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肿瘤相关巨噬细胞作用和靶向治疗的研究进展

王煦苏[1]，徐娟[2] 综述 贾雪梅[2] 审校

[1. 南京医科大学妇产科学系，南京 211166；2. 南京医科大学附属妇产医院(南京市妇幼保健院)妇产科，南京 210004]

[摘 要] 肿瘤微环境是一种复杂的细胞生态环境，其在向恶性肿瘤过渡期间与肿瘤细胞一起进化并提供支持。巨噬细胞特别富集并且存在于肿瘤进展的所有阶段，在原发性肿瘤中，肿瘤相关巨噬细胞(tumor associated macrophage，TAM)可以刺激血管生成并增强肿瘤细胞的侵袭，运动、内渗和耐药等能力，这些活动中的每一项都有不同的作用机制。

[关键词] 肿瘤相关巨噬细胞；作用机制；靶向治疗

Research progress of tumor-associated macrophages in function and targeted therapy

WANG Xusu[1], XU Juan[2], JIA Xuemei[2]

[1. Department of Obstetrics and Gynecology, Nanjing Medical University, Nanjing 211166; 2. Department of Gynecology, Women's Hospital of Nanjing Medical University (Nanjing Maternity and Child Health Care Hospital), Nanjing 210004, China]

Abstract The tumor microenvironment is a complex ecology that evolves with and provides support to tumor cells during the transition to malignancy. Macrophages are particularly abundant and are present at all stages of tumor. In the primary tumor, macrophages can stimulate angiogenesis and enhance tumor cell invasion, motility, intravasation and drug resistance. Each of these activities has a different mechanism.

Keywords tumor-associated macrophages; mechanism; targeted therapy

随着肿瘤的生长，恶性肿瘤细胞与邻近的实质细胞、间质细胞和募集的免疫细胞之间不断相互作用。这些细胞与细胞外基质和可溶性介质一起形成肿瘤微环境(tumor microenvironment，TME)[1]。巨噬细胞是TME中数量最多的正常细胞之一，大量证据[2]表明在体内肿瘤原发和转移部位的巨噬细胞呈现一种促肿瘤的表型。肿瘤相关巨噬细胞(tumor associated macrophage，TAM)在大多数类型的恶性肿瘤中可促进肿瘤血管生成，介导癌细胞从原发灶逃逸到循环中，并抑制抗肿瘤免

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通信作者 (Corresponding author)：贾雪梅，Email: xmjia@njmu.edu.cn

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疫反应的发生。它们还有助于癌细胞在肺部等远处脏器渗出、增殖并形成转移灶。此外，TAM还可以拮抗放化疗、抗血管生成药和靶向药的抗肿瘤作用及诱导肿瘤干细胞产生并促进其生长等。已有实验研究发现，清除巨噬细胞可抑制肿瘤的发展和转移，表明已获得恶性表型的巨噬细胞对肿瘤细胞至关重要。因此，这种恶性表型巨噬细胞可能成为癌症的重要治疗靶点[3]。

1 TAM的来源

TAM的起源目前仍有争议。最初，小鼠肿瘤中的TAM被认为主要来源于血液单核细胞[4]，传统上也认为人TAM来源于循环中的单核细胞。然而，最近研究[5-6]表明：在脑和胰腺癌的一些小鼠模型中，TAM来自血液单核细胞和胚胎巨噬细胞，但仅后者可促进已形成的肿瘤的生长。同时，最新研究发现许多组织中的巨噬细胞起源于发育期间在组织中沉积的胚胎巨噬细胞(特别是来自卵黄囊中沉积的巨噬细胞)。这些胚胎巨噬细胞独立于成人造血系统，可通过局部增殖作用来维持自身生长[7]。尽管对TAM的来源及其募集和分化机制的研究还处于起步阶段，但是随着对这些机制探索的不断深入，寻找针对这些促肿瘤TAM靶向治疗方法的可能性也越来越大。

2 TAM促肿瘤作用机制

2.1 促进血管生成

Wnt蛋白异常表达参与乳腺癌发生发展过程，Wnt7b在乳腺癌中表达明显升高。MMTV-PyMT小鼠为乳腺癌转基因小鼠，在该小鼠模型中，巨噬细胞合成的Wnt7b靶向血管内皮细胞，刺激其产生血管内皮生长因子(vascular endothelial growth factor，VEGF)，启动血管生成[8]。有研究[9]发现TAM也在恶性胶质瘤模型中促进新生血管的形成。TIE2为内皮特异性亚家族酪氨酸激酶，特异性表达于内皮细胞和早期造血细胞，研究发现部分TAM表面表达TIE2，这些$TIE2^+$的巨噬细胞通常通过与表达ANG2(TIE2配体，一种内皮细胞特异性促血管生成因子)的内皮细胞结合，从而沿着血管的近腔表面排列，且它们与肿瘤血管生成和肿瘤缺血后恢复高度相关，靶向ANG2或TIE2可以抑制血管生成[10-11]。

