

脓毒症时血管内皮细胞与血管平滑肌细胞相互作用的进展

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【摘要】 血管内皮细胞(EC)与平滑肌细胞(SMC)是炎症反应中的靶细胞及效应细胞,其结构和功能异常在微循环障碍、脓毒性休克及多器官功能损伤中起着重要作用。本综述回顾了脓毒症时血管EC和SMC的结构功能改变及EC/SMC双向调节作用的相关研究进展,揭示了血管EC和SMC介导的细胞间信号传递对脓毒症的发生发展具有重要的意义。EC和SMC的旁分泌及自分泌构成了细胞间相互调节的网络,改善血管EC和SMC有可能加强对循环系统的控制,支持血流动力学,恢复组织灌注,使细胞代谢正常化,从而降低脓毒症患者的病死率,但具体机制尚有待进一步阐明。

【关键词】 脓毒症; 内皮细胞; 平滑肌细胞

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【Abstract】 Vascular endothelial cells (EC) and smooth muscle cells (SMC) are target and effector cells of inflammation, and they play an important role in inflammatory responses. The abnormal structure and function of EC and SMC play a significant role in microcirculation disturbance in septic shock and multiple organ dysfunction. This review was meant to discuss the changes in structure and function of EC and SMC and their bidirectional regulation. The cellular linkage of EC and SMC is essential for the interactions between them, and it contributes to the course of sepsis. Paracrine and autocrine as produced by EC and SMC constitute a network for mutual adjustment. Replication of the interaction between EC and SMC facilitates the potential to support hemodynamics, tissue perfusion and cellular metabolism, thereby lower the mortality rate of sepsis. However, the detailed and specific mechanisms remain to be disclosed.

【Key words】 Sepsis; Endothelial cell; Smooth muscle cell

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脓毒症是严重创伤、休克及感染等临床急危重症患者的常见严重并发症之一,进一步发展可导致脓毒性休克、多器官功能障碍综合征(MODS)^[1]。一份来自北美的流行病学调查结果显示,美国每年有75万例脓毒症患者,其中9%发展为严重脓毒症,3%发展为脓毒性休克,超过21万人(28%)死亡^[2]。虽然对脓毒症病理生理机制进行的研究涉及了细胞和分子机制^[3],但病死率仍居高不下,最主要的因素是顽固性血管低反应和多器官功能衰竭(MOF)^[4]。脓毒症时由于液体摄入量减少,血管内的液体转移进入组织间隙,导致机体有效循环血容量减少^[5]。虽经足量液体复苏,但血流动力学依然不稳定;即使应用血管活性药物使血管收缩压得到一定程度的改善,但机体存在的组织低灌注(乳酸性酸中毒)和器官功能障碍仍未得到明显改善^[6-7]。此外,脓毒症时产生的多种细胞因子和酸中毒对心肌产生抑

制作用,使心脏收缩力减退,心室扩大,射血分数降低;更重要的是造成血管内皮细胞(EC)和平滑肌细胞(SMC)损伤,改变细胞微环境,使EC与SMC的双向调节作用紊乱,机体对血管活性物质反应低下,进一步导致血流动力学紊乱以及血管功能障碍^[8-9]。现就脓毒症时血管EC和SMC的结构功能改变及EC与SMC的双向调节作用的相关研究进展进行阐述。

1 脓毒症时血管EC、SMC的结构和功能受损

血管EC和SMC是炎症反应的靶细胞及效应细胞,其结构与功能异常在微循环障碍、脓毒性休克及多器官功能损伤中起着重要作用,与免疫系统的功能异常共同视为脓毒症发生发展的病理基础^[10-11]。

1.1 脓毒症时EC的结构和功能改变: 正常的EC主要发挥抗凝作用,可有效防止血栓形成。而EC损伤时会参与外源

性凝血过程,加重血栓的形成。脓毒症时,EC的凝血功能也发挥着重要作用。脓症患者是否存在凝血功能障碍,或者凝血功能是否得到纠正与预后息息相关^[12]。当EC结构和功能发生改变时,将不利于脓毒症患者的预后。

正常的EC相互连接,覆盖于血管内膜表面,形成一个连续的细胞单层结构以维持血管内膜光滑,从而起到有效的被覆屏障作用。连续的细胞单层结构形成了广大的面积,通过EC的空隙改变血管通透性,为血液和组织提供物质交换。EC释放前列环素(PGI₂)、一氧化氮(NO)、内皮源性超极化因子(EDHF)等来舒张血管,释放内皮素(ET)、血栓素A₂(TXA₂)、血管紧张素II(Ang II)等收缩血管,以维持血管张力^[13]。EC通过信号转导释放多种炎性介质来介导炎性细胞向损伤组织聚集,并合成分泌白细胞介素-8(IL-8)、单核细胞趋化蛋白-1(MCP-1)等多种趋化因子,介导白细胞从血管迁移至炎症损伤部位,参与炎症反应。

