DOI:10.3872/j.issn.1007-385x.2024.12.012

·综 述·

肿瘤诱导髓源性抑制细胞分化的重要调节器——干扰素调节因子8的研究进展

Research progress in interferon regulatory factor 8 as an important regulator of tumor-induced myeloid-derived suppressor cell differentiation

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[摘 要] 髓源性抑制细胞(MDSC)是近年来发现的一群具有未成熟分化特性及强免疫抑制功能的髓系细胞,其在肿瘤组织中数量显著增加,通过多种途径诱导机体免疫耐受和疾病进展。肿瘤诱导MDSC分化并使其在组织聚集的机制复杂,其中干扰素调节因子8(IRF-8)作为关键的调节因子,在这一过程中起着重要作用。IRF-8属于干扰素调节因子家族,可以调控免疫反应、炎症和肿瘤免疫。在肿瘤诱导MDSC分化的过程中,IRF-8的具体作用机制尚未完全明确,但已有研究表明其可能通过调控相关信号通路、与其他免疫调节因子相互作用的方式影响MDSC的分化。未来研究将进一步深入探讨IRF-8在肿瘤诱导MDSC分化中的具体作用机制,包括其如何与其他信号分子相互作用、调控哪些关键基因的表达等。这些研究将有助于理解MDSC在肿瘤免疫中的作用,为开发针对MDSC的靶向治疗药物提供理论基础,从而恢复或重建机体的抗肿瘤功能。因此,本文探讨了IRF-8作为肿瘤诱导MDSC分化的重要调节器,其研究进展对于揭示MDSC在肿瘤免疫中的来源、作用机制、开发新的免疫治疗策略的重要意义。

[关键词] 干扰素调节因子8;髓源性抑制细胞;髓系细胞;肿瘤源性因子;分化
[中图分类号] R730.3; R730.5 [文献标识码] A [文章编号] 1007-385x(2024) 12-1254-06

在多种类型的癌症疾病中,患者外周血中会出现高水平的循环髓系细胞群。髓系细胞是最丰富的造血细胞,在适应性免疫中发挥关键作用[1]。髓系细胞的表型和功能可被肿瘤影响而改变,从而转化为免疫抑制细胞群[2],这种现象是因为髓系群体受到肿瘤来源的因子(tumor derived factor, TDF)调控,从而导致髓系细胞的分化异常,并可获得促瘤能力[3-4]。髓源性抑制细胞(myeloid-derived suppressor cell, MDSC)作为一种具有显著免疫反应抑制功能的髓系细胞群体,在肿瘤细胞免疫逃逸、促进肿瘤生长和转移方面扮演着关键角色[5]。干扰素调节因子8(interferon regulatory factor-8, IRF-8)主要存在于造血细胞中,是多个髓系细胞分化的重要调控因子[6]。IRF-8作为一种重要的转录因子,其在MDSC分化中的作用备受关注。研究[7]表明,IRF-8在肿瘤发生以及抗肿瘤免疫中发挥重要作用。它不仅可以调节多种生理过程,如细胞分化等;还能通过调控MDSC的分化,影响肿瘤免疫应答。本文主要概述了IRF-8在髓系细胞发育过程中的调控作用,尤其是肿瘤背景下IRF-8诱导MDSC生成的作用机制,旨在为MDSC的靶向治疗提供新的思路。

1 IRF-8对髓系细胞分化的调控作用

IRF-8,干扰素共有序列结合蛋白,是干扰素调节因子家族的重要组成部分。该家族一般分为IRF-1、IRF-2、IRF-3、IRF-4等。IRF-8是由DNA结合域和IRF相关结构域组成,这是与其他转录因子如IRF1和IRF2结合所必需的[8]。

IRF-8是骨髓细胞生成的“主调节因子”,在髓系祖细胞(common myeloid progenitors, CMP)向单核细胞、巨噬细胞和树突状细胞系的分化及数量平衡中必不可少[9-10]。IRF-8在造血干细胞(hematopoietic stem cells, HSC)中低表达[11],在浆细胞样树突状细胞(plasmacytoid dendritic cell, pDC)中高表达[12-13]。基因表达的调控不是一个线性的过程,而是一系列染色质修饰相互作用的结果。在粒细胞谱系中,IRF-8在粒细胞祖细胞(granulocytic progenitor, GP)中低表达,而在成熟的中性粒细胞中不表达IRF-8[6, 14]。CCAAT增强子结合蛋白α(CCAAT enhancer-binding protein α, C/EBPα)调控中性粒细胞生成[15],IRF-8抑制C/EBPα的激活,使中性粒细胞分化异常,数量减少[16]。GATA结合蛋白2(GATA binding protein 2, GATA2)是造血功能的主要调控因子,促进巨核细胞

