

骨髓来源抑制细胞在创伤后全身炎症反应免疫抑制中作用的研究进展

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[摘要] 创伤应激可导致宿主产生过度的全身炎症反应, 这些异常是由于对感染的不受控制的反应而发生的, 而后期多种机制的作用会导致机体免疫功能处于抑制状态, 从而增加脓毒症、多器官衰竭和死亡的风险。免疫抑制机制可调节宿主在清除抗原同时防止继发组织损伤和促进组织修复, 而骨髓来源的抑制细胞是介导免疫抑制的主要活性细胞之一, 在不同的病理生理时期发挥不同的作用, 在创伤早期主要功能是促进组织修复和伤口愈合, 而创伤远期可能导致持续性炎症、免疫抑制和分解代谢综合征。本文从多发创伤后免疫炎症反应的不同病理生理阶段, 探讨骨髓来源的抑制细胞早期的短暂激活和后期的持续病理激活介导的免疫抑制机制对疾病及转归的积极和消极作用。

[关键词] 髓源抑制细胞; 创伤; 全身炎症反应; 免疫抑制; 免疫调节

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Study on immunosuppressive effect of bone marrow-derived suppressor cells in trauma induced inflammatory response

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[Abstract] Traumatic stress can lead to an excessive systemic inflammatory response in the host, which occurs as a result of an uncontrolled response to infection, while later multiple mechanisms can lead to a suppressed immune function, which increases the risk of sepsis, multiple organ failure, and death. The immunosuppressive mechanism can regulate the host to clear antigens while preventing secondary tissue damage and promoting tissue repair. As one of the main active cells mediating immunosuppression, myeloid derived suppressor cells from bone marrow play different roles in different pathophysiological periods, and their main function is to promote tissue repair and wound healing in the early stage of trauma. Long-term trauma may lead to persistent inflammation, immunosuppression, and catabolic syndrome. Based on the different pathophysiological stages of immunoinflammatory response after multiple trauma, this paper explores the positive and negative effects of the immunosuppressive mechanism mediated by the temporary activation of myeloid derived suppressor cells in the early stage and the continuous pathological activation in the later stage on the disease and outcome.

[Key words] Myeloid-derived suppressor cells; Trauma; Systemic inflammatory response syndrome; Immunosuppression; Immune regulation

全身炎症反应 / 系统性炎症反应综合征(systemic inflammatory response syndrome, SIRS) 是宿主在各种应激源作用下产生的过度的免疫炎症反应, 以高水平的促炎性细胞因子为特点, 导致早期(1 周内)的脏器功能损伤; 随之的是宿主代偿性抗炎性反应综合征

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(compensatory anti-inflammatory response syndrome, CARS), 以抑制性抗炎性细胞因子为特点, 控制早期的过度炎症反应对组织造成的损伤, 但若持续激活可导致宿主免疫麻痹, 是远期(2 周后)不良预后的主要原因^[1-3]。在这一级联反应中, 骨髓来源的抑制细胞(myeloid derived suppressor cells, MDSCs) 作为一群异质性的免疫活性细胞发挥着关键作用^[4]。近年来,

MDSCs 的性质和生物学作用变得更加清晰,并且参与不同疾病多病理状态下的免疫调节机制^[5-6]。多发创伤作为全球致死、致残率较高的意外事件,是导致宿主发生 SIRS/CARS 的主要应激源,作为 CARS 主要效应因子的 MDSCs 与临床转归及预后有密切联系^[3]。本文从创伤后免疫炎症反应的不同阶段,探讨 MDSCs 介导的免疫抑制机制的最新研究进展。

1 MDSCs 激活及生物作用

MDSCs 是由髓系祖细胞和未成熟髓系细胞组成的异质群体,其特征是缺乏与完全分化的髓系细胞相关的表面标志物,但它们在形态上与粒细胞和单核细胞相似^[4-6];另外一小群具有 MDSCs 特征的骨髓前体细胞也已在人类中发现并命名为“早期 MDSCs”,这些细胞可在感染部位积聚并发挥广泛的免疫抑制效应^[7-9]。近年来众多的研究表明 MDSCs 分化与免疫反应的病理性激活有直接相关性^[10-13]。经典的 MDSCs 激活是对病原体和组织损伤的反应,主要通过损伤相关分子模式(damage associated molecular patterns,DAMPs)、病原体相关分子模式(pathogen-associated molecular patterns,PAMPs)和 Toll 样受体途径。MDSCs 短暂的骨髓激活可在刺激消除后终止,然后骨髓细胞恢复稳态,而若宿主遭受持续的应激刺激则导致 MDSCs 病理性激活,进而从骨髓中募集、调节分化并诱导自身增殖,宿主组织分泌的各种活性分子如前列腺素 E_2 、肿瘤坏死因子- α (tumor necrosis factor- α ,TNF- α)、白细胞介素(interleukin,IL)-1、IL-6、IL-13 等促炎性细胞因子会反馈增强这一过程^[11]。MDSCs 激活后在 SIRS/CARS 发展过程中表现出双重功能。在早期阶段,MDSCs 通过控制过度炎症,从而保护宿主避免早期促炎反应导致的器官损伤;若炎症反应持续强化,则会促使 MDSCs 更倾向诱发宿主的慢性危重疾病(chronic critical illness,CCI),持续性炎症免疫抑制及分解代谢综合征(persistent inflammatory immunosuppression and catabolic syndrome,PICS)而变得有害,增加患者的死亡风险^[14-15]。

