



基于髓源性抑制细胞的食药菌多糖抗肿瘤免疫作用机制

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摘要: 髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)是一种异质性的免疫调节细胞。在癌症机体中, MDSCs 是主要的免疫抑制细胞, 通过多种途径诱导 T 淋巴细胞衰竭和凋亡, 促进肿瘤细胞逃逸, 从而导致肿瘤不受控制地生长, 是癌症治疗的主要障碍。目前, MDSCs 是癌症药物研究的热点和关键靶点。近年来, 研究报道显示多糖可下调 MDSCs 在癌症患者及肿瘤实验动物体内数量和比例, 并诱导免疫抑制功能丧失。食药菌多糖是天然多糖的主要来源, 可以通过多种途径激活肿瘤免疫应答, 其抑制 MDSCs 功能的研究报道逐年增多, 目前研究主要集中在香菇多糖、灵芝多糖等部分种类。因此, 本文简要描述髓源性抑制细胞在癌症中的免疫抑制功能, 然后详细地综述食药菌多糖对髓源性抑制细胞作用的研究进展, 以期为食药菌多糖在肿瘤免疫药物开发及辅助增强(如免疫检查点抑制剂)等免疫治疗提供新思路。

关键词: 食药菌多糖; 髓源性抑制细胞; T 细胞; 免疫作用

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Edible and medicinal fungal polysaccharides inhibit the immunosuppressive functions of myeloid-derived suppressor cells (MDSCs) on cancers

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Abstract: Myeloid-derived suppressor cells (MDSCs) are heterogeneous immunomodulatory cells. In the instance of cancers, they exert immunosuppressive functions. To be specific, they induce T cell exhaustion and apoptosis through multiple pathways to promote the escape of tumor cells from destruction by the immune system and sustain cancer progression. Thus, they are the main obstacle in the fight against cancers. At the moment, MDSCs are the focus in development of anti-cancer drugs and the key targets of the drugs. It has been reported that polysaccharides reduced the count and proportion of MDSCs in cancer patients and tumor-bearing mice and eliminate the immunosuppression. Natural edible and medicinal fungal polysaccharides can activate immune response to tumors through multiple pathways, and there has been an explosion of research on the suppression of the immunosuppressive function of MDSCs. The currently available studies mainly focus on polysaccharides from *Lentinula edodes* and *Ganoderma lucidum*. In this review, we briefed the immunosuppressive mechanism of MDSCs in the cases of cancers, and then summarized the effects of edible and medicinal fungal polysaccharides on MDSCs, hoping to provide a new mindset for the development of anti-tumor drugs and auxiliary enhancement of immunotherapy such as immune checkpoint inhibitors with edible and medicinal fungal polysaccharides.

Keywords: edible and medicinal fungal polysaccharides; myeloid-derived suppressor cells; T cell; immune effect

髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)是肿瘤微环境癌细胞免疫逃逸的主要参与细胞,介导一个强大的免疫抑制网络、诱导 T 细胞凋亡、促进癌细胞免疫逃逸,从而导致肿瘤生长不受控^[1]。目前,肿瘤免疫治疗迅速发展,旨在通过识别和有效清除癌细胞以及防止原发肿瘤转移从而恢复和提高抗肿瘤免疫^[2],而 T 淋巴细胞是免疫系统中清除肿瘤的有力“工具”,免疫检查点抑制剂、过继 T 细胞

治疗、癌症疫苗等基于 T 细胞的免疫疗法给癌症患者带来了很大的福音,但目前受益的癌症患者仍为少数^[3]。

2018 年,免疫检查点抑制剂已被批准用于 14 个癌症病种的治疗,被称为“广谱抗肿瘤药物”,在治疗中表现出显著的临床疗效,但具有响应的患者人数仅占 12.46%^[4]。患者反应差异与肿瘤微环境引起的免疫抑制效应密切相关^[5]。高水平 MDSCs 被证明与癌症患者临床分期、转移