[基金项目] 国家自然科学基金(No. 82174146);河南省卫生健康委员会国家中医临床研究基地科研专项(No. 2021JDZY098)
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生成，并在嗜碱性粒细胞分化中至关重要[17]。研究[14, 18]发现，转录因子GATA2介导IRF-8的下游路径，抑制GP的分化。IRF-8促进嗜酸性粒细胞的生成，GATA结合蛋白1（GATA binding protein 1, GATA1）调控嗜酸性粒细胞分化。在IRF-8$^{-/-}$的小鼠模型中，嗜酸性粒细胞祖细胞（eosinophil lineage-committed progenitor, EoP）中GATA1低表达，EoP分化抑制，嗜酸性粒细胞数量减少[19]。Krüppel样因子4（Krüppel-like factor 4, KLF4）通过诱导IRF-8，间接调控单核细胞分化的下游基因的表达。同时，IRF-8与PU.I结合，影响单核细胞的生成[20]（图1）。

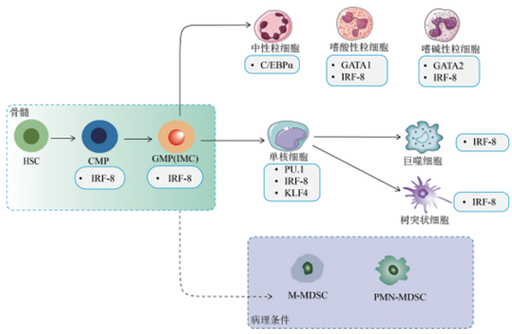

图1　生理和病理条件下的髓样细胞分化过程和相关转录因子

2　IRF-8在MDSC分化中的调控作用

生理状态下，HSC在骨髓中分化为CMP，而CMP继续分化为粒系单核系祖细胞（granulocyte-monocyte progenitor, GMP）。这些未成熟的髓系细胞（immature myeloid cell, IMC）转移至不同的外周器官后分化为成熟的髓系细胞。然而，在肿瘤等复杂疾病的病理环境中的炎性信号能够引起骨髓细胞分化的重编程，导致异质性骨髓细胞群的积累，并具有强大的免疫抑制活性，这群异质性细胞群被称为MDSC[21]（图1）。根据MDSC表面分子标志物、形态以及免疫抑制功能的形成机制不同，主要可以分为单核细胞型 MDSC（monocyte-MDSC, M-MDSC）、粒细胞型MDSC（granulocyte-MDSC, G-MDS）[22]。在小鼠中，MDSC的表面标记为CD11b^{+}Gr1^{+}。根据Gr1 抗原表位不同，将MDSC分为CD11b^{+}Ly6C^{low}Ly6G^{+}MDSC和CD11b^{+}Ly6C^{hi}Ly6G^{-}MDSC[23]。在肿瘤背景下，MDSC在骨髓中大量产生，通过扩增-激活-招募等级联反应后被运送到肿瘤微环境（tumor microenvironment, TME）中[24]。然而，MDSC确切分化机制尚不完全清楚。

早期的研究[25]通过流式细胞术分析表明，在小鼠造血系统中，IRF-8在GMP阶段已有表达。GMP可根据Ly6C和CD115的表达差异分为不同的亚群。研究[26]发现，Ly6C^{+}CD115^{+}细胞主要产生单核细胞，而Ly6C^{+}CD115^{-}细胞主要产生粒细胞。因此，GMP又被分为单核系祖细胞（monocytic progenitor, MP）和粒系祖细胞。IRF-8在GMP发挥作用，以调控MP和GP分别向单核细胞和中性粒细胞分化[25]。正常情况下，造血干细胞和多能祖细胞沿着一系列谱系，限制性地分化为更成熟的细胞阶段，而肿瘤等复杂疾病重塑了这一过程。

荷瘤小鼠中，IRF-8的表达在MDSC的两个亚群中均显著降低。与此同时，IRF-8的缺失对PMN-MDSC亚群的分化影响更明显[27]。上调MDSC中IRF-8的表达可以恢复正常髓系细胞的分化并降低疾病的活动性，最终显著消除其对肿瘤的促进作用[28]。同样，在B16-F10黑色素瘤模型中，与野生型小鼠相比，IRF-8基因缺失型小鼠的脾脏和肿瘤中积累了更多的MDSC[29]，但其异常增殖的分子机制尚不完全清楚。有研究[30]发现，在乳腺癌或结肠癌小鼠中分选出的MDSC中，IRF-8的沉默与Fas的下调导致这些细胞的凋亡减少，这表明IRF-8不仅是MDSC分化的负调控因子，而且还可以间接抑制它们的存活[31]。在结肠炎相关结直肠癌中，MDSC通过释放大量IL-10，激活结肠上皮细胞中的STAT3，上调IRF-8启动子上的DNA甲基转移3b[32]。这些研究均表明，IRF-8的缺失导致MDSC比例增加，进而使有效T细胞活化和浸润受损，抗肿瘤免疫能力减弱[33]。在癌症中，IRF-8通常被沉默，导致MDSC的积累，从而促进肿瘤生长和免疫逃避。重新激活MDSC中的IRF8表达可以降低其抑制功能并增强抗肿瘤免疫力[34]。