2 MDSCs 介导的免疫抑制在创伤早期的积极作用

无论是感染或是创伤应激诱发的宿主过度的 SIRS 是导致早期器官功能不全甚至死亡的主要原因,作为伴随的 CARS 的主要效应因子的 MDSCs 则发挥保护性抑制作用,限制炎症反应程度、促进损伤的组织细胞修复^[16]。一项局灶性急性脑创伤(trumatic brain injury,TBI)大鼠模型研究表明,MDSCs 可在 TBI 发生后向脑组织浸润,其作为脑损伤的反应因子甚至早于小胶质细胞,在直接抑制神经免疫炎症反应的同时与组织常驻胶质细胞交互作用,共同保护损

伤的脑组织^[17]。在钝性胸外伤模型的研究中显示,MDSCs 可通过抑制细胞免疫介导的炎症损伤和阻止抗原诱导的 T 细胞反应保护肺组织的二次损伤^[18]。刀豆凝血素 A 诱导的急性肝损伤模型中,亦发现 MDSCs 的早期增殖激活,通过抑制 TNF- α 、INF- γ 等前炎症细胞因子水平和升高 IL-10 等抗炎症因子水平,减轻肝脏损伤和促进组织修复^[19]。在动物骨折模型和人类骨关节损伤研究中均发现,MDSCs 可抑制活跃的炎性 T 细胞增殖,降低骨关节炎和增强骨生物学转化促进骨折愈合^[20]。Zhang 等^[21]研究表明,中药提取物姜黄素亦是促进 MDSCs 增殖和提高 MDSCs 基因表达而发挥动物骨折模型骨愈合作用,进一步验证了 MDSCs 在骨创伤早期的保护性作用。总之,在创伤早期,宿主继发的过度的促炎性反应可进一步损伤组织器官,处理炎症和水肿的是防止进一步损伤的基础;MDSCs 的短暂激活可抑制促炎症反应程度和时限,限制炎症反应对组织的二次损害、促进损伤组织修复,具有积极的生物学效应。

3 MDSCs 介导的免疫抑制在创伤远期的宿主免疫麻痹作用

多发创伤是当前全球主要致死性事件之一,尽管部分患者能够及时收住重症监护病房,但晚期死亡率仍非常高,死亡原因多与病程后期免疫麻痹继发感染、营养不良等不良事件相关^[22]。在 TBI 后免疫麻痹患者中,MDSC 的免疫抑制机制发挥重要作用^[23]。有研究表明,MDSC 作为急性损伤的免疫抑制效应物,脑损伤产生的 DAMPs 可促进骨髓 MDSCs 持续增殖和释放,引起 T 细胞无反应并触发可导致 T 细胞凋亡的信号转导途径^[24-26]。Cheng 等^[27]建立了多发创伤的大鼠模型,结果表明多发创伤远期 MDSCs 迅速增殖,通过抑制 T 细胞功能而增加实验动物继发感染的易感性,是预后不良的危险因素,而介导这一结局的机制是多发创伤后 MDSCs 通过抑制 CD4 T 细胞增殖和降低 γ 干扰素产生发挥了抑制 T 细胞的作用。Hofstee 等^[28]研究发现,骨折大鼠模型不愈合时可继发金黄色葡萄球菌感染,感染和预后不良组动物存在循环持续的高水平 MDSCs,提示 MDSCs 介导的免疫抑制直接参与了宿主的免疫麻痹。相似的结论亦认为创伤后持续 1 周以上的高水平 MDSCs 和 IL-10 是创伤愈合不良的危险因素^[29]。已知烧伤会导致骨髓成分和功能发生剧烈变化,包括烧伤小鼠脾脏、骨髓和组织内的 MDSCs 急剧增加^[30]。Everett 等^[31]研究证实,L-精氨酸浓度在烧伤后期内下降 80%,通过 L-精氨酸的给药可以降低感染铜绿假单胞菌的烧伤小鼠的细菌毒力,败血症发

生和死亡率,提示 MDSCs 通过则可产生高水平的 Arg-1 和 iNOS 将 L- 精氨酸分解代谢,导致 CD3 ζ 链的表达降低,导致淋巴细胞增殖能力和细胞免疫受损。Heim 等^[32]的研究表明,MDSCs 可通过分泌 IL-10 抑制单核 / 巨噬细胞内 IL-1 β 、TNF- α 等炎症因子的分泌,阻碍单核 / 巨噬细胞对金黄色葡萄球菌的清除,导致感染的持存在。综上所述,创伤组织损伤迁延不愈及伴随的高强度促炎症反应可持续病理性激活 MDSCs,使宿主长期处于免疫抑制甚至麻痹状态(淋巴细胞减少,精氨酸酶 -1 和诱导型一氧化氮合酶的增加,活性氧的释放,程序性细胞死亡受体 -1/ 表达程序性死亡配体 -1 的过度表达和 IL-10 分泌增加等是其免疫抑制的指标,进而增加脓毒症、多器官衰竭和死亡的风险。以上提示 MDSCs 的动态监测在病情预后评估和指导抗炎干预中发挥关键的作用。

4 结论和展望

创伤后免疫炎症反应是宿主对创伤应激的复杂的“应对反应”,目的是清除损伤坏死的组织碎片并修复组织和恢复功能,而免疫抑制机制在保证清除抗原的同时防止过度反应次生的二次组织损伤之间保持平衡中起到关键作用。MDSCs 是一组具有免疫抑制特性的固有免疫细胞,是组织损伤的早期应答者之一,其主要功能是促进组织修复和伤口愈合并阻止不受控制的炎症和维持免疫稳态^[33]。然而,若创伤长期迁延不愈,可导致 MDSCs 不断的病理性激活、持续发挥免疫抑制作用,而使宿主进入免疫麻痹状态,PICS 过程中发现的 MDSC 并未降低促炎反应而增强了抗炎反应,最终导致死亡率增加^[34]。因此,对创伤患者进行动态 MDSCs 监测及实施干预可作为评估疾病预后和治疗靶点,具有广阔的实用前景。

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