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·综述·

巨噬细胞迁移抑制因子与肿瘤关系的研究进展

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【摘要】 巨噬细胞迁移抑制因子(MIF)作为一种多效性细胞因子和宿主免疫的调节分子,在机体免疫和疾病中发挥重要作用。MIF具有癌基因特性,其高表达可促进癌细胞存活、增殖、迁移、侵袭、转移、血管生成并抑制凋亡。MIF与抗肿瘤免疫密切相关,基于MIF为靶点的特异性抑制剂目前尚未得到广泛应用。本文就MIF在肿瘤发生和进展中的作用、机制、治疗靶点等方面的研究进展进行综述,展望基于MIF为靶点的抑制剂运用在肿瘤防治中的意义。

【关键词】 巨噬细胞迁移抑制因子;肿瘤;免疫;靶向治疗;抑制剂

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【**Abstract**】 Macrophage migration inhibitory factor (MIF), as a multipotent cytokine and regulatory molecule of host immunity, plays an important role in immunity and disease. MIF possesses the characteristics of oncogene, and MIF overexpression can promote cancer cell survival, proliferation, migration, invasion, metastasis, angiogenesis, and inhibit apoptosis. MIF is closely related to anti-tumor immunity. At present, the inhibitors specific for MIF have not been widely used. This article summarizes the research progress on the contribution, mechanism, and therapeutic targets of MIF in tumorigenesis and progression, and looks forward to the significance of the application of inhibitors based on MIF in tumor prevention and treatment.

【**Key words**】 Macrophage migration inhibitory factor; Tumor; Immune; Targeted therapy, Inhibitor

巨噬细胞迁移抑制因子(macrophage migration inhibitory factor,MIF)也称为糖基化抑制因子,早期被鉴定为可溶性淋巴因子,根据其在体外抑制巨噬细胞随机迁移的特性而命名[1]。MIF也是垂体受细菌脂多糖刺激后衍生的一种分泌蛋白,在内毒素血症与感染性休克反应中起重要作用[2]。人MIF基因位于22号染色体(22q11.2),受启动子区域中的两个多态性位点调控,其一为-794处的可变核苷酸串联重复(CATT5-8,rs5844572),其二为-173 (G/C)处的单核苷酸多态性(SNP,rs755622)[3]。MIF基因编码的蛋白是一种由115个氨基酸组成的分子量为12.5 kDa的同源三聚体,可储存在细胞质中或分泌到细胞外,其主要的细胞表面受体是Ⅱ型跨膜蛋白CD74和G蛋白偶联的功能受体CXC家族趋化因子受体2和4 (CXCR2和CXCR4)。多种细胞表达MIF,包括免疫细胞、脏器实质细胞及肿瘤细胞[4-5]。随着对MIF的特性研究的不断深入,对其认识已从一种可调节单核/巨噬细胞运动和负性调节糖皮质激素诱导的免疫抑制的细胞因子,发展为众多细胞和生物学过程的多效调节剂。近年来研究提示MIF参与肿瘤发展的多个进程,本文旨在总结MIF在肿瘤发生发展中的作用及其机制,并展望以MIF为抗癌治疗靶点的可行性。

1　MIF在肿瘤中的作用

多种恶性肿瘤中都可以观察到MIF的异常高表达,大部分肿瘤中除了癌组织中MIF的表达增加外还会伴有外周循环MIF水平的增加,其高表达提示预后不良[6-9]。MIF在恶性肿瘤中的功能和相关作用靶点基因见表1。