负荷以及对化疗和免疫治疗的抵抗有关^[6]。MDSCs 在癌症或相关免疫治疗中有作为生物标志物的潜能^[7-8]。因此, 靶向抑制 MDSCs 的功能, 阻断其形成的免疫抑制网络、解除其对杀伤性 T 细胞的抑制、促进杀伤性 T 细胞增殖和浸润、发挥杀伤肿瘤细胞的效应和抑制肿瘤生长, 是肿瘤免疫治疗的重要策略, MDSCs 也成为了相关治疗药物、辅助药物开发的靶点和热点。

食药用菌是我国传统药物的主要组成部分, 现代药理研究报道其具有超过 130 种功能^[9], 富含多种活性物质, 如三萜类、甾醇类、生物碱及大分子物质多糖和多糖复合物等^[10]。本团队一直从事食药用菌资源及其活性物质和功能方面的研究, 已报道多种食药用菌具有功能活性, 包括抗肿瘤^[11-12]、降血糖^[13]、降血脂^[14]、降尿酸^[15]、抗炎^[16]、调节免疫力^[17]等。据统计, 关于食药用菌的临床报告已超过 600 份, 主要是集中在食药用菌多糖及其复合物(如糖蛋白)在抗肿瘤、免疫调节及免疫肿瘤等方面的研究^[9]。本团队苏冀彦等研究报道了灵芝孢子多糖显著下调了脾脏和肿瘤组织中免疫检查点 PD-1 和 CTLA-4 的表达, 恢复了耗尽的肿瘤浸润淋巴细胞^[18-19]。随着对食药用菌多糖与肿瘤免疫逃逸机制研究的深入, 发现食药用菌多糖可以抑制 MDSCs 功能, 进而激活 T 细胞的活性。在近期研究中, 本文作者发现乳腺癌荷瘤小鼠的肿瘤组织微环境中富集了大量的髓系细胞(CD11b⁺), 但在灰树花多糖处理组肿瘤中 CD11b⁺和 Ly6G⁺的表达下调, 提示食药用菌多糖及其多糖复合物可作为 MDSCs 的潜在抑制剂。在本文中我们将简要描述 MDSCs 发现史及其在肿瘤微环境的免疫抑制功能, 综述已报道的食药用真菌多糖靶向抑制 MDSCs 功能的作用机制。

1 髓源性抑制细胞

髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)指专门在病理环境中发现的异质性的未成熟髓系细胞群, 是基于活化的 T 细胞与骨髓细胞共培养导致 T 细胞的功能抑制被发现的一类细胞。图 1 简单描述了 MDSCs 的发现过程, 自 1929 年发现癌症与骨髓异常生成相关以来, 随着科学家对此类来源于骨髓异常细胞研究的深入, 其表型特征、定义、命名及功能逐渐明确和清晰^[20-23]。MDSCs 由粒细胞或多形核细胞(granulocytic or polymorphonuclear, PMN-MDSC)和单核细胞(monocytic, M-MDSC)组成^[24]。在小鼠中, M-MDSCs 定义为 CD11b⁺Ly6C^{hi}Ly6G⁻, 而 PMN-MDSCs 定义为 CD11b⁺Ly6C^{lo}Ly6G⁺。在人类中, M-MDSCs 定义为 CD11b⁺CD33⁺CD14⁺CD15⁻HLA-DR^{lo/-}, 而 PMN-MDSCs 定义为 CD11b⁺CD33⁺CD14⁻CD15⁺HLA-DR⁻^[25]。

