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肿瘤微环境对MDSCs扩增的调控

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摘　要

骨髓来源的抑制性细胞(Myeloid-derived suppressor cells, MDSCs)是巨噬细胞、粒细胞、树突状细胞(dendritic cells, DCs)的前体集合，这群细胞形态、表型和功能各异，但都具有极强的免疫抑制性。近年来，MDSCs的神秘面纱被逐步揭开，尽管其他多种生理及病理条件都可以对其扩增产生影响，但肿瘤微环境(tumor microenvironment, TME)对MDSCs扩增的调控机制始终是研究热点。本文就肿瘤微环境对MDSCs扩增的调控机制进行综述，并进一步总结MDSCs对于当前抗肿瘤治疗手段的临床价值。

关键词

骨髓来源的抑制性细胞，肿瘤微环境，免疫治疗，靶向治疗

Modulation of Myeloid-Derived Suppressor Cells Amplification by Tumor Microenvironment

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Abstract

Myeloid derived suppressor cells (MDSCs) are the collection of various precursor cells including macrophages, granulocytes and dendritic cells (DCS). These cells have different morphology, phenotype and function, but they all have strong immunosuppression. In recent years, the mystery of MDSCs has been gradually unveiled. Although many other physiological and pathological condi-

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tions can affect its amplification, the regulatory mechanism of tumor microenvironment (TME) on MDSCs amplification has always been a research hotspot. This paper reviews the regulatory mechanism of tumor microenvironment on the amplification of MDSCs, and further summarizes the clinical value of MDSCs for the current anti-tumor treatment.

Keywords

MDSCs, TME, Immunotherapy, Targeted Therapy

1. 引言

MDSCs 是一组具有异质性的不成熟细胞群，一直以来都很难精确描述其表型。目前较为公认的分类主要为以下两种：粒细胞或多形核 MDSCs (granulocytes or polymorphonuclear MDSCs, PMN-MDSCs)和单核细胞 MDSCs (monocyte MDSCs, M-MDSCs)。在小鼠中，MDSCs 的表型通常为 $CD11b^+Gr1^+$，进一步又分为两种亚型：粒细胞 MDSCs ($CD11b^+Gr1^+Ly6C^-Ly6G^+$)和单核细胞 MDSCs ($CD11b^+Gr1^+Ly6C^+Ly6G^-$)。而在人类中，MDSCs 的表型通常为 $Lin^{-/Low}CD33^+CD11b^+HLA\text{-}DR^-$，进一步分为单核细胞 MDSCs (Mo-MDSCs，$Lin^{-/Low}CD33^+CD11b^+HLA\text{-}DR^-CD14^+CD15^-$) 和 CD15+ 粒细胞 MDSCs (G-MDSCs, $Lin^{-/Low}CD33^+CD11b^+HLA\text{-}DR^-CD14^-CD15^+$)两种亚型。研究表明，人类还存在第三种相对较少的 MDSCs，包括一些具有集落形成活性的细胞和其他骨髓前体细胞，这些细胞被称为早期 MDSCs (early MDSCs, eMDSCs)，表型为 $Lin^-HLA\text{-}DR^-CD33^+CD11b^+CD14^-CD15^-$，但这群细胞尚未在小鼠中检出[1] [2]。此外，在脐带血及转移性小儿肉瘤患者的外周血中还存在一群表型特征为 $HLA\text{-}DR^+CD33^+$or $CD33^{-/low}$ 的细胞群，因其与成纤维细胞具有相似形态而被命名为纤维细胞样 MDSCs (fibroblast myeloid-derived suppressor cells, fMDSCs) [3] [4]。

2. MDSCs 的来源

2.1. 经典的髓系激活反应

生理条件下，骨髓间充质干细胞的分化和成熟由粒细胞巨噬细胞集落刺激因子(granulocyte macrophage colony stimulating factor, GM-CSF)驱动[5]。当机体接收到相对强的信号，比如 Toll 样受体(Toll-like receptors, TLR)配体、病原体相关分子模式(pathogen-associated molecular patterns, PAMP)和损伤相关分子模式(damage-associated molecular patterns, DAMP)等[6] [7]，髓腔内经典的髓系激活途径将被激活，这个过程强烈但并不持久，可以使骨髓间充质干细胞分化成具有免疫活性的巨噬细胞、粒细胞和树突细胞，对于维持先天性和适应性免疫系统的正常功能起到至关重要的作用[8]。