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表1 MIF在癌症中的功能特征

Table 1 Functional characteristics of MIF in cancer

癌症类别	功能	作用靶点	参考文献
头颈部鳞状细胞癌	促增殖、促血管生成、促迁移和侵袭、抑制凋亡、EMT	MMP9、CD74、CXCR2、CCL4、IL-8	[10-12]
食管鳞状细胞癌	促增殖、促血管生成、促迁移和侵袭	GSK3β、cyclin D1、MMP7、c-myc、c-Jun、IL-8、VEGF、β-catenin	[13-14]
胃癌	促增殖、促血管生成、MET	cyclin D1、p27	[15-16]
结直肠癌	促增殖、促血管生成、促迁移和侵袭、抑制凋亡、MET	CXCR4、Hsp90、p38、CD74、VEGF、MMP-9	[16-19]
肝癌	促增殖、促血管生成、促迁移和侵袭、抑制凋亡	HPO、AP1、CD74、VEGF、IL-8	[20-22]
非小细胞肺癌	促增殖、促血管生成、促迁移和侵袭、抑制凋亡、EMT	CXCR4、IL-6、IL-8、VEGF、Rac1	[23-26]
乳腺癌	促增殖、促血管生成、促迁移和侵袭、抑制凋亡	VEGF-C、Hsp90、EGFR、HMGB1、TLR4、IL-2、CD74、CD206、TNF-α、	[27-32]
前列腺癌	促增殖、促血管生成、促迁移和侵袭、抑制凋亡、EMT	CD74、ERK、AKT、HBP1、SOX-4、β-catenin	[33-35]
黑色素瘤	促增殖、促血管生成、促迁移和侵袭、抑制凋亡、	CD74、IFN-γ、VEGF、PD-L1、TSP-1	[7, 36-39]
胶质瘤	促增殖、促血管生成、促迁移和侵袭、抑制凋亡、EMT	CD74、CXCR4、VEGF、IL-8、NKG2D	[40-44]

注：EMT，上皮-间质转化；MET，间质-上皮转化；MMP，基质金属蛋白酶；CXCR2，CXC趋化因子受体2；CCL4，C-C基序趋化因子配体4；IL，白细胞介素；GSK3β，糖原合成酶激酶3β；cyclin D1，细胞周期蛋白D1；VEGF，血管内皮生长因子；β-catenin，β-连环蛋白；Hsp90，热休克蛋白90；HPO，肝细胞生成素；Rac1，Rho GTPase 酶家族成员之一；EGFR，表皮生长因子受体；HMGB1，高迁移率族蛋白B1；TLR4，Toll样受体4；TNF-α，肿瘤坏死因子-α；HBP1，HMG框转录因子1；ERK，细胞外调节蛋白激酶；SOX-4，性别决定区Y框转录因子4；IFN-γ，γ干扰素；PD-L1，细胞程序性死亡配体1；TSP-1，血小板反应蛋白1；NKG2D，自然杀伤(NK)细胞和$CD8^+$T细胞上的激活性免疫受体。

Note: EMT, epithelial mesenchymal transformation; MET, mesenchymal epithelial transformation; MMP, matrix metalloproteinase; CXCR2, CXC chemokine receptor 2; CCL4: C-C motif chemokine ligand 4; IL, interleukin; GSK3β, glycogen synthase kinase 3β; VEGF, vascular endothelial growth factor; Hsp90, heat shock protein 90; HPO, Hepatopoietin; Rac1, a member of Rho GTPase family; EGFR, epidermal growth factor receptor; HMGB1, high mobility group protein B1; TLR4, Toll like receptor 4; TNF-α, tumor necrosis factor-α; HBP1, HMG box transcription factor 1; ERK, extracellular regulated protein kinase; SOX-4, Y-box transcription factor 4 of sex determination region; IFN-γ, γ Interferon; PD-L1, programmed cell death ligand 1; TSP-1, platelet reactive protein 1; NKG2D, an activated immune receptor on natural killer (NK) cells and $CD8^+$T cells.