2.2 诱导肿瘤干性，促进肿瘤生长

近来有研究表明TAM可以诱导肿瘤干细胞(cancer stem cell，CSC)产生并维持其生长。如Won等[12]发现巨噬细胞分泌的IL-6可以通过IL-6/STAT3途径诱导肝癌细胞上干细胞分子标志物CD133的表达。Yang等[13]发现巨噬细胞分泌的表皮生长因子(epidermal growth factor，EGF)可以通过EGF/EGFR通路激活STAT3诱导的Sox2的表达，进一步促进其他CSC相关分子标志物的表达，和肿瘤干性的形成等。Yang等[14]发现在非小细胞肺癌中，TAM通过分泌IL-10诱导非小细胞肺癌细胞上干细胞分子标志物Sox2，Oct4和c-Myc的表达，激活JAK1/STAT1/NF-κB/Notch1信号通路，促进肿瘤细胞生长，使其具备肿瘤干细胞样特性，导致非小细胞肺癌患者更差的预后。Shi等[15]研究发现TAM分泌的多效生长因子(pleiotrophin，PTN)可以与恶性胶质瘤上的受体PTPRZ1结合，激活PTPRZ1信号通路，刺激脑恶性胶质瘤干细胞的形成，从而促进肿瘤的生长。此外，TAM还可以分泌一些细胞因子来促进干细胞的维持。有研究[16]发现胰腺导管癌细胞产生的干扰素β(interferon β，IFN-β)，可以诱导TAM中干扰素刺激的基因15(IFN-stimulated gene 15，ISG15)的分泌，ISG15进一步作用于胰腺导管癌干细胞，促进其自我更新与维持。

2.3 促进肿瘤细胞迁移

$TIE2^+$的TAM促进肿瘤细胞迁移进入血液循环[17]。研究[18-19]发现巨噬细胞可以通过一个旁分泌环促进肿瘤细胞定向迁移，这个旁分泌环由肿瘤细胞分泌的集落刺激因子-1(colony stimulating factor-1，CSF-1)和巨噬细胞来源的EGF或EGF家族配体组成。肿瘤细胞和巨噬细胞互相交锁连接沿胶原纤维快速流动，最终肿瘤细胞聚集在血管周围并“逃逸”入血管中。此外，巨噬细胞可以产生一些促肿瘤细胞迁移的分子，包括骨粘连蛋白[20]、组织蛋白酶[21-22]以及转化生长因子-β(transforming growth factor-β，TGF-β)[23]。因此，清除TAM或者通过基因敲除减少它们主要的生长因子CSF-1的分泌，可减少循环肿瘤细胞数量并抑制肿瘤细胞迁移[18]。

2.4 抑制其他免疫细胞的活化

主要组织相容性复合体(major histocompatibility

complex，MHC)是一组编码哺乳动物主要组织相容性抗原的基因群的统称。人类的MHC产物通常被称为人类白细胞抗原(human leukocyte antigen，HLA)。巨噬细胞和树突状细胞表达经典和非经典的MHC-I分子，通常参与抗原递呈，激活T细胞。然而，巨噬细胞也可以表达HLA分子，以膜结合或可溶形式抑制自然杀伤(NK)细胞和活化的T细胞亚群的活化。例如，有研究[24]指出TAM表达HLA-E结合杀伤细胞免疫球蛋白样受体CD94(也称为NKG2)不仅可以直接抑制NK细胞活性，还可抑制NK细胞迁移至淋巴结、抑制其分泌γ-干扰素(interferon-γ，IFN-γ)，进一步抑制$CD8^+$T细胞的活化[25]；TAM表达HLA-G结合抑制性白细胞免疫球蛋白样受体LIT-2，可以抑制活化的T细胞亚群的活化[26]。然而，TAM表面HLA配体和抑制性受体的表达及其如何发挥TAM免疫抑制效应的功能还有待进一步明确。

