•综述•

靶向肿瘤相关巨噬细胞药物的研究进展

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摘要: 肿瘤严重威胁人类生命健康, 近年来其发病率和死亡率在全球范围内迅速增加。肿瘤治疗药物经历了细胞毒疗法、靶向疗法和免疫疗法的发展, 其中肿瘤免疫治疗已经成为近年来快速发展起来的新兴抗肿瘤疗法, 但其也存在一些相关的不良反应。肿瘤微环境是由免疫细胞、肿瘤血管、成纤维细胞、细胞外基质等多种成分构成的复杂动态环境, 肿瘤微环境显著影响免疫治疗的效果。肿瘤微环境中的巨噬细胞被称为肿瘤相关巨噬细胞, 近年来越来越多的研究表明肿瘤相关巨噬细胞在肿瘤免疫调节中起着重要作用, 特别是在肿瘤免疫监控及免疫逃逸等方面发挥关键调节作用。目前, 越来越多针对肿瘤相关巨噬细胞的抗肿瘤免疫治疗策略正处于研发阶段。基于肿瘤相关巨噬细胞在肿瘤免疫微环境中的重要作用以及其可以作为肿瘤免疫治疗的潜在靶点, 本文对肿瘤相关巨噬细胞的亚型与功能、肿瘤相关巨噬细胞在肿瘤中的主要作用, 近年来靶向肿瘤相关巨噬细胞的抗肿瘤策略相关研究以及药物研发现状进行综述, 以期为肿瘤免疫治疗提供新的思路。

关键词: 免疫治疗; 肿瘤微环境; 肿瘤相关巨噬细胞; 药物靶点

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Research progress in drugs targeting tumor associated macrophage

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Abstract: Tumor brings great threat to human public health. In recent years, incidence rate and mortality of tumor were rapidly increased in the world. Anti-tumor therapies have undergone the development of cytotoxic therapy, targeted therapy, and immunotherapy. Among them, tumor immunotherapy is rapidly developed and becomes an important anti-tumor therapy in recent years, although it also brings some related side effects. Tumor microenvironment (TME) is composed of immune cells, vascular vessels, fibroblasts, the extracellular matrix, etc. TME significantly affects the efficacy of immunotherapy. Macrophages in the TME are named as tumor associated macrophages (TAMs). Recently, increasing studies have shown that TAMs play an important role in the regulation of tumor immunity, especially in tumor immune surveillance and immune escape. Currently, more and more anti-tumor immunotherapy strategies targeting TAMs are at the development stage. Based on the important role of TAMs in the TME and their potential as therapeutic targets in tumor immunotherapy, we first reviewed the subtypes and functions of TAMs, as well as the roles of TAMs in tumors. Furthermore, we summarized the research progress on anti-tumor strategies targeting TAMs and the current status of drug targeting TAMs. The

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current review will provide new ideas and novel insights for tumor immunotherapy.

Key words: immunotherapy; tumor microenvironment; tumor associated macrophage; drug target

癌症严重威胁人类生命健康。根据世界卫生组织 (WHO) 下属的国际癌症研究机构 (International Agency for Research on Cancer, IARC) 发布的癌症最新数据, 2020年全球新发癌症病例1 929万, 其中男性1 006万例, 女性923万例; 2020年全球癌症死亡病例996万例, 其中男性553万例, 女性443万例。在21世纪, 癌症预计将超过心血管疾病, 成为大多数患者过早死亡的主要原因。IARC调查数据中令人震惊的是乳腺癌首次超过肺癌成为全球最常被诊断出的癌症类型[1]。

目前治疗肿瘤的药物经历了细胞毒药物、靶向药物、免疫治疗药物的发展。肿瘤免疫治疗是近年来快速发展起来的新型疗法, 主要作用通过激活机体的免疫系统而非肿瘤细胞, 通过增强机体对肿瘤的自然免疫防御、重塑免疫微环境等方式清除肿瘤细胞。目前常见的肿瘤免疫疗法包括单克隆抗体疗法、免疫检查点阻断剂疗法、过继细胞疗法、溶瘤病毒疗法和肿瘤疫苗等。各种肿瘤免疫新疗法不断涌现并取得令人兴奋的进展, 被学术界认为是继传统治疗、靶向治疗后, 肿瘤治疗史上的第三次革命[2]。但肿瘤免疫治疗也存在反应率低及细胞因子风暴等问题, 同时患者皮肤会出现红肿、干燥、水泡等, 类似流感症状, 以及很多心脏相关疾病等不良反应[3]。