1.1 调节细胞增殖、周期和凋亡 MIF调节细胞增殖可通过调控p53的表达活性和功能来实现。一方面MIF的Cys81与p53的Cys242和Cys238可相互结合，另一方面，MIF还可通过稳定p53-MDM2复合物间接降低p53活性，促进细胞增殖和细胞周期进程并抑制凋亡[45]。MIF与其同源受体CD74 (MHCII的不变链)结合，诱导其磷酸化和CD44的募集，激活原癌基因SRC启动下游磷酸化信号[46-47]，包括cyclin D1的转录、视网膜母细胞瘤(Rb)蛋白的磷酸化、促分裂素原活化蛋白激酶/细胞外信号调节激酶(MAPK/ERK)和磷脂酰肌醇三激酶/丝氨酸/苏氨酸激酶(PI3K/AKT)信号途径等多种促细胞增殖和抗凋亡途径[48-49]。此外，MIF通过激活核因子κB (NF-κB)从而诱导抗凋亡基因的表达并促进细胞增殖[50]。MIF也可干扰Rb-E2F通路，通过E2F依赖机制影响细胞增殖[51]。有研究揭示了MIF也可能通过与Jun激活域结合蛋白1 (JAB1/CSN5)结合负性调控转录因子激活蛋白-1 (AP-1)的活性，并抑制JAB1诱导的JNK激活和细胞周期蛋白依赖性激酶抑制剂p27/Kip1的降解，从而导致细胞周期停滞和细胞凋亡[4, 52-53]。除上述信号传导通路外，Liu等[54]通过微阵列研究发现MIF还可激活c-Myc和抑制叉头框蛋白O4 (Foxo4)依赖通路来正向调控细胞周期进程；当MIF基因敲低后，细胞周期进程的调节因子如细胞周期素(Cyclin)、细胞周期素激酶(CDK)、Cdk活化激酶(CAK)和细胞周期后期促进复合物(APC/C)被下调，细胞周期素激酶抑制剂(CKI)家族成员被上调，从而阻滞细胞周期于G_0/G_1期。总体上，MIF调节细胞增殖、周期和凋亡的机制较为复杂。

1.2 调节上皮-间质转化及肿瘤迁移和侵袭 已证实，MIF可通过下调E-cadherin和上调N-cadherin促进肿瘤细胞的侵袭和转移[55]，靶向调控MIF可影响肿瘤细胞上皮间质转化(EMT)。研究显示，肿瘤细胞分泌的MIF可以吸引间充质干细胞，并且通过参与MIF-CXCR4趋化轴激活ERK和JNK通路，诱导间充质干细胞向肿瘤募集，从而促进肿瘤的迁移和侵袭[56]。多种肿瘤中MIF过表达与EMT密切相关，但不同肿瘤中MIF介导EMT及肿瘤迁移和侵袭机制略有差异。胶质母细胞瘤中MIF和CXCR4的过表达协同促进EMT [41]，而非小细胞肺癌中CXCR4的过表达也能诱导MIF产生和CXCR4自分泌循环，驱动EMT和肿瘤球生成从而促进肿瘤侵袭[24]。Parol-Kulczyk等[35]在前列腺癌探索MIF胞浆到胞核的移位过程中发现其可能与转录因子如SOX-4的失调相互作用，使β-catenin上调并激活EMT过程。在乳腺癌中MIF可通过ERK/HMGB1/TLR4/NF-κB通路，上调EMT相关蛋白并调节乳腺癌细胞迁移[28]。

