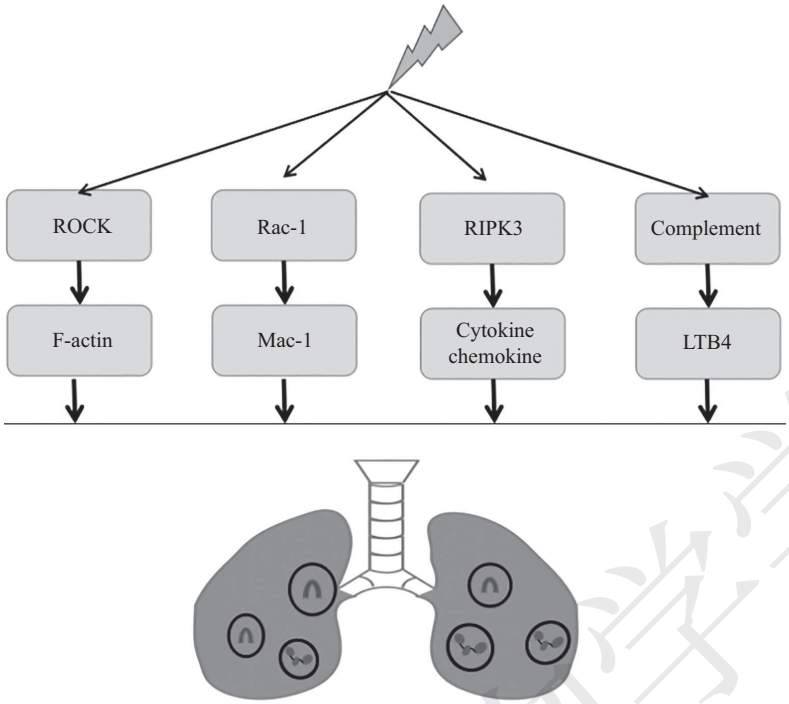

图4 脓毒症时, 更多中性粒细胞募集至肺部

Fig.4 More neutrophils recruit to lung vasculature in sepsis

3, RIPK3)是丝氨酸苏氨酸蛋白激酶家族的成员。*RIPK3*缺失的脓毒症小鼠中性粒细胞募集到肝脏和肺部的数量明显减少、生存延长并且肝脏和肺部的损伤减轻[46]。在脓毒症时RIPK3通过调节细胞因子和趋化因子的产生促进中性粒细胞募集到肝脏、肺部导致组织损伤(图4)。

5 小结与展望

脓毒症是由于免疫系统对感染过度反应造成机体损伤而形成的一种复杂的临床综合征[47]。虽然脓毒症的死亡率有所下降, 但死亡率仍然很高。中性粒细胞在感染性疾病尤其是脓毒症中发挥十分重要的作用。然而脓毒症时, 中性粒细胞的功能发生异常, 加剧疾病的进展。中性粒细胞不能及时迁移募集至感染部位, 更多的迁移隔离在非感染器官造成远端器官的损伤。

脓毒症时, 中性粒细胞的各种功能的改变会影响疾病的进程, 明确这些改变对于疾病的影响可以帮助临床寻找新的治疗靶点, 制定新的治疗方案。目前研究表明, 某些小分子药物在小鼠脓毒症模型中证明有较好的疗效, 未来在这一方面深入研究可能会有很大的突破。例如, TLRs信号分子通路中多个分子参与调节中性粒细胞的迁移和募集; 特异性抑制或活化某些分子在很大程度上改善脓毒症的结局。整合素在中性粒细胞迁移过程中发挥重要作用, 特异性调节整合素的表达可以减轻远端器官的损伤。中性粒细胞表面一些特异性分子在脓毒症发病过程中发挥重要作用, 靶向抑制或活化也可提高脓毒症的生存率。这些小分子的临床效果也需要进一步的研究。

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