肿瘤微环境 (tumor microenvironment, TME) 是肿瘤细胞、间质细胞、上皮细胞、成纤维细胞和包括T细胞、树突状细胞、巨噬细胞等在内的免疫细胞之间相互作用、共同构成的复杂动态环境[4-6]。肿瘤微环境中存在的巨噬细胞又称之为肿瘤相关巨噬细胞 (tumor associated macrophage, TAM)。近年来, 越来越多的研究显示, TAM在肿瘤免疫调节等方面发挥重要作用[5,7]。TAM在乳腺癌免疫微环境中所占比重较高, 甚至能够达到乳腺癌组织的30%～60%[8,9]。TAM具有较高的异质性, 其功能复杂多样, 其中包括促进肿瘤增殖和转移, 促进肿瘤新生血管及诱导抑制性免疫微环境产生等[10]。TAM在肿瘤免疫抑制及免疫逃逸等方面发挥关键调节作用, 近年来有越来越多针对TAM的抗肿瘤靶向治疗策略处于研发阶段[11,12]。基于TAM在肿瘤免疫微环境中的重要作用, 本综述首先对TAM与肿瘤免疫之间的关系进行梳理, 在此基础上对近年来靶向TAM的抗肿瘤策略相关研究和药物研发现状进行总结, 以期为肿瘤免疫治疗提供新的思路。

1 TAM与肿瘤免疫

近年来越来越多的研究显示, TAM具有很强的可塑性, TAM与肿瘤细胞免疫逃逸等密切相关。

1.1 TAM的亚型

TAM的分型较为复杂, 且随着肿瘤进展过程处于动态调节中, 其可以简单分为两种极化类型 (图1), 即M1型经典激活的巨噬细胞和M2型交替激活的巨噬细胞[13]。M1型巨噬细胞能够杀伤肿瘤细胞、抵御机体病原体入侵, 起抑制肿瘤作用, 而M2型巨噬细胞能够促进肿瘤细胞增殖和转移, 具有促进肿瘤作用。M2型巨噬细胞是肿瘤微环境中主要的巨噬细胞类型[14]。M1型巨噬细胞受白细胞介素 (interleukin, IL)-1β、干扰素 (interferon, IFN)-γ、肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α) 和脂多糖等的刺激, 并通过产生多种细胞因子, 如IL-1、IL-8、IL-6、TNF-α与ROS来抑制肿瘤生长[15]。M1型巨噬细胞能够通过激活辅助性T细胞1 (help T cell 1, Th1) 来增强其对肿瘤细胞的杀伤作用, 从而促进抗肿瘤免疫应答[16]。与之相反, M2型交替激活巨噬细胞能够被IL-4和IL-13激活, 分泌大量的IL-10及小部分IL-12、IL-23, 减弱肿瘤部位的炎症反应, 从而抑制机体抗肿瘤免疫应答[17]。此外, M2型巨噬细胞还能够通过抑制T淋巴细胞的活性进而抑制T淋巴细胞对肿瘤的杀伤作用[18,19]。M1与M2型巨噬细胞的细胞类型并不是固定的, 在肿瘤进展过程中, 肿瘤微环境可以调控两种类型的巨噬细胞进行相互转化, 其细胞类型具有高度可塑性。但TAM分子类型较为复杂, 不能简单视为M1与M2两种亚型, 近年来也发现$CD169^+$、TCR^+等分子分型的TAM[18], 以及按组织来源分为组织驻留巨噬细胞 (tissue-resident macrophages, TRMs) 和骨髓来源的血液单核细胞等[20]。

1.2 TAM在肿瘤的主要作用

1.2.1 TAM促进肿瘤的侵袭和转移 TAM能够通过分泌基质金属蛋白酶 (matrix metalloproteinase, MMP)、组织蛋白酶 (cathepsin) 等物质破坏细胞之间的紧密连接与基底膜, 从而促进肿瘤细胞的侵袭与转移过程[21,22]。在乳腺癌中, TAM来源的组织蛋白酶B (cathepsin B) 能够促进乳腺癌细胞发生转移、侵袭, 导致乳腺癌细胞的肺转移[23]。此外, TAM还能够通过提高肿瘤组织和机体全身水平血管内皮生长因子 (vascular endothelial growth factor, VEGF)、脂钙素-2 (Lcn-2)、几丁质酶-3样蛋白1 (CHI3L1)、MMP9等蛋白

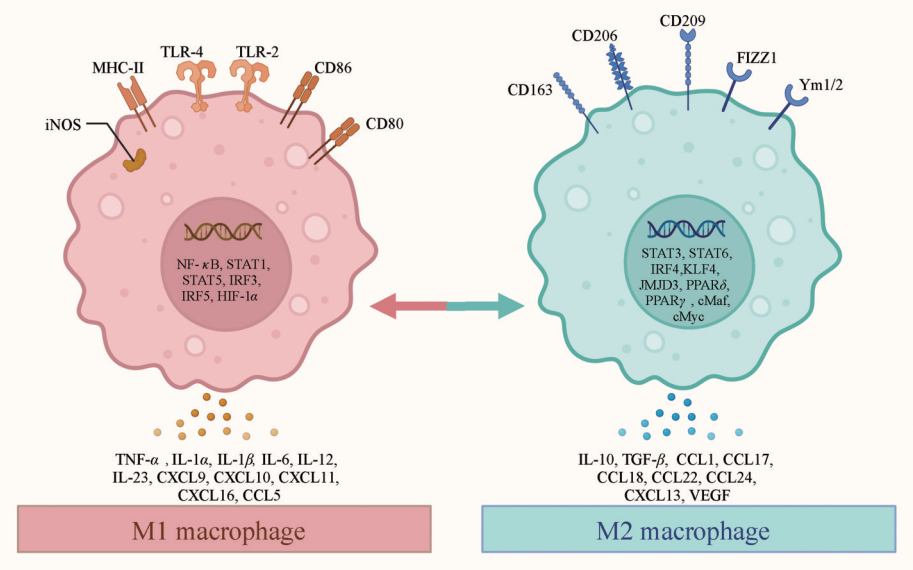

Figure 1 Two major subtypes of tumor-associated macrophages. Figure was created by Biorender (biorender.com/)