MDSCs 作为一种免疫调节细胞, 依赖所处机体状态发挥正向或负向调节作用。在组织修复、伤口愈合再生等过程中, MDSCs 防止炎症失控和维持机体免疫反应动态平衡^[26]。但在癌症等病理条件形成的炎症刺激下, MDSCs 长期扩张, 免疫抑制功能增强, 促进疾病的进展^[27-28]。在肿瘤微环境中, MDSCs 因正常的分化途径受阻而成为不成熟的异质性细胞群, 发挥抗肿瘤的免疫抑制作用, 被认为是肿瘤逃逸和进展的关键因素。但在条件改变下, MDSCs 会被促分化为具有免疫抑制作用的巨噬细胞^[29], 或被诱导分化为成熟的髓样细胞, 如树突细胞和巨噬细胞, 从而降低其数量和比例, 抑制其免疫抑制功能。如维生素 A 的代谢物全反式维甲酸在体内外诱导 MDSCs 分化为成熟的抗原提呈细胞, 同时减少其抑制 T 细胞的功能^[30]。

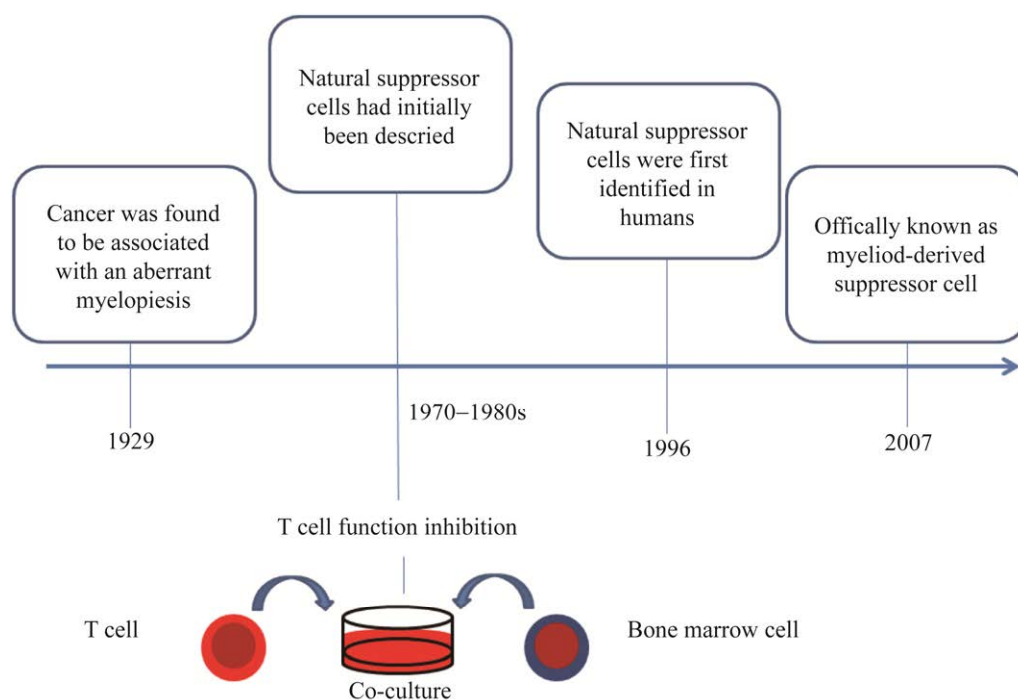


图 1 髓系来源抑制细胞的发现过程

Figure 1 Discovery process of myeloid-derived suppressor cells.

2 肿瘤微环境中 MDSCs 对 T 细胞的抑制作用

MDSCs 虽然可以作用于不同的免疫细胞，但主要靶细胞是 T 细胞，其抑制 T 细胞的增殖和活性、促进癌细胞逃逸以及促进肿瘤扩散和转移^[31]。目前研究显示，MDSCs 主要是通过耗竭 T 细胞所需的营养、增加氧化应激、阻止 T 细胞迁移、诱导免疫抑制细胞和表达抑制性免疫检查点等途径来抑制 T 细胞的增殖和活性^[1,7]。

MDSCs 通过调控精氨酸酶-1 (arginase-1, ARG-1) 和一氧化氮合酶来分解 L-精氨酸或者消耗半胱氨酸进而抑制 T 细胞的增殖活化^[32-33]。其还通过产生活性氧和活性氮增加肿瘤微环境内的氧化应激反应来损害 T 细胞的功能^[34-35]。抗原未成熟的 T 细胞被 L-选择素(CD62L)导向引流肿瘤部位的次级淋巴结或实体肿瘤内激活进