脓毒症时微循环血流量减少,特别是小血管,使功能性的血管密度减低,非灌注和暂时灌注的血管比例增加,导致氧供调节受损,使EC之间的通透性增加,从而造成被覆屏障损伤,循环中大量物质由EC间隙进入组织中,造成组织水肿^[14]。脓毒症时EC通过表达多种细胞因子及黏附分子[如细胞间黏附分子-1(ICAM-1)、血管细胞间黏附分子-1(VCAM-1)、E-选择素]、炎性介质[如细胞因子IL-1、IL-3、IL-6、IL-8、肿瘤坏死因子(TNF)]、趋化因子等参与炎症反应^[15-16]。这些炎性介质之间的相互作用可放大炎症反应,导致促炎反应和抗炎反应失调,进一步加重脓毒症;EC也参与凝血的启动、调节及纤溶系统的激活和抑制;EC凋亡是脓毒症病程中的一个重要事件^[17]。

EC线粒体生成过多的活性氧簇(ROS)是脓毒症发病机制中的上游因素^[18]。线粒体本身存在抗氧化系统,且该系统的功能与线粒体生物合成密切相关,而ROS的生成及清除均与线粒体生物合成密切相关。脓毒症时EC线粒体的动态变化在一定程度上决定着EC的结构与功能,对脓毒症时EC线粒体的干预必定是研究脓毒症EC病理过程的重要措施,是发现干预新靶位的环节^[19]。

内皮微粒(EMPs)是EC激活或凋亡状态下释放的亚微米级颗粒,由EC囊泡化产生^[20-22]。细菌脂多糖(LPS)、细胞因子、补体复合物、聚集的低密度脂蛋白或ROS可通过激活EC产生EMPs, Ca²⁺升高在EMPs释放过程中也发挥了重要作用。脓毒症时此类活化的血管内皮细胞微粒增加,EMPs被证实具有促凝、促炎、加重内皮功能障碍和促进血管生成等作用^[23],但对EMPs生成的调节作用尚为空白。

1.2 脓毒症时SMC的结构和功能改变:SMC是血管中层唯一的细胞成分,位于血管中膜。正常的SMC通过PGI₂、NO、EDHF、ET、TXA₂、Ang II等刺激血管舒张或收缩来调节血管张力,通过分泌和释放血管调节因子维持血管正常功能。受体通过探测周围环境变化,将刺激信号转导到胞内,改变细胞表型,产生促平滑肌增殖的物质,促进SMC增殖、肥大或分泌细胞外基质(ECM),协同EC促进血管重建。SMC细胞

内游离钙离子([Ca²⁺]_i)、膜电位、SMC线粒体跨膜电位以及血管EC和SMC的肌-内皮连接结构及表型等在维护血管舒缩功能上十分重要,脓毒症时均可发生明显的改变^[24]。

SMC线粒体功能紊乱在脓毒症和多器官功能障碍发生中具有非常重要的作用^[25]。线粒体本身的损害导致细胞缺氧,此时线粒体受损,ATP合成障碍,引起能量代谢障碍,造成组织中的能量减少。SMC线粒体损伤后一个重要的变化是发生线粒体通透性转变(MPT),其中线粒体通透性转变孔(MPTP)开放是重要原因^[26]。MPTP高通透性开放可引起线粒体氧化磷酸化解耦联及ATP水解加速, MPTP开放是线粒体损伤从可逆向不可逆过渡的一个关键因素。因此,增加MPTP的关闭能力或降低MPTP的开放程度能够对脓毒症的SMC损伤起到保护作用。

SMC中的[Ca²⁺]_i水平是反映细胞内收缩舒张耦联状态最直接有效的指标。内皮源性舒张因子(EDRF)、内皮源性收缩因子(EDCF)、EDHF和促SMC生长因子等与SMC表面受体结合后,都要通过胞质内[Ca²⁺]_i增高这一信号转导机制来发挥作用^[27]。目前发现的受体操纵型钙通道(ROC)和电压调控的钙通道(VOC)是SMC重要的钙通道,其中VOC是SMC外Ca²⁺进入细胞内的主要途径,当SMC受体激活时,胞外的Ca²⁺通过VOC进入SMC内并触发钙池释放Ca²⁺,引起SMC内[Ca²⁺]_i升高,使SMC收缩;同时SMC内钙池储存有大量Ca²⁺,受某些刺激时也可向细胞质中释放大量Ca²⁺。研究脓毒症时SMC内[Ca²⁺]_i的动态变化,是明确脓毒症时SMC内收缩舒张耦联状态的主要途径,也将是干预SMC功能、血管功能的主要靶位。

2 EC与SMC的相互作用及其对脓毒症的影响

2.1 肌内皮缝隙连接(MEGJ):MEGJ是SMC和EC之间除可扩散的媒介以外的一种电连续性,存在于相邻EC以及EC和SMC之间。MEGJ是EC与SMC之间信息传递的重要组织结构,对EC与SMC的交流及血管扩张起重要作用^[28-29]。EC受损及血管内环境损伤改变会使MEGJ消失。以MEGJ为结构基础的接触介导性信息联系方式在EC损伤后的修复过程中发挥重要作用,通过该联系方式不但可以调整EC的迁移和增殖,同时也是SMC接受EC产生第二信息的重要途径,对维持SMC的收缩表型十分重要。