表达, 促进小鼠三阴性乳腺癌模型的转移[24]。有研究表明, 绝大多数的肿瘤细胞转移和血管内渗过程都与肿瘤细胞与巨噬细胞的相互作用有关[25]。与此同时, TAM 也能够通过分泌细胞外基质 (extracellular matrix, ECM) 重塑蛋白来调节肿瘤组织重构, 从而促进肿瘤细胞的侵袭和转移过程[26]。

1.2.2 TAM 能够促进肿瘤血管生成 TAM 能够分泌多种血管生成调节因子, 如尿激酶型纤溶酶原激活物 (uPA)、血小板衍生生长因子-β (platelet derived growth factor β, PDGF-β)、VEGF、TNF-α、IL-1β、CXCL8、MMP7、MMP9 和 MMP12 等来促进肿瘤血管生成[27]。血管生成素 2 (angiopoietin 2, ANG2) 属于血管生成素家族成员, 能够通过调节血管生成素酪氨酸激酶蛋白受体 2 (TEK receptor tyrosine kinase Tie2, TIE2) 促进肿瘤血管生成, 同时还能够通过调节 TIE2 表达水平调控 TAM 的促血管生成活性。抑制 ANG2 能够抑制 $TIE2^+$巨噬细胞的促血管生成能力, 阻断小鼠原位乳腺癌肿瘤血管生成, 抑制乳腺癌进展和转移[28]。此外, TAM 还能够通过分泌 Wnt7b (Wnt family member 7b) 调控内皮细胞 Wnt/β-catenin 信号通路, 促进肿瘤血管生成[29]。

1.2.3 TAM 能够促进肿瘤耐药 研究表明, 在肿瘤耐药的肿瘤微环境中巨噬细胞的比例显著增加, 提示在肿瘤组织产生耐药的过程中有 TAM 的参与[30]。抗血管生成药物阿柏西普 (Zaltrap/Aflibercept) 能够通过结合 VEGF 与胎盘生长因子 (placental growth factor, PLGF) 抑制复发胶质母细胞瘤患者的血管生成, 发挥抗肿瘤作用。但 TAM 能够通过分泌 MMP9 使得患者对阿柏西普产生耐药性, 巨噬细胞所分泌的相关细胞因子可以作为患者不良预后的生物标志物[31]。许多乳腺癌患者在接受紫杉醇治疗后, 乳腺癌中的巨噬细胞浸润水平与组织蛋白酶表达显著升高。在体外共培养实验研究中发现, 巨噬细胞能够通过分泌组织蛋白酶 B 和组织蛋白酶 S 保护肿瘤细胞不被紫杉醇、依托泊苷和多柔比星等化疗药物杀伤。同时使用化疗药物和组织蛋白酶抑制剂能够显著增加化疗药物的体内外治疗效果[32]。此外, TAM 还能够通过激活 MAPK/ERK 激酶 (MEK) 来抑制紫杉醇对乳腺癌的治疗效果, 通过清除乳腺癌组织中的巨噬细胞或者抑制 MEK 能够增强乳腺癌对紫杉醇化疗的敏感性[33]。在给予多柔比星及顺铂化疗的小鼠乳腺癌模型中, 肿瘤微环境中的乳腺癌细胞能够通过分泌 CCL2 招募 $CCR2^+$巨噬细胞, 巨噬细胞通过分泌 MMP9 促进肿瘤细胞血管渗漏, 帮助肿瘤细胞发生转移[34]。与此同时, TAM 还能够促进肿瘤微环境中肿瘤干细胞的增殖, 进而促进肿瘤进展[35]。

1.2.4 TAM 具有免疫抑制效应 TAM 是肿瘤微环境中重要的具有免疫调节功能的细胞, 能够抑制肿瘤微环境中发挥主要抗肿瘤免疫效应的细胞毒性 T 淋巴细胞的有效应答。不幸的是, 在肿瘤微环境中 TAM 能够通过多种机制直接或间接抑制细胞毒性 T 淋巴细胞的作用, 从而促进肿瘤免疫逃逸与肿瘤进展[36]。TAM 能够分泌多种细胞因子 (如 VEGF、IL-4、IL-10、PDGF-β)、细胞趋化因子 (如 CCL2、CCL17、CCL5) 和多种蛋白酶 [如环氧合酶-2 (cyclooxygenase-2, COX-2)、精氨酸酶 1 (arginase-1, ARG1)、组织蛋白酶 K (cathepsin K)