3　肿瘤调控IRF-8影响MDSC生成

3.1　肿瘤分泌的细胞因子对IRF-8的调控

在肿瘤患者中，MDSC的表型和异质性受到TME中肿瘤相关细胞因子的影响。如粒细胞-巨噬细胞集落刺激因子（granulocyte-macrophage colony-stimulating factors, GM-CSF）、粒细胞集落刺激因子（granulocyte colony-stimulating factor, G-CSF）、转化生长因子β（transforming growth factor-β, TGF-β）等[35-36]。这些因子激活的信号通路对转录因子IRF-8起到一定的调控作用，从而影响MDSC的分化和形成。

生理条件下，GM-CSF能够驱动骨髓细胞生成[37-38]；而在实体瘤患者血清中，GM-CSF、G-CSF、恶性细胞和基质细胞等分泌的因子增多，随后这些细胞因子诱导骨髓过度造血，产生大量IMC。有一小部分IMC分化为正常细胞，但多数IMC常分化为

MDSC[39]。乳腺癌小鼠模型中，肿瘤分泌大量G-CSF，使IMC异常积累，并且具有MDSC的表型特点[40]。WAIGHT团队[41]的研究发现，GM-CSF和G-CSF调控STAT3或STAT5的磷酸化，下调IRF-8的转录，进一步影响MDSC的分化。STAT3的抑制剂FLLL32[42]和STAT5抑制剂匹莫嗪[40]通过G-CSF或GM-CSF阻断IRF-8，染色质免疫沉淀实验证明STAT3或STAT5与IRF-8启动子直接结合。在小鼠骨髓性白血病中发现，IRF-8是STAT5的直接靶点，并且STAT5的沉默影响了IRF-8的表达；相反，激活STAT5会抑制IRF-8的转录[43]。IL-6在TME中广泛表达，并且与MDSC的产生密切相关。研究证明IL-6可以抑制IRF-8的表达，从而促进MDSC的生成[44]。

在黑色素瘤微环境中，LYDEN团队[45]研究发现，分化抑制因子1（inhibitor of differentiation 1，Id1）在未成熟髓系细胞病理活化为MDSC中发挥中心作用，TGF-β诱导下游转录因子Id1上调，IRF-8表达降低，在TME中MDSC的数量增多。然而，Id1是直接结合IRF-8启动子抑制其表达还是通过间接机制发挥作用尚未确定。IL-10是一种免疫抑制因子，其通过抑制IRF-8的表达，导致骨髓中GMP向MDSC分化偏向。这种偏向促进MDSC的生成，从而抑制肿瘤免疫应答[46]。IL-1β是一种重要的炎症介质，在TME中也被广泛表达。研究[47]表明，IL-1β可以通过抑制IRF-8的表达或活性来促进MDSC的生成。这种作用可能与IL-6和STAT3信号通路有关。

肿瘤细胞通过持续性地分泌细胞因子阻断髓系细胞直接感知环境刺激和炎症细胞因子的功能，进而影响髓系细胞的分化。

3.2　肿瘤分泌的外泌体对IRF-8的调控

外泌体（exosome）是几乎所有细胞类型都分泌的膜性结构，作为细胞间通信的关键信使，将生物活性物质传递给受体细胞，进而影响受体细胞的分化及功能[48]。有研究[49]发现，在脂多糖诱导的内毒素休克小鼠模型中，miR-127-5p-IRF8轴促进MDSC的生成。已有研究[50]表明，肿瘤来源的外泌体（tumor cell-derived exosome, TDE）能够通过影响骨髓分化促进免疫抑制性细胞亚群的产生。例如，黑色素瘤释放的外泌体抑制髓系细胞分化为树突状细胞，诱导其分化为M-MDSC，抑制T细胞的增殖；乳腺癌细胞来源的外泌体通过miR-9和miR-181a调控JAK/STAT信号通路，使髓系细胞异常分化为MDSC[51-52]。研究[53]表明，IRF8在狼疮发育过程中通过AMPK/mTOR信号通路影响M-MDSC分化，受miR-451a调控。肿瘤分泌的外泌体通过携带miRNA，可以调控IRF-8的表达。这种调控可能不仅在分子水平上直接作用于IRF-8，还通过影响细胞微环境和转录因子网络间接调控IRF-8的功能。这些机制共同作用，影响MDSC的分化，从而在肿瘤免疫逃逸中发挥重要作用。深入研究这些机制有助于开发新的肿瘤免疫治疗策略。（图2）