2.2 缝隙连接蛋白(Cx):Cx是构成MEGJ的主要蛋白,尤其是Cx37、Cx40、Cx43以及Cx45。相邻的EC之间通过低阻力的MEGJ进行联系,促进了电连续性和超极化的传播,对微循环中的血管扩张起到关键作用。EC可以同时表达Cx37、Cx40和Cx43,其中Cx37表达量最高。Cx43是维持EC连续性及完整性所必需的,在大动脉和血流异常区域的表达较高。SMC可以协同表达Cx43、Cx40、Cx45和Cx37,以Cx43表达量最高。不同的连接子由不同的连接蛋白构成,不同类型的缝隙连接通道又由不同的连接子构成,因此,电导率和通透性以及门空通道可构成不同类型、不同功能的缝隙连接^[30]。不同Cx形成的缝隙连接具有不同的通透性,可选择性地穿过不同的第二信使,如环磷酸鸟苷(cGMP)、环

磷酸腺苷(cAMP)、Ca²⁺或三磷酸肌醇(IP3)^[31]。

2.3 组织因子途径抑制物(TFPI):TFPI为内源性丝氨酸蛋白酶抑制剂,主要由EC合成,SMC中也有少量表达^[32]。TFPI是外源性凝血途径中最主要的生理性负性因子,在凝血途径启动后才会通过与FVIIa和FXa结合来发挥抗凝作用^[33]。脓毒症时,组织因子(TF)与血浆中FVII、FXa结合以激活外源性凝血途径。近年来研究表明,TFPI除有上述作用外,还对某些细胞具有调控作用。TFPI重组蛋白对SMC具有明显的抑制作用,同时也可诱导EC凋亡^[34-36]。

2.4 EC的自分泌和旁分泌:正常EC的自分泌和旁分泌有抑制EC和SMC增殖的作用;而受损的EC自分泌和旁分泌可促进SMC的增生,但对EC自身的调节尚未明确。EC在调节血管SMC的生长和产生一系列生长因子方面发挥了重要的作用,这些生长因子包括血小板源性生长因子(PDGF)、碱性成纤维细胞生长因子(bFGF)、胰岛素样生长因子-1(IGF-1)以及生长抑制因子(如肝素)。EC来源的ET-1是一个潜在的血管收缩剂,在血管平滑肌上也有抗恶性细胞增殖的作用,其合成受NO抑制。EC的损伤导致了抗增殖和促增殖刺激间的平衡紊乱,引起内皮增生^[37-40]。

脓毒症时,血管异常意味着血管EC与SMC间的平衡机制被打破。SMC在维持血液流动、调节血管紧张性以及调节炎症和免疫过程中发挥了重要作用^[41]。而EC在调节分子和细胞穿越血管壁的过程中是被动的,在调节平滑肌的过程中是主动的^[42]。既考虑到EC和SMC的单独作用,又考虑到两个细胞的相互调节作用,才能对进一步研究脓毒症的血管生理学和病理机制变化产生更重要的意义。

此外,脂肪周围组织(PVAT)也可以影响SMC,同时也潜在影响了EC的功能,这种影响既依赖于脂肪来源的脂肪因子,也依赖于还原型烟酰胺腺嘌呤二核苷酸磷酸(NADPH)氧化酶产生的ROS。因此,来自EC的可扩散的媒介可以影响靠近血管腔内侧的血管平滑肌。来自PVAT的可扩散的媒介可通过外膜层调节血管功能,但有研究发现,PVAT来源的可转移因子在大鼠胸主动脉不受内皮约束,而是内皮依赖的血管舒张行为^[43]。NO、过氧化物以及H₂O₂有助于脂联素的生成,而脂联素可通过PDGF来抑制SMC的迁移和增殖,这种抑制作用是PVAT通过内皮依赖和非依赖机制完成的^[43]。脂联素可通过磷脂酰肌醇3-激酶/苏氨酸激酶(PI3K/AKT)的合成以及蛋白激酶(AMPK)信号通路促进NO的产生。同时,脂联素也抵消了高糖诱导的氧化应激效应,表明PVAT是促氧化和抗氧化的来源^[44]。

3 展 望

血管EC与SMC之间的连接方式介导的细胞间信号传递在细胞之间的相互调节,对脓毒症的发生发展具有重要意义。EC和SMC的旁分泌及自分泌构成了细胞间相互调节的网络,对了解细胞间的相互调节机制及其在病理条件下的变化具有重要意义,并可能成为干预病变的新靶点^[45]。因此,改善血管EC和SMC功能可有效加强循环系统的控制及血流动力学支持,恢复组织灌注,使细胞代谢正常化,从而降

低病死率。目前对于脓毒症时血管EC与SMC间相互调节作用的研究尚处于起始阶段,很多问题尚未明确,如多少介质进行了跨膜传递?介质进入另一细胞后的信号转导过程如何?以上问题均有待进一步阐明,为探索细胞间信号传递开拓新的领域,并为干预其病理变化寻找新的靶点。

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