和基质金属蛋白酶MMP等], 从而直接抑制$CD8^+$ T淋巴细胞和$CD4^+$ T淋巴细胞对肿瘤细胞的杀伤功能[37]。与此同时, TAM还能够通过分泌多种细胞因子、细胞趋化因子及蛋白酶等募集自然调节性T细胞 (regulatory T cells, Tregs) 并诱导适应性调节T细胞产生, Tregs细胞能够通过分泌抑制性免疫因子或通过直接抑制效应性T细胞的免疫应答来发挥免疫抑制功能。除Tregs外, 骨髓来源抑制性细胞 (myeloid-derived suppressor cells, MDSCs) 也是免疫微环境中另一重要的抑制性免疫细胞。脑恶性胶质瘤中的TAM能够通过CCL2的分泌, 进而招募$CCR2^+$ MDSCs来抑制肿瘤免疫应答, 促进恶性胶质瘤进展[38]。TAM不仅能够招募免疫抑制性T细胞, 还能够通过表达干扰素调节因子IRF8等多种途径来促进肿瘤微环境中$CD8^+$ T淋巴细胞的耗竭, 进而促进肿瘤进展[39,40]。此外, TAM还能够通过自分泌TNF-α和IL-10来诱导自身PD-L1表达上调, 进而抑制肿瘤特异性的T细胞免疫应答, 促进肿瘤进展。并且在肝癌患者中, TAM PD-L1表达水平越高往往与患者更高的死亡率和更低的生存率有显著关联[41]。

2 靶向TAM的抗肿瘤策略和药物研发现状

TAM在肿瘤的发生发展中发挥关键作用 (图2), 目前已有多种针对TAM的在研药物处于临床研究阶段。主要有两种针对TAM治疗策略, 一种是清除肿瘤微环境中具有促瘤作用的TAM, 包括诱导巨噬细胞凋亡或者阻断细胞因子或趋化因子等对巨噬细胞的招募等; 另一种方式是对TAM进行重编程, 诱导促瘤的M2型巨噬细胞转化为具有抗肿瘤作用的M1型巨噬细胞。现阶段, 针对TAM开发的药物研发主要围绕以下一些靶点展开。

2.1 巨噬细胞集落刺激因子1受体 (colony stimulating factor 1 receptor, CSF1R) 抑制剂研发现状

CSF1R信号通路在TAM的增殖和活化过程发挥关键作用[42], 通过抑制CSF1R能够有效抑制肿瘤免疫微环境中TAM的募集, 具有显著的抗肿瘤活性[43]。靶向调控CSF1R也是研究最多的针对TAM的药物开发策略, 目前有多个CSF1R单克隆抗体或者小分子抑制剂已获批上市或正处于临床研究阶段。Surufatinib (HMPL-012) 是一种能够选择性靶向CSF1R、VEGFR1-3和FGFR1的小分子抑制剂, 基于其SANET-ep III期临床试验的结果, sulfatinib在中国获批用于非胰腺来源的神经内分泌瘤[44]。Emactuzumab (RG-7155) 是由罗氏制药和Celleron Therapeutics共同开发的CSF1R抑制剂, 用于治疗腱鞘巨细胞瘤、卵巢癌和腹膜恶性肿瘤等, 目前主要处于II/III期临床试验阶段[45,46]。Axatilimab (SNDX-6352) 是由Syndax Pharmaceuticals和英赛德公司 (Incyte Corporation) 联合开发的选择性CSF-1R抑制剂, 用于治疗慢性移植物抗宿主病、特发性肺纤维化及胆管癌等[47]。培西达替尼 (pexidartinib, PLX3397) 是由日本第一三共株式会社 (Daiichi Sankyo) 研发的CSF1R单克隆抗体, 目前正在进行III期临床试验, 主要用于治疗滑膜肉瘤[48]。在2019年美国FDA批准培西达替尼用于治疗对手术治疗无效、伴有功能受限或具有较高发病频率的症状性腱鞘巨细胞瘤成人患者[49]。BLZ945是美国安进公司 (Amgen) 研发的CSF1R小分子抑制剂, 目前正在进行多项临床试验, 包括治疗具有脑转移的淋巴瘤和胶质母细胞瘤

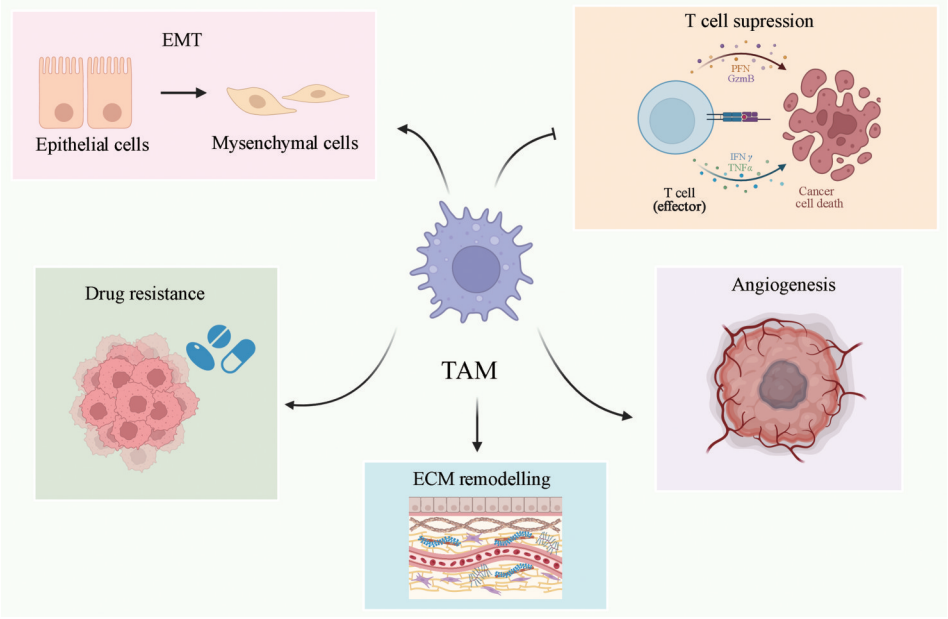

Figure 2 The major functions of tumor-associated macrophage in tumor. Figure was created by Biorender (biorender.com/)