2.2. 肿瘤微环境与 MDSCs

机体持续受到相对微弱的刺激，如长期感染、肿瘤、肥胖等慢性疾病时，经典的髓系激活反应将受到抑制，骨髓间充质干细胞正常分化受阻，一群相对不成熟的前体细胞大量扩增，机体正常的免疫反应将受到一定程度的抑制。TME 是包括 MDSCs、免疫抑制性 DCs 和肿瘤相关巨噬细胞(tumour-associated

macrophages, TAMs)在内的多种免疫抑制细胞群的温床，对骨髓细胞的分化影响显著[9]。并且 MDSCs 的病理性激活与病理性刺激的暴露时间呈正相关[10]。

MDSCs 的扩增现象可发生于不同类型的肿瘤中，在尿路上皮癌、胰腺癌、肺癌和乳腺癌等多种肿瘤均可检测到其表达增高，这一过程主要受肿瘤源性趋化因子调控，而与肿瘤类型无明显相关性[6]。

肿瘤细胞和肿瘤相关基质细胞释放的相关细胞因子，如粒细胞集落刺激因子(granulocyte colony-stimulating factor, G-CSF)、GM-CSF、巨噬细胞集落刺激因子(macrophage colony-stimulating factor, M-CSF)、血管内皮生长因子(vascular endothelial growth factor, VEGF)和干细胞因子(stem cell factor, SCF)等，可以干扰正常的骨髓细胞分化和成熟[11]。这些细胞因子一方面可以加速骨髓间充质干细胞的成熟。另一方面，可以催化异常分化的细胞群对免疫系统产生强烈的抑制作用[4]。有研究表明，分别使用 GM-CSF、M-CSF 和 G-CSF 刺激骨髓间充质干细胞分化而成的 fMDSCs，在表达 MDSCs、DCs 和纤维细胞的表型标志物的同时，后续还可以通过增加吲哚胺 2,3-双加氧酶(2,3-dioxygenase, IDO)的表达诱导 Treg 细胞生成[11]。

此外，肿瘤来源的炎性细胞因子(如 IL-1β、IL-6、TNF-α 等)可以通过促进趋化因子(主要包括 CXC 趋化因子家族，如 CXCL-8、CCL2、CCL5、CCL11、CXCL10 等)的分泌，促进未成熟的骨髓前体细胞分化成 MDSCs 并进一步分化为具有免疫抑制性的巨噬细胞和 DCs [12] [13]。同时，肿瘤细胞来源的 TGF-β 可以通过 TGF-β/SMADs 途径调节中性粒细胞极化为促肿瘤表型的中性粒细胞[14]。而 TLR 家族中的核因子-κB (nuclear factor kappa-B, NF-κB)则是通过诱导一些炎性介质如 COX2 和 PGE2 的分泌以增强 MDSCs 的募集，并帮助肿瘤细胞实现免疫逃避[15]。

这些细胞因子绝大多数通过转录因子发挥作用，相关转录因子主要包括信号转导和转录激活因子 1 (signal transducer and activator of transcription 1, STAT1)、STAT3、STAT5、STAT6 及 NF-κB 等[16] [17] [18] [19]。其中，处在主导地位的是 STAT3。在转移性瘤细胞中，肿瘤来源的 IL-6 和 IL-10 可以重塑 STAT3 通路，继而诱导 MDSCs 扩增并促进巨噬细胞极化为免疫抑制亚型[20] [21]。不仅如此，STAT3 还可以通过增强一些钙结合蛋白(如 S100A8 和 S100A9)的表达促进 MDSCs 扩增，并进一步增强其免疫抑制活性[22]。此外，STAT3 及其他具有氧敏感性的转录因子(如 STAT1、STAT6 和 NF-κB)以及一些肿瘤源性炎症因子(如 IFN-γ、TNF-α、IL-1、IL-4 和 IL-13，以及 TGF-β)可以作用于 NADPH 氧化酶(NADPH oxidase, NOX)家族，并上调活性氧(reactive oxygen species, ROS)水平，进一步促进骨髓前体细胞向 MDSCs 分化，同时强化肿瘤微环境的免疫抑制活性，并促进肿瘤微血管生成，促进肿瘤生长及转移[23] [24] [25]。