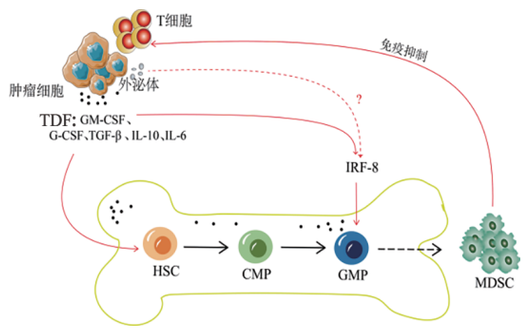

图2　肿瘤细胞分泌的细胞因子和外泌体调控IRF-8，影响MDSC分化

4　靶向IRF-8干预MDSC异常分化的治疗策略及IRF-8的临床应用

TME中存在的MDSC通过抑制免疫应答来促进肿瘤的进展。干扰MDSC的分化和功能已成为提高肿瘤免疫治疗效果的潜在策略之一。作为调控MDSC分化的重要因子，干预IRF-8可能会影响MDSC的数量和功能，从而抑制肿瘤的发展，并增强免疫治疗的效果。最近的研究[54-55]发现，MDSC的分化依赖于细胞酪氨酸激酶的信号传导，在健康C57BL/6小鼠中，低剂量化疗药物紫杉醇可以显著减少$CD11b^{+}Gr\text{-}1^{+}$未成熟髓系细胞的数量。为了解释低剂量紫杉醇治疗下MDSC数量减少的分子机制，实验以体外诱导骨髓前体细胞生成MDSC，以超低浓度紫杉醇处理骨髓前体细胞，这些条件下，紫杉醇不会损伤骨髓前体分化的MDSC或刺激MDSC凋亡，而是刺激骨髓前体细胞向树突状细胞分化[56]。LILIANA的研究团队[57]发现了一种新型免疫调节剂，称为非常小的颗粒（very small size particle, VSSP），VSSP将GMP分化分流到单核/巨噬细胞和树突状细胞，提高骨髓依赖的转录因子IRF-8的表达，使癌症患者MDSC数量下降，并恢复为正常的髓系表型。

作为一种转录因子，IRF-8异常表达可能与许多疾病的发生发展相关。通过检测IRF-8的表达水平或其功能状态，可以为临床提供重要的诊断和治疗指导。值得注意的是，免疫组织化学（immunohistochemistry, IHC）染色能将恶性血液肿瘤的病变细胞显示出来，可作为一种新的病理指标，显示单核细胞白血病和B淋

巴细胞白血病中白血病细胞[58]。最近研究[59]发现，IRF-8的IHC有望作为骨髓活检中单核细胞白血病的可靠指标，研究调查了单核细胞祖细胞的基因表达谱，从而在90例急性单核细胞白血病患者中验证了IRF-8的表达，细胞标记染色百分比与原细胞计数之间有非常高的相关性。该指标在单核细胞增多症和其他亚型的急性髓系白血病中均为阴性。

另一方面，IRF-8也在非造血细胞中表达，已有研究[60]发现，IRF-8在肺癌组织中的表达异常降低，可作为凋亡调节因子抑制非小细胞肺癌（non-small cell lung cancer, NSCLC）细胞体外增殖和体内致瘤潜能，并与NSCLC患者的预后相关。

5 结 语

在一些肿瘤模型中，不同的致癌因素会不同程度地影响未成熟髓系细胞向MDSC转化。肿瘤免疫学中，越来越多的致癌基因和肿瘤抑制基因具有复杂的功能，可以修改细胞因子和趋化因子网络，调控养骨髓来源的免疫抑制性细胞，特别是PMN-MDSC和M-MDSC。

髓系细胞具有快速的迭代周期，肿瘤环境对骨髓造血过程的影响更加显著，这使得那些具有促进肿瘤特性的髓系细胞获得了竞争优势。近年来的研究表明，IRF-8在调控MDSC分化中发挥着重要作用。一些研究发现，IRF-8的表达水平与MDSC的数量呈负相关，通过表达IRF-8可以抑制MDSC的分化，从而提高机体的抗肿瘤免疫应答。此外，一些研究还发现，肿瘤微环境中的一些信号通路（如STAT3、STAT5等）可以调控IRF-8的表达，从而影响MDSC的数量和活性。未来研究可以进一步探究IRF-8在肿瘤免疫治疗中的作用机制，包括其与其他免疫调节因子的相互作用、调控IRF-8表达的信号通路以及开发针对IRF-8的靶向治疗策略等。总的来说，研究MDSC分化调控中的IRF8对于深入理解肿瘤免疫逃逸机制、开发新的肿瘤免疫治疗策略具有重要意义。

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［收稿日期］ 2024-07-20 ［修回日期］ 2024-10-27
［本文编辑］ 向正华