(NCT02829723)[50]。JNJ-40346527是美国强生 (Johnson & Johnson) 公司研发的CSF1R小分子抑制剂, 目前处于II期临床试验, 用于治疗复发或难治性霍奇金淋巴瘤[51]。IMS-935是由美国Immuneering Corporation研发的CSF1R抑制剂, 是一种口服小分子药物, 用于治疗不同类型的癌症, 如乳腺癌、肝癌和结肠直肠癌等, 目前处于临床I/II期研究阶段。ARRY-382由Array BioPharma公司研发的CSF1R选择性抑制剂, 目前正在进行I/II期临床试验, 主要与派姆单抗 (pembrolizumab) 联用治疗晚期实体瘤[52]。CSF1R-IH4是由英赛德公司研发的CSF1R抑制剂, 目前正在进行I/II期临床试验, 研究其在治疗实体瘤 (如结肠癌) 中的疗效。Vimseltinib (DCC-3014) 是由Deciphera Pharmaceutical公司研发的一种高选择性的CSF1R开关控制激酶抑制剂, 目前正在进行III期临床试验以评估其用于治疗腱鞘巨细胞瘤的有效性[53]。Q702是一种口服Axl/Mer/CSF1R选择性抑制剂, 由韩国上市公司Qurient Co., Ltd开发。目前Q702联合帕博利珠单抗 (pembrolizumab) 用于治疗包括食道癌在内的多种晚期实体瘤, 正处在IB/II期临床试验中[54]。西奥罗尼 (chiauranib/CS2164) 是由深圳微芯生物科技股份有限公司研发的一种对包括CSF1R在内的多种激酶具有选择性抑制作用的多重激酶抑制剂, 其目前正在进行针对晚期实体肿瘤的临床Ib/II期试验[55]。以上是目前主要的在研CSF1R抑制剂, 目前绝大多数CSF1R抑制剂开发都只处于临床研究阶段, 一些CSF1R抑制剂单药的临床试验结果不太理想甚至提前终止, 其原因可能为TAM具有较大的异质性和CSF1R抑制剂特异性的问题。对TAM进行更加精密的分型以及提高CSF1R抑制剂靶向性可能是未来靶向TAM药物开发的重要研究方向。

2.2 CCR2抑制剂研发现状

细胞趋化因子CCL2能够招募TAM向肿瘤组织中浸润, 阻断肿瘤内CCL2/CCR2信号通路能够抑制TAM的浸润水平, 抑制肿瘤进展与肿瘤转移[56-58]。INCB 39110是由Incyte公司开发的口服CCR2抑制剂, 该化合物已经进入II期临床试验, 用于治疗晚期实体瘤和胰腺癌等。PF-04136309是由辉瑞公司 (Pfizer) 开发的口服CCR2抑制剂, 用于治疗晚期实体瘤, 目前该药物已经进入II期临床试验[59]。CCX872是由ChemoCentryx公司开发的口服CCR2抑制剂, 用于治疗晚期实体瘤, 目前该药物已经进入II期临床试验[60]。Carlumab (CNTO 888) 是靶向CCL2的特异性单克隆抗体, 其能够抑制由CCL2介导的TAM向肿瘤组织的募集。Carlumab在临床前乳腺癌和前列腺癌小鼠模型中, 显示出良好的疗效, 但在临床试验中未观察到有效的反应率[61]。此外, 还有很多处于临床前研究的CCR2抑制剂, 也具有良好的抗肿瘤活性[62,63]。CCR2抑制剂的开发面临和CSF1R抑制剂同样的问题, 如何对巨噬细胞进行更加精确的分型或者寻求更好的联合给药策略可能是未来重要的研究方向。