2.5 降低肿瘤免疫治疗效果

程序性死亡受体1(programmed death-1，PD-1)是一种重要的免疫抑制分子，其与配体PD-L1结合启动T细胞的程序性死亡，使肿瘤细胞获得免疫逃逸。细胞毒性T淋巴细胞相关抗原4(cytotoxic T lymphocyte-associated antigen-4，CTLA-4)又名CD152，是一种白细胞分化抗原，是T细胞上的一种跨膜受体，与CD28共同享有配体B7分子，而CTLA-4与B7分子结合后诱导T细胞无反应性，参与免疫反应的负调节。近年来，PD-1抗体和CTLA-4抑制性抗体阻断治疗发展得如火如荼，临床研究取得了巨大进展，成为许多特定癌症患者有效的治疗方法，是肿瘤免疫治疗的热点之一。James P. Allison和Tasuku Honjo因在“免疫检验点”研究中的突出贡献获得了2018年诺贝尔生理学或医学奖，Allison发现了CTLA-4具有T细胞“刹车”功能，而Honjo发现了免疫检查点PD-1[27]。B7家族很多成员作为PD-1和CTLA-4的配体参与肿瘤的发生发展，其中B7-H4作为B7超家族中相对较新的成员，参与抑制T细胞的活化[28]。有研究[29-30]发现：TAM上可表达PD-1和CTLA-4等抑制性受体，也可以表达B7-H4等抑制性配体，B7-H4在TAM上的表达与肺癌和胃癌的临床分期相关，晚期患者的表达显著高于早期患者。B7-H4的抑制恢复了TAM的刺激功能并有助于肿瘤消退[28]。此外，越来越多的证据[31-32]表明：TAM的浸润增多与不良预后和免疫检查点抑制剂耐药相关。最新研究[33]还发现：TAM可以吞噬结合到T细胞上的PD-1抗体。然而，如何靶向并消除巨噬细胞对肿瘤免疫治疗的负面影响，提高免疫治疗效果仍具有挑战性，因为TME中的许多细胞表达PD-L1和B7分子[34-36]。

2.6 分泌细胞因子、趋化因子和酶

TAM还分泌一系列细胞因子、趋化因子和酶，通过将天然调节性T(nTreg)细胞募集到TME中，以及通过诱导$CD4^+$T细胞分化为适应性调节性T(iTreg)细胞，直接或间接抑制$CD4^+$和$CD8^+$T细胞的效应功能[37]。Curiel等[38]证明TAM分泌的CCL22可将$CCR4^+$nTreg细胞募集到人卵巢癌肿瘤并促进肿瘤生长。在结肠直肠癌中，由TAM分泌的CCL20募集$CCR6^+$nTreg细胞至肿瘤处[39]。在TME中诱导iTreg细胞是一个复杂的过程，机制尚不完全清楚。然而，TGF-β和IL-10可以通过上调$CD4^+$T细胞中关键调节转录因子Foxp3诱导免疫抑制功能[40]。已发现TAM在包括小鼠和人癌症的不同病理情况下表达IL-10和TGF-β[41]。Denning等[42]证实肠道免疫系统中的巨噬细胞可通过分泌IL-10和TGF-β诱导iTreg细胞生成。

2.7 消耗*L*-精氨酸

L-精氨酸是T细胞活化的必要物质。TAM可消耗*L*-精氨酸从而抑制T细胞活性。Doedens等[43-44]研究证实：TAM可通过分泌精氨酸酶I(arginase I，ArgI)导致*L*-精氨酸代谢为尿素和*L*-鸟氨酸。*L*-精氨酸的缺乏使T细胞对于抗原刺激钝化，并抑制了T细胞抗原受体(T cell receptor，TCR)介导的CD3ζ链再表达[45-46]。因此，ArgI的表达也被认为是抗炎性巨噬细胞的标志之一[47]。

2.8 诱导肿瘤耐药

在TME中，TAM可以与肿瘤细胞相互作用，促进肿瘤化疗耐药的发生[48]。Zheng等[49]发现TAM可以通过P-选择素糖蛋白配体-1(P-selectin glycoprotein ligand-1，PSGL1)和细胞间黏附分子-1(intercellular cell adhesion molecule-1，ICAM-1)介导的细胞与细胞直接接触，赋予骨髓瘤细胞化学耐药性，保护肿瘤细胞免受美法仑和地塞米松介导的细胞凋亡。TAM也可以通过释放可溶性产物(即通过旁分泌机制)诱导化疗耐药。例如，在缺氧环境下，TAM可以通过释放外泌体，将miR-233转移到与TAM共培养的上皮性卵巢癌细胞中，激活卵巢癌细胞中PTEN-PI3/AKT通路，从而增强卵