1.3 MIF与缺氧微环境及肿瘤血管新生 缺氧作为肿瘤微环境(TME)的关键标志和决定因素，一方面是由肿瘤快速生长引起的，另一方面缺氧条件被证明会在肿瘤中诱导特定基因的表达，从而赋予癌细胞生存优势，即允许和促进肿瘤细胞在这种环境中的厌氧生长、转移扩散和治疗抵抗。在缺氧诱导的TME中，缺氧诱导因子-1 (HIF-1)表达增加并诱导一系列基因产物来促进肿瘤生长与适应。MIF是缺氧诱导基因转录激活并导致表达上调的靶点之一，MIF和含活性亚基的HIF-1α之间存在相互协同的关系。HIF-1α可与MIF的5'-UTR中的缺氧反应元件结合来驱动MIF的转录和表达，并受到CAMP反应原件结合蛋白(CREB)表达的调节[57]。反之，MIF能通过p53依赖的方式激活缺氧介导的HIF-1α形成的反馈回路来促进肿瘤缺氧适应[58]，还可通过阻止蛋白酶体介导的降解、与CSN9信号体亚基5(CSN5)和HIF-1α结合形成三元复合物等机制最大限度地稳定HIF-1α[59]，这反过来又促进了HIF-1α的转录并放大了肿瘤缺氧反应[60]。另外，MIF还是HIF-1α限制细胞衰老的关键效应物[61]。同样，机体致瘤机制和TME需要诱导血管新生来满足肿瘤细胞的新陈代谢，血管生成的增加受血管生成细胞因子的自发分泌直接调节的机制已被大多数研究证明。一些体外肿瘤实验研究描述了MIF的促血管形成和内皮细胞迁移作用，并发现抗MIF抗体作为血管生成抑制剂在部分肿瘤中显著抑制了肿瘤生长和血管形成。多种肿瘤研究中MIF被证明与VEGF和/或CXC趋化因子如IL-8生成增加有关(表1)；或可通过下调抗血管生成因子TSP-1的表达而作用于血管生成，从而间接刺激肿瘤血管新生和促进肿瘤生长。MIF在体内可与血管生成相关信号级联促进内皮细胞向血管内皮的分化，在体外可诱导内皮细胞的迁移和管状形成，其内在机制可能依赖于MAPK和PI3K，并与MEK1/2、ERK1/2、ELK-1、PIK3和AKT磷酸化水平的时间依赖性增加有关[62]。MIF与缺氧微环境及肿瘤血管新生的紧密联系不仅表明MIF在肿瘤中具有重要作用，而且还可以探索更多的MIF抑制剂和血管生成诱导剂等，通过干扰TME及血管形成来开辟新的治疗选择。

1.4 MIF与肿瘤免疫生物学 近年来“肿瘤免疫编辑”学说受到了较多的关注，其中一个重要的概念是肿瘤经过免疫清除(elimination)、平衡(equilibrium)和逃逸(escape)的“3E”阶段来逃避免疫监视。癌症背景下，适应性免疫中的T、B淋巴细胞主要发挥肿瘤细胞的清除作用，先天性免疫中具有免疫抑制特性的效应细胞群体如肿瘤相关巨噬细胞(TAM)、肿瘤相关中性粒细胞(TAN)、树突状细胞(DC)和髓源性抑制细胞(MDSCs)等异常产生并募集到TME中，可建立起免疫耐受环境，这些都与恶性肿瘤的侵袭性和免疫逃逸显著相关[63]。机体中MIF不仅通过多种机制在致癌转化和肿瘤进展中干扰癌细胞，也可通过影响多种免疫细胞从而在调节宿主先天性免疫和适应性免疫反应中发挥重要作用。MIF不仅可以通过参与包括诱导MDSCs[32]，抑制细胞毒性T淋巴细胞(CTL)和NK细胞[64]，巨噬细胞的M1极化[65]和DC成熟[66]等多种方式来干扰免疫激活，削弱抗肿瘤免疫从而建立免疫逃逸微环境，还能影响适应性免疫系统的Th1和Th2两种免疫途径，从而显示出不同的细胞因子谱并诱导不同的反应[67]。Balogh等[68]使用小鼠乳腺癌模型发现MIF表达缺陷可诱导一种特殊形式的细胞死亡，即免疫原性细胞死亡(ICD)，导致产生强大的抗肿瘤免疫反应，其标志是活化的DC丰度增加和产生IFN-γ的肿瘤浸润性T细胞增加。Zhang等[32]也证明，通过siRNA诱导的TME中MIF减少可通过减少全身免疫抑制来诱导抗肿瘤免疫反应。由此得知，原发性肿瘤中的MIF表达可以保护癌细胞免于ICD并抑制体内抗肿瘤免疫反应，并促进肿瘤生长。