2.3 靶向CD47-SIRPα免疫检查点的药物研发现状

人体正常细胞能够通过表达CD47与巨噬细胞表面表达的信号调节蛋白α (signal-regulatory protein α, SIRPα) 相互作用, 向巨噬细胞传递“自己人, 别吃我”信号来避免巨噬细胞对自身的误伤, 但肿瘤细胞能够通过高表达CD47来躲避具有抗肿瘤活性的巨噬细胞杀伤[64,65]。因此, 通过抑制CD47-SIRPα轴可能具有重新恢复促瘤作用的TAM对肿瘤细胞杀伤能力的效应[66]。目前, 已有靶向CD47的单克隆抗体Hu5f9-G4、CC-90002和TTI-621等在临床研究阶段[67-69]。尽管I期临床结果显示, CC-90002在复发/难治性血液系统恶性肿瘤患者中具有良好的耐受性, 但是该临床试验最终由于未观察到客观响应而以失败告终。基于CC-90002较好的耐受性和药代动力学特性, 提高其给药剂量并联合其他单克隆抗体是一个后续值得探索的治疗策略[70]。此外, 尽管Hu5f9-G4在多种血液病肿瘤中取得良好的疗效, 但由于CD47广泛表达于正常细胞中, 通过单独阻断CD47-SIRPα通路往往会导致血小板减少、自发性溶血等一些严重不良反应[70-73]。如果通过与其他抗体药物联合治疗后, 可能发挥显著的治疗效果。CD47单抗Hu5F9-G4与利妥昔单抗联合给药能够有效治疗复发弥漫性大B细胞淋巴瘤和滤泡性淋巴瘤[74]。如何减少阻断CD47-SIRPα信号通路的不良反应以及如何通过联合给药方式以增加该疗法的治疗效果, 可能是未来靶向CD47-SIRPα途径的药物研发的重要课题, 同时针对这一思路也有多项临床试验正在开展, 如将TTI-621与rituximab、nivolumab联合用于治疗血液肿瘤与实体肿瘤, Hu5F9-G4与azacitidine联合用于治疗血液肿瘤等[75]。

2.4 驱动巨噬细胞向M1表型极化的药物研发现状

将具有促肿瘤作用的M2型巨噬细胞转化为具有抗肿瘤作用的M1型巨噬细胞能够有效地抑制肿瘤生长。目前针对驱动巨噬细胞向M1型极化有多种研究策略与相应的治疗药物处于研发阶段。CD40主要表达于B淋巴细胞和髓系细胞表面, CD40能够与树突细胞表面CD40配体结合促进树突细胞产生细胞因子和趋化因子, 诱导共刺激分子的表达, 增强抗原向T细胞的递呈[76,77]。此外, CD40还能够驱动M2型巨噬细胞向M1表型发生极化[78,79]。CP-870,893是由罗氏公司

开发的人源化单克隆CD40抗体, 在I期临床试验中与紫杉醇等化疗药物联用于晚期实体瘤的治疗中显示出良好的治疗效果[80]。达妥珠单抗 (SEA-40或SGN-40) 是由西雅图遗传学公司 (Seattle Genetics) 研发的人源化CD40单克隆抗体。目前多项临床试验结果表明, 达妥珠单抗在治疗复发性或难治性晚期多发性骨髓瘤、复发或难治性非霍奇金淋巴瘤、弥漫大B细胞淋巴瘤具有良好的治疗效果, 无严重不良反应发生[81-83]。ChiLob7/4是英国南安普敦大学研发的嵌合体激动剂抗CD40抗体, I期临床试验结果表明ChiLob7/4对CD40阳性的实体肿瘤或淋巴瘤患者具有良好的治疗效果[84]。目前, 全世界约有20多种CD40抗体药物处于临床研究阶段, 用于肿瘤或其他免疫疾病的治疗。

Toll样受体 (Toll-like receptor, TLR) 是一种先天免疫模式识别受体 (图3), 它能够被入侵的细菌颗粒或病毒核酸激活使巨噬细胞向M1型极化[85]。目前有1个TLR9配体 (IMO-2055) 与2个TLR7配体 (imiquimod和852A) 在临床试验中针对巨噬细胞重编程测试其抗肿瘤活性[86]。此外, 有研究表明激活IκB/NF-κB通路能够调节巨噬细胞向M1型转化[87], 而硼替佐米能够通过抑制IκB的降解, 促进NF-κB活化, 促使巨噬细胞由M2型向M1型极化, 从而发挥抗肿瘤作用[88]。

嵌合抗原受体巨噬细胞 (chimeric antigen receptor-macrophage, CAR-M) 是将巨噬细胞工程化修饰嵌合抗原受体后以增强巨噬细胞抗原特异性的吞噬功能和肿瘤清除能力。Klichinsky等[89,90]首次提出CAR-M的想法并构建了能够靶向HER2的CAR-M, 发现其不仅表现出优秀的体内外抗肿瘤活性, 同时CAR-M能够增加促炎细胞因子的分泌, 促进M2型巨噬细胞向M1型转化, 上调对T细胞的抗原递呈并抵抗免疫抑制性的细胞因子。

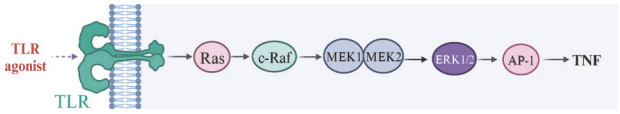

Figure 3 Toll-like receptor signaling pathway. Figure was created by Biorender (biorender.com/)