而发挥作用。MDSCs 则可通过肿瘤坏死因子转换酶，切割 CD62L，抑制 T 细胞向肿瘤部位的迁移^[36]。据报道，脾脏 MDSCs 也诱导 CD4⁺ 和 CD8⁺ T 细胞以及脾脏 B 细胞上的 L-选择素下调，导致淋巴结中 CD8⁺ T 细胞归巢和抗原依赖性激活减少^[37]。

扩大肿瘤微环境免疫抑制性细胞群是癌细胞逃避免疫监视的关键策略。研究表明，MDSCs 促进 Treg 细胞的发育和诱导，还可以将巨噬细胞转变为具有免疫抑制特征和低 IL-12 表达的 M2 样表型，增强其对 T 细胞的抑制作用，从而促进肿瘤生长^[38-39]。其产生的趋化因子、细胞因子和其他抑制性介质会进一步损害抗肿瘤免疫。如 MDSC 通过分泌转化生长因子- β (transforming growth factor- β , TGF- β) 促进游离 T 细胞分化为调节性 T 细胞^[40]，通过缺氧诱导因子-1 α (HIF-1 α) 调节趋化因子 CCL4 和 CCL5

的合成和分泌,并募集 Treg 细胞以阻断 CD8⁺ T 细胞向肿瘤部位的迁移^[41]。另外, MDSCs 可通过抑制性检查点调节因子 PD-L1 和 galectin-9 诱导 T 细胞抑制^[7]。因此,抑制 MDSCs 的活性是提升免疫检查点抑制剂免疫治疗效应的重要策略和途径。目前,部分 MDSCs 抑制剂联合免疫检查点抑制剂的临床研究正在进行。

3 食药真菌多糖解除 MDSCs 免疫抑制功能的策略

目前,超过 300 多种天然多糖在被研究,其主要功能为刺激宿主的免疫系统^[42],因此,多糖是发现肿瘤免疫治疗药物及免疫治疗辅助药物的丰富来源。从天然产物中研究和研究靶向 MDSCs 的化合物具有重要意义。本文侧重综述食药真菌多糖与 MDSCs 的作用策略,主要包括清除机体 MDSCs、抑制 MDSCs 在骨髓、外周淋巴器官脾脏及肿瘤组织的积累以及抑制 MDSCs 介导的免疫抑制。

3.1 多糖消除 MDSCs 的作用

在健康人体,MDSCs 的含量很低,占循环内细胞的 1%,不会发生免疫抑制,仅少量存在于骨髓和脾脏中。但在癌症和一些病理情况下,MDSCs 的分化能力发生了改变,且肿瘤患者循环中 MDSC 亚群的扩增超过感染性和炎症性疾病的扩增^[43]。Sun 等报道了香菇多糖(lentinan, LNT)依赖免疫激活抗膀胱癌的内在机制,LNT 提升机体 CD4⁺、CD8⁺ T 细胞和活化的巨噬细胞数量和比例,并上调 IFN- γ 和 IL-2 的表达。同时,LNT 清除 MDSCs 和 Treg 细胞,下调所占比例,抑制抗炎细胞因子 IL-10 和 TGF- β 表达^[44]。大量临床数据研究显示,大多数乳腺癌变建立了高度抑制的肿瘤微环境,MDSCs 比例很高,与疾病分期和肿瘤负荷相关^[45]。在小鼠

癌症模型中,脾切除被证明可以减少肿瘤浸润的 MDSCs 数量,并导致肿瘤消退,脾 MDSCs 可能也有助于肿瘤的发生^[46]。本课题组利用鼠源乳腺癌 4T1 细胞构建移植瘤小鼠模型,研究十多种食药真菌多糖的抗肿瘤活性,发现模型组的小鼠的脾脏较正常组来说明显肿大,红骨髓发生了明显的紊乱,且发现脾脏中有许多细胞存在多核、细胞核变大或者细胞体积增大的情况。在经香菇、红菇和灰树花等食用菌的粗多糖给药后,具有较好的抑瘤效果,且脾脏得到了明显的修复。