其他转录因子也可以通过多种机制影响 MDSCs 的扩增。STAT1 在一氧化氮(nitric oxide, NO)和精氨酸酶-1 (Arginase 1, ARG1)介导的免疫抑制反应中发挥重要作用，而这一过程是 MDSCs 扩增的重要环节之一[26]。STAT5 可以通过上调 B 细胞淋巴瘤/白血病-2 基因(B cell lymphoma XL, Bcl-XL)的表达和下调 BCL-2 相关蛋白的表达，促进 MDSCs 扩增，这一作用在 PMN-MDSCs 中尤为显著。而 STAT6 通路可以被 IL-4 和 IL-13 激活，并通过诱导 ARG1 及 NOX2 表达进一步调节 ROS 介导的氧化应激反应，从而打造出免疫抑制微环境，为 MDSCs 的扩增提供可能[27]。

肿瘤细胞及其间质细胞也会以外泌体的形式释放一些亚细胞成分，包括 MiRNAs、信号肽和脂质等，以此促进 MDSCs 的扩增。近年来，随着公众对 MiRNAs 的研究逐渐深入，已有众多研究证实其可以通过多种潜在机制在 MDSCs 的扩增中发挥重要作用[28] [29]。例如 miR-224-5p 靶向 SMAD4 和 TNF-α 诱导非小细胞肺癌细胞相关 MDSCs 扩增[30]。而 miR-45 和 miR-203a-3p 可以抑制 SMAD3 阻断 TGF-β 通路，逆转促肿瘤表型 PMN-MDSCs 极化，解除一部分免疫抑制效应[31]。下调 miR-17-92 和 miR-1519c 以抑制 HIF-1α 的表达，可一定程度上促进抗肿瘤免疫反应并减少肿瘤微血管形成，抑制肿瘤生长及转移[32]。

3. 临床意义

有研究表明，在包括黑色素瘤、非小细胞肺癌等多种瘤种中，III、IV 期患者体内 PMN-MDSCs、M-MDSCs 和 Treg 细胞的表达明显高于 I、II 期肿瘤患者，这进一步证实了 MDSCs 与肿瘤的恶性程度及转移呈正相关。MDSCs 不仅可以通过重塑肿瘤微环境以帮助肿瘤细胞“逃避”免疫监视，还可以通过多种机制促进恶性肿瘤的发展和转移，弱化抗肿瘤治疗疗效并影响患者预后[33]。因此，探索 MDSCs 的扩增机制对于临床实践具有特殊意义。

3.1. 靶向 MDSCs 以增强抗肿瘤效应

实际上，MDSCs 不仅可以作为可靠的生物标志物来预测肿瘤患者预后，还可以作为全新的肿瘤治疗靶点以应用于临床实践[34]。

作为 MDSCs 扩增过程中最关键的转录因子，STAT3 已然成为首要研究热点。舒尼替尼是一种多靶点小分子酪氨酸激酶抑制剂，可以广泛作用于 VEGFR-2、血小板衍生生长因子受体 b (platelet-derived growth factor receptor b, PDGFR-b)、c-kit 和干细胞因子等多个靶点，进而阻断 STAT3 以抑制 MDSCs 的扩增[35] [36]。在前列腺癌中，天然化合物 Galiellalactctone 可以通过下调 STAT3 激活基因以抑制 STAT3 磷酸化进一步阻断 MDSCs 的扩增[37] [38]。

与此同时，还可以通过减少 MDSCs 扩增过程中的细胞因子来以实现抗肿瘤效应。姜黄素是一种 IL-6 阻断剂，在乳腺癌中，可以通过减少 IL-6 的分泌有效减少 MDSCs 的数量[39]。而 BMP4 则可抑制 NF-κ 活性并进一步降低 G-CSF 在人和小鼠乳腺癌中的表达，继而在一定程度上阻断 MDSCs 的扩增[40]。有研究表明，水飞蓟素可以降低 CCR2 的表达，从而下调恶性黑色素瘤和乳腺癌中 MDSCs 的特异性归巢[41] [42]。