2.5 其他靶向肿瘤相关巨噬细胞策略

肿瘤是一种快速生长、代谢活跃的恶性组织, 通过TAM输送和产生营养物质的获取是肿瘤微环境中代谢调控的重要组成部分。因此通过营养获取和代谢控制抑制TAM的促肿瘤作用, 也是目前靶向TAM的重要研究方向[91,92]。此外, TAM还能够通过表达PD-L1、B7-H4等免疫检查点来抑制肿瘤免疫应答, 因此靶向TAM表面的免疫检查点也成为调控TAM的免疫抑制活性的重要研究方向之一[93]。由于M1型巨噬细胞可以靶向并吞噬肿瘤细胞, 因此工程化改造的巨噬细胞 (engineering macrophages) 也可作为药物递送的载体, 以期实现抗肿瘤药物的靶向递送。除了巨噬细胞自身可作为药物递送的直接载体, 巨噬细胞分泌的外泌体由于具有和巨噬细胞相似的膜特征, 也可作为抗肿瘤药物递送的载体。此外, 将巨噬细胞膜提取后包覆上纳米粒也可以作为一种药物载体进行抗肿瘤药物的靶向递送[94]。但是, 目前此类研究大多处于临床前研究阶段。

目前靶向TAM处于临床研究阶段的候选药物, 如表1总结所示。

Table 1 Candidate drugs currently in clinical research stage targeting tumor associated macrophages

Type	Drug candidate	Clinical stage	Indication	Combination treatment	NCT number
CSF1R inhibitor	PLX3397 (Plexxikon)	Phase I	Unresectable sarcoma	Sirolimus	NCT02584647
		Phase I/IIa	Advanced melanoma and other solid tumors	Pembrolizumab	NCT02452424
		Phase Ib/II	Metastatic breast cancer	Eribulin	NCT01596751
		Phase Ib/II	Glioblastoma	Radiation therapy and temozolomide	NCT01790503
	BLZ945 (Novartis)	Phase I/II	Advanced solid tumors	PDR001	NCT02829723
CSF1R monoclonal antibody	LY3022855 (IMC-CS4; Eli Lilly)	Phase I/II	Melanoma	Vemurafenib and cobimetinib	NCT03101254
	Emactuzumab (RO5509554/RG7155; Roche)	Phase II	Platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer	Paclitaxel and bevacizumab	NCT02923739
		Phase III	Tenosynovial giant cell tumor	NA	NCT05417789
		Phase Ib	Relapsed or refractory non-Hodgkin lymphoma	Atezolizumab	NCT03369964
		Phase I	Advanced solid tumors	Atezolizumab	NCT02323191
		Phase I	Advanced solid tumors	RO7009789	NCT02760797
	AMG820 (Amgen)	Phase Ib/II	Select advanced solid tumor cancer	Pembrolizumab	NCT02713529
	ARRAY-382 (Pfizer)	Phase I/II	Advanced solid tumors	Pembrolizumab	NCT02880371
	Cabiralizumab (Bristol Myers Squibb)	Phase Ib/II	Triple-negative breast cancer	Nivolumab with neoadjuvant chemotherapy	NCT04331067