阐明和调控肿瘤免疫逃逸反应是诊断和防治肿瘤的关键。MIF在参与肿瘤免疫逃逸和维持免疫微环境中具有重要作用。例如，卵巢癌和恶性神经胶质瘤中衍生的MIF通过下调NK细胞和$CD8^+$ T淋巴细胞上的NKG2D，从而抵消两者介导的肿瘤免疫监视，这有助于促进恶性肿瘤的免疫逃逸[43, 69]。另外，胶质瘤中MIF可通过调节Rho相关卷曲螺旋形成蛋白激酶1(ROCK1)活性增强自噬并抑制DC的成熟和功能[66]，还可激活MDSCs[70]从而抑制免疫排斥和逃避免疫监视。神经母细胞瘤产生的高水平MIF通过IFN-γ途径导致活化诱导的T细胞死亡，有助于逃避免疫监视[64]。综上，MIF与肿瘤免疫生物学密切相关，在肿瘤治疗中具有巨大的潜力和价值。

2 基于MIF的靶向治疗

针对MIF靶向治疗的部分药物已运用于临床试验。目前阻断MIF的治疗策略主要是通过抑制MIF蛋白或拮抗MIF受体来靶向MIF信号传导。主要包括小分子抑制剂、单克隆中和抗体(抗MIF、CD74、CXCR2/4抗体)和小干扰RNA (siRNA)。小分子抑制剂主要包括(S,R)-3-(4-羟基苯基)-4,5-二氢-5-异恶唑乙酸甲酯(ISO-1)、4-碘-6-苯基嘧啶(4-IPP)和CP-SI-1306/2705，其他通过多种筛选方式发现并探索中的抑制剂有IMG122、SCD-19、AV411 (异丁司特)、p425、HDACi (组蛋白去乙酰化酶抑制剂)等，其中大部分针对的是MIF的互变异构酶活性，通过活性位点的结合、变构、修饰、解离等多种方式使其失活[71-74]。由于互变异构酶活性位点紧邻的氨基酸残基与MIF-CD74复合体的形成关系密切，因而这些抑制剂

不仅干扰 MIF 的结构或活性，还能影响MIF-CD74相互作用和相关信号传导[75]。研究最广泛的 MIF 抑制剂 ISO-1 已在动物实验中发现其显著抑制了前列腺癌、结直肠癌、胆囊癌、骨肉瘤、肺腺癌、胶质母细胞瘤、胰腺癌和黑色素瘤的生长[76]。最近的一项研究还发现 ISO 可通过 TGF-β/Smad4 轴抑制鼻咽癌细胞的 EMT[77]。另外，针对恶性肿瘤的多种治疗方式联合应用也显示出了良好的效果，例如阻断 MIF-CD74 信号传导会增强 $CD8^+$ T 细胞浸润并驱动 TME 中巨噬细胞的M1极性化，其与抗细胞毒性T淋巴细胞相关抗原 4 (CTLA-4)药物联合使用可以使黑色素瘤更好地响应免疫检查点抑制剂(ICB)治疗并克服对其的耐药[78]。总之，基于MIF的癌症靶向治疗可以有效影响癌细胞的增殖、迁移、侵袭等恶性进展特征，具有广阔的应用前景。

3 展望

综上所述，MIF在癌症的发生和发展中发挥多种功能，其靶点治疗已受到越来越多的关注。今后需要在如下几个方面深入研究：(1)探索不同肿瘤中的表达特征、信号通路、相关调节通路的上下游分子及相关性，如靶向MIF的非编码RNA是否具有共性，加深对其生物学内在机制的认识并建立寻找治疗靶点的分子基础；(2)部分MIF特异性抑制剂在体外肿瘤模型的应用得到了比较好的结果，但因药物副作用、给药方式、经济成本等多种原因限制了其在临床患者体内应用的可行性，后续亟待开发针对MIF适用性更强的靶向分子。同时，注重通过基因编辑技术和细胞疗法等多种治疗手段攻关难题，探索与其他治疗方式进行组合联用等新思路来推动肿瘤治疗。(3) MIF与肿瘤免疫的关系，仍需要在多种肿瘤中得到支持验证，从而扩展MIF抑制剂使用指征的覆盖率。(4)不同类别抑制剂的使用在临床上尚待开展相关队列研究，以阐明MIF表达及靶向干预对肿瘤患者的安全性、有效性。

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