3.2. MDSCs 和免疫检查点抑制剂

此外，MDSCs 的存在与免疫检查点抑制剂的特异性耐药性相关。有研究表明，减少肿瘤微环境中 $CXCR2^{+}CD11b^{+}Ly6G^{hi}$MDSCs 和 $S100A9^{+}$MDSCs 的数量可显著增加 T 细胞浸润，并增强抗－程序性死亡 1(programmed death 1, PD-1)免疫治疗的抗肿瘤效果[43] [44] [45]。这种优势也反映在抗－程序性细胞死亡配体 1 (programmed cell death-Ligand 1, PD-L1)和细胞毒性 T 淋巴细胞相关蛋白 4 (cytotoxic T-lymphocyte associated protein 4, CTLA-4)抑制剂中[34] [46] [47]。

同时 MDSCs 会在 TEM 的多种细胞因子的刺激下进一步分化为 TMA，在多重机制的参与下触发免疫抑制，影响免疫检查点抑制剂的疗效，部分或完全阻断相关环节可有效增强抗肿瘤免疫反应。有研究证实，在小鼠肿瘤模型中，阻断 PI3Kγ 的表达不仅能促进 NF-κB 的激活，同时还会阻断 C/EBPβ 的活化效应，对恢复 CD8+T 细胞的细胞毒作用具有积极意义，并与检查点抑制剂治疗具有协同作用[48] [49]。此外，白细胞免疫球蛋白样受体 B2 (eukocyte immunoglobulin-like receptor B2, LILRB2)不仅能促进 PMN-MDSCs 的扩增和 Treg 的浸润，还能使肿瘤组织中炎性表型的髓系细胞向 M2 型(促肿瘤型巨噬细胞)分化，抑制 T 细胞功能。而 LILRB2 阻断剂与免疫检查点抑制剂联合使用可有效增强免疫检查点抑制剂的疗效，延长非小细胞肺癌患者的无进展生存期(progression-free survival, PFS) [50]。

3.3. MDSCs 和酪氨酸激酶抑制剂。

在 EGFR 驱动基因突变阳性的肿瘤中，酪氨酸激酶抑制剂(epidermal growth factor receptor-tyrosine kinase inhibitor, EGFR-TKIs)主要通过增加细胞毒性 $CD8^{+}$T 细胞数量和 DCs 的数量、减少 $Foxp3^{+}$Treg 的积累及阻断 M2 型巨噬细胞极化影响免疫微环境，导致 PD-1/PD-L1 的表达下调，减缓肿瘤发生发展的进

程[51] [52]。但这种抗肿瘤反应通常不会持久。随后，具有免疫抑制功能的 MDSCs 以及肿瘤相关因子(如 IL-10 和 CCL-2)会随之上调，最终导致 EGFR TKIs 耐药[53]。澳大利亚的一项研究发现，那些高表达 FoxP3$^+$Treg 细胞和 M-MDSCs 的慢性髓系白血病(Chronic myeloid leukemia, CML)患者在 EGFR-TKIs 治疗之后往往很难获得理想的 PFS[52]。

另一项研究表明，在小鼠和非小细胞肺癌患者中，CD14+S100A9+单核 MDSCs 来源的巨噬细胞可通过将经典 NF-B 途径转化为新的 RELB 途径，诱导 miR-21 和 miR-181b，介导肿瘤细胞对 EGFR-TKIs 的耐药性。消除 MDSCs 可以改善 EGFR-TKIs 耐药，延长非小细胞肺癌患者的 PFS [44] [54]。同时，MDSCs 本身也可以作为预测 TKIs 治疗预后的有效生物标志物[54]。