Continued

Type	Drug candidate	Clinical stage	Indication	Combination treatment	NCT number
CD47/SIRPα monoclonal antibody	Hu5F9-G4 (Stanford University)	Phase Ib/II	Solid tumors and advanced colorectal cancer	Cetuximab	NCT02953782
		Phase Ib/II	Urothelial carcinoma	Multiple immunotherapy-based treatments	NCT03869190
	BI 754091 (OSE Immunotherapeutics)	Phase I	Advanced solid tumours	BI 754091	NCT03990233
CD47 fusion protein	TTI-621 (Trillium)	Phase I	Hematologic malignancies and selected solid tumors	Nivolumab or rituximab	NCT02663518
	Maplirpacept (Pfizer)	Phase I	Advanced hematological malignancies	Azacitidine, venetoclax, carfilzomib, dexamethasone, anti-CD20 targeting agent, isatuximab	NCT03530683
	ALX148 (ALX Oncology)	Phase II	Advanced head and neck squamous cell carcinoma	Pembrolizumab	NCT04675294
		Phase II	Advanced head and neck squamous cell carcinoma	Pembrolizumab and chemotherapy	NCT04675333
Chemokine inhibitor	Carlumab (CCL2 antibody; Centocor)	Phase II	Metastatic castrate-resistant prostate cancer	NA	NCT00992186
	BMS-813160 (CCR2/CCR5 antagonist; Bristol Myers Squibb)	Phase II	Advanced renal cell carcinoma	Nivolumab	NCT02996110
		Phase I/II	Advanced solid tumors	Chemotherapy or nivolumab	NCT03184870
		Phase II	Non-small cell lung cancer or hepatocellular carcinoma	Nivolumab	NCT04123379
	PF-4136309 (CCR2 antagonist; Pfizer)	Phase II	Borderline resectable and locally advanced pancreatic adenocarcinoma	FOLFIRINOX	NCT01413022
	Maraviroc (CCR5 antagonist, Pfizer)	Phase I	Metastatic colorectal cancer	Pembrolizumab	NCT03274804
		Phase I	Advanced metastatic colorectal and pancreatic cancer	Nivolumab and ipilimumab	NCT04721301
CD40 antibody	CP-870,893 (Pfizer; UPenn)	Phase I	Solid tumors	NA	NCT02225002
		Phase I	Metastatic solid tumors	Paclitaxel and carboplatin	NCT00607048
		Phase I	Pancreatic carcinoma	Gemcitabine	NCT01456585
	SEA-CD40 (Seagen)	Phase I	Advanced malignancies	Pembrolizumab, gemcitabine, and nab-paclitaxel	NCT02376699
	APX005M (Apexigen)	Phase I	Advanced melanoma or renal cell carcinoma	Nivolumab and ipilimumab	NCT04495257
		Phase I	Metastatic melanoma	Pembrolizumab	NCT02706353
		Phase II	Esophageal and gastroesophageal junction cancers	Chemoradiation	NCT03165994
		Phase I/II	Metastatic pancreatic adenocarcinoma	Gemcitabine and nab-paclitaxel with or without nivolumab	NCT03214250
	RO7009789 (Roche)	Phase I	Metastatic solid tumors	Vanucizumab or bevacizumab	NCT02665416
		Phase I	Pancreatic carcinoma	Nab-paclitaxel and gemcitabine	NCT02588443
	CDX-1140 (Roswell Park Cancer Institute)	Phase I	Unresectable and metastatic solid tumors	Radiotherapy, CDX-301 and poly-ICLC	NCT04616248
	NG-350A adenoviral vector (PsiOxusTherapeutics Ltd)	Phase I	Metastatic or advanced epithelial tumours	Pembrolizumab	NCT05165433
TLR3 agonist	Hiltonol (Oncovir, Inc.)	Phase II	Solid tumors	Dendritic cells	NCT01734564
	Poly-ICLC (Ludwig Institute for Cancer Research)	Phase I/II	Biopsy-accessible cancers	Tremelimumab and IV durvalumab	NCT02643303
	BO-112 (Highlight Therapeutics)	Phase II	Colorectal or gastric cancer	Pembrolizumab	NCT04508140
	BO-112 (Highlight Therapeutics)	Phase II	Unresectable malignant melanoma	Pembrolizumab	NCT04570332
TLR7 agonist	SHR2150 (Chinese PLA General Hospital)	Phase I/II	Unresectable/metastatic solid tumors	Chemotherapy plus PD-1 or CD47 antibody	NCT04588324
	TransCon (Ascendis Pharma)	Phase I/II	Advanced or metastatic solid tumors	Pembrolizumab	NCT04799054
	BDC-1001 (Bolt Biother)	Phase I/II	Advanced HER2-expressing solid tumors	Nivolumab	NCT04278144
TLR9 agonist	CMP-001 (Checkmate Pharmaceuticals)	Phase II	Melanoma	Nivolumab	NCT04401995

3 总结与展望

随着新技术与新方法 (各种组学和单细胞测序) 的发现, 多个学科不断交叉融合, 越来越多的肿瘤免疫药物 (PD-1抗体、PD-L1抗体和CTLA-4抗体) 相继出现, 肿瘤免疫治疗取得突飞猛进。2018年美国的詹姆斯·艾利森与日本的本庶佑因为在免疫治疗肿瘤方面做出的巨大贡献被授予诺贝尔生理学或医学奖。相较于传统化疗, 肿瘤免疫治疗表现出更强的疗效与更好的耐受性。随着免疫治疗的进展, 也出现了一些问题, 如只有约20%的肿瘤患者对免疫治疗有反应及出现皮肤红肿及心肌炎等不良反应, 这些问题亟待未来进一步解决[95]。

肿瘤微环境是肿瘤不可分割的一部分, 肿瘤微环境能够影响抗肿瘤免疫治疗的效果[96]。巨噬细胞是肿瘤微环境的重要组成部分, 也是抗肿瘤免疫应答的重要组成部分。肿瘤微环境中的M1型巨噬细胞具有很强的抗原递呈能力, 通过释放促炎因子和激活I型T细胞应答, 从而发挥抗肿瘤作用[97]。而损伤巨噬细胞的吞噬功能能够抑制肿瘤细胞的抗原递呈, 从而抑制抗肿瘤免疫应答[98]。肿瘤微环境中的巨噬细胞具有可塑性, 存在M1与M2型巨噬细胞极化现象, 其中M1巨噬细胞主要参与促炎反应, M2巨噬细胞主要参与抗炎反应[99]。TAM具有促进肿瘤的侵袭和转移、促肿瘤血管生成、促肿瘤耐药和抑制肿瘤免疫反应等作用。靶向TAM的药物研究正成为研究热点[100]。此外, 由于肿瘤的异质性和患者个体免疫微环境的不同, 同一免疫治疗药物在不同肿瘤的免疫治疗效果不同。同一免疫治疗药物在同种肿瘤的不同患者治疗效果也不同。免疫疗法并不能在所有个体、所有肿瘤上表现出良好的治疗效果, 不良反应事件也不尽相同。随着单细胞测序、空间组学、大数据及人工智能的发展及多个学科的交叉合作, 更多的研究重点应放在TAM极化机制、TAM的靶点优化、TAM个性化差异等研究。

未来, 随着各种组学 (尤其单细胞组学与空间组学)、大数据、人工智能等新技术和新方法的发展, 对肿瘤微环境中TAM不断深入了解, 一定会设计和开发出个性化、高效、不良反应小的靶向TAM药物, 提高和促进肿瘤的免疫治疗。

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