3.2 多糖减少 MDSCs 的积聚作用

灵芝在中国已有几千年的食药历史,含有多种生物活性成分。本团队之前研究报道了灵芝孢子^[47]、皱盖假芝提取物^[48]、灵芝麦角甾醇^[49]和白肉灵芝提取物^[50]等具有抗肿瘤活性。Wang 等报道了灵芝多糖 GLP 能明显抑制肿瘤生长,减少小鼠脾脏和肿瘤组织中 MDSCs 积聚,且提升小鼠脾脏中 CD4⁺ 和 CD8⁺ T 细胞百分比,明显增强 Th1 型细胞因子(IFN- γ 和 IL-12)的产生。进而揭示 GLP 通过增强 MDSCs 细胞内 CARD9、p-Syk 和 p-p65 的表达,并下调吡啶胺 2,3-双加氧酶蛋白表达的信号途径 CARD9-NF- κ B-IDO 抑制 MDSCs 的分化^[51]。竹荪是我国名贵的食用菌,据报道,其具有抗炎、增强免疫、抗肿瘤、保护神经、护肝以及修复辐射所致免疫损伤等作用^[52]。江洪等研究发现,竹荪多糖 DP15 延长了 LLC 移植瘤小鼠生存期,显著下调 MDSCs 细胞比例,并发现 DP15 通过上调促凋亡因子 P53 表达和下调促增殖因子 Bcl-2 表达诱导 MDSCs 凋亡^[53]。

3.3 多糖抑制 MDSCs 介导的免疫抑制作用

在癌症状态,MDSCs 的分化被阻止,且特异性地抑制 T 细胞,促进肿瘤的免疫和转移。2012 年,秦志海团队报道了香菇多糖 MPSSS

抑制 MDSCs 的分化和功能。MPSSS 抑制纤维瘤 McgR32 细胞在小鼠体内增殖, 抑瘤效果与 MDSCs 在外周血中比例降低有关, 并证实 MPSSS 通过上调 MHC II 和 F4/80 在 MDSCs 的表达, 诱导 MDSCs 向 M1 样巨噬细胞转化, 并以剂量依赖的方式逆转其对 CD4⁺ T 细胞的抑制作用^[54]。2017 年, 该团队进一步研究发现, MPSSS 能通过激活 p38 和 ERK 去磷酸化, 显著抑制永生化髓系免疫抑制细胞系 MSC2 细胞的精氨酸酶活性和降低细胞膜受体 TNFR2 的表达, 抑制 T 细胞的增殖。此外, MPSSS 还通过激活 p38 损伤 MSC2 细胞的免疫抑制功能, 诱导 MSC2 细胞分化为 M1 型巨噬细胞, 削弱其免疫抑制功能。这些结果表明, MPSSS 是一种潜在的针对 MDSCs 的抗肿瘤治疗候选药物^[55]。Liu 等报道了姬松茸多糖通过与 MDSCs 细胞表面 TLR2 特异结合, 促进 MDSCs 分泌 IL-12 及降低 ARG1 的表达, 使其向具有抗肿瘤活性的 M1 型细胞极化, 并发现 MDSCs 促进 CD4⁺ T 细胞向 Treg 细胞分化的作用下调, 阻止肿瘤细胞逃逸, 抑制肿瘤生长^[56]。

4 食药真菌多糖靶向 MDSCs 增强化疗和免疫治疗作用的研究

食药菌多糖联合放疗、化疗策略, 在人类临床癌症研究中已进行了不少评价, 在许多病例中, 相关的副作用和生活质量得到了改善^[9]。MDSCs 在多种癌症中存在, 是化疗和免