巢癌细胞的耐药性[50]。类似的，Binenbaum等[51]发现在胰腺导管腺癌的原发灶和肝转移灶中，TAM可以通过外泌体转运miR-365，升高细胞内的三磷酸核苷酸(triphosphate-nucleotide，NTP)和胞苷脱氨酶(cytidine deaminase，CDA)含量，促进细胞内吉西他滨的代谢。有证据[52]表明TAM还可以通过间接抑制TME中T细胞的细胞毒活性来介导化疗耐药，在没有巨噬细胞和IL-10的情况下，IL-12能够激活$CD8^+$T细胞反应，从而增强肿瘤细胞对化疗药的敏感性，而TAM分泌的IL-10可能通过激活树突状细胞对损伤相关分子模式(damage associated molecular patterns，DAMPs)的反应抑制其在化疗期间产生IL-12的能力，从而导致化疗耐药的产生。此外，有研究[53]表明：TAM也与内分泌治疗的耐药相关。他莫昔芬治疗可以解除雌二醇对NF-κB的抑制，导致促炎微环境的形成，促炎微环境招募TAM，使其与$ERα^+$的乳腺癌细胞相互作用，促进肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)和IL-6的产生，进一步诱导STAT3和NF-κB的激活，促进cyclinD1及c-Myc等与他莫昔芬耐药相关基因的表达。

3 巨噬细胞作为治疗靶点

迄今为止巨噬细胞作为治疗靶点仍是基于动物实验。在胶质母细胞瘤小鼠模型中抑制CSF-1R可以导致肿瘤体积显著减小和小鼠的存活率显著提高。这种CSF-1R抑制作用虽然并未清除TAM，但可以导致它们再次转化为受粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony stimulating factor，GM-CSF)调节的抗肿瘤状态[22]。在宫颈癌和乳腺癌模型中也可以看到类似的结果[54]。与此同时，CSF1-R的小分子抑制剂也被证明可以消耗一些TAM，在肿瘤“恢复”期间抑制了巨噬细胞介导的免疫抑制作用，从而显著增强肿瘤对化疗的敏感性[55-56]。这些影响似乎不仅限于化疗，因为TIE^+TAM的敲除明显增强了抗血管生成试剂的治疗功效[57-58]。在其他模型中，肿瘤的低剂量放疗可以将巨噬细胞重新编程为协同T细胞免疫疗法的活化状态[59]。巨噬细胞还可以增强单克隆抗体的治疗功效[60]。此外，最近将巨噬细胞作为靶点的临床药物也取得新的进展。已知GAS6是酪氨酸蛋白激酶受体家族ATM(Axl，Tyro3和MerTK)的配体，研究发现肿瘤细胞可以通过微环境“教化”巨噬细胞分泌GAS6，反过来，GAS6可以通过其受体来滋养肿瘤细胞的生长，促进其耐药。最近，几种特异性靶向AXL抑制剂已进入早期临床试验，包括BGB324(早期名为R428；与厄洛替尼联合应用于非小细胞肺癌：NCT02424617)和BPI-9016M(在晚期实体瘤中安全使用：NCT02478866)。靶向AXL的单克隆抗体(YW327.6S2)和AXL诱饵受体(GL2I.T)目前也处于临床前开发阶段[61-62]。

4 结语

通过去除或靶向TAM可能成为治疗恶性肿瘤的潜在靶点。因为这些二倍体正常细胞可以避免导致药物抗性增强的肿瘤细胞突变率。尽管目前因为泛巨噬细胞治疗方法靶向所有巨噬细胞而具有全身毒性，但随着未来对不同来源巨噬细胞的理解，更精准地只针对TAM的靶向治疗将成为可能[63]。与此同时，更重要的是，需要定义不同癌症和特定组织中不同的巨噬细胞亚群以推进这些靶向选择。另一种治疗策略是通过去除巨噬细胞的免疫抑制活性来增强化学疗法或免疫疗法的效果。在这个方面，临床前数据表明可以将获得的几种方法结合起来，通过使用中和抗PD-1、抗PD-L1或抗CTLA4抗体来抑制适应性调节性T细胞从而改善已经取得的抗肿瘤临床结果[64]。

综上所述，TAM的来源、TAM与肿瘤间相互作用的分子机制还有待未来进一步探索，研究TAM在TME中如何发挥作用，对肿瘤的诊断、治疗和预后意义深远，为以后靶向TAM的治疗提供了新的方向。

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