3.4. MDSCs 和化疗及放疗

此外，化疗的有效性也会受到肿瘤来源的 MDSCs 的影响。在非小细胞肺癌和黑色素瘤中，S100A9 蛋白可以驱动 CD11b$^+$CD14$^+$MDSCs 肿瘤特异性归巢，以逃避铂化合物的细胞毒性作用[55]。在一项针对乳腺癌新辅助治疗的临床研究中，减少患者化疗前 MDSCs 的数量可以有效提高新辅助化疗的病理完全缓解(PCR)，改善患者的预后[56] [57]。而肿瘤来源的 MDSCs 和 Treg 细胞已被证明比其他免疫细胞更能抵抗辐射，对放疗效果具有一定影响。阻断 MDSCs 的扩增可以有效改善放疗抵抗，增加放疗的敏感性，同时促进放疗的免疫激活作用[58]。

4. 总结

毫无疑问，无论是在正常生理条件下，还是在病理环境中，骨髓细胞对维持机体免疫平衡都具有重要意义。

先前大量研究已证明，TME 通过多种途径影响 MDSCs 的分化及扩增。首先，肿瘤细胞及其基质细胞释放大量细胞因子以干扰骨髓细胞正常分化和成熟途径。这些细胞因子一方面可以加速骨髓前体细胞的成熟，另一方面，可以催生出对免疫系统有很强抑制作用的 MDSCs。这些细胞因子，包括炎性因子、生长因子、趋化因子、肿瘤坏死因子等，通过不同转录因子发挥作用，这个过程主要涉及 STAT1、STAT3、STAT5、STAT6 及 NF-κB，其中，又以 STAT3 最为重要。其次，肿瘤细胞及相关基质细胞通过外泌体的形式释放出一些亚细胞成分，这些成分包括一些 MiRNAs、信号肽和脂质等，研究表明，这些成分在 MDSCs 扩增及招募、肿瘤微血管生成等过程中起到积极作用。此外，TME 本身处于一种乏氧状态，在这种环境中，HIF (主要是 HIF-1α)诱导 MDSCs 扩增并上调其表面 PD-L1 的表达，从而导致免疫耐受[59]。

正如前文所述，TME 通过多种途径调控 MDSCs，同时，这部分肿瘤相关 MDSCs 又可以重塑免疫抑制 TME，激活 TAM 和 Treg 细胞以帮助肿瘤细胞逃避免疫监测，从而促进恶性肿瘤的发展和转移。因此，抑制其中某个或多个环节以达到阻断甚至消除 MDSCs，即可在一定程度上增强机体抗肿瘤免疫反应。事实上，这也是近年来临床免疫治疗一个热点。如舒尼替尼、Galiellalactctone、姜黄素、Silymarin 等药物都已在一些癌种中被证实可以通过阻断相应通路减少 MDSCs 生成，进而达到抗肿瘤治疗的目的。同时，靶向 MDSCs 治疗还与临床上现有的抗肿瘤治疗手段具有协同作用。有研究证明，消除肿瘤微环境内抑制性 CXCR2$^+$CD11b$^+$Ly6G^{hi}MDSCs 和 S100A9$^+$MDSCs 可以显著增加 T 细胞活性，增强抗 PD-1/PD-L1 及 CTLA4 疗效[43] [45] [46]。此外，在小鼠及非小细胞肺癌患者中有研究证实，消除 CD14$^+$S100A9$^+$MDSCs 可以改善 TKIs 耐药性，延长无进展生存。并且，有研究证实：高表达 FoxP3$^+$Treg 和 M-MDSC 患者在接受 TKIs 治疗时，PFS 明显缩短，因此阻断 MDSCs 扩增不仅可以增强 TKIs 治疗效果，其本身也可以用作预测 TKIs 治疗预后的有效生物标志物[52] [54]。临床上传统治疗手段，如化疗及放疗也可以在消除 MDSCs 后得到明显的获益。

总而言之，肿瘤微环境促进 MDSCs 扩增的机制是一个庞大而复杂的体系网络，现有的研究或许只是冰山一角，本文对其进行的综述也只是管中窥豹，但基于其对于临床上免疫治疗、靶向治疗及放化疗均有独特价值，其详尽的作用机制亟待我们进行深入探索，并争取早日有更多研究可以应用于临床，为更多肿瘤病人带来希望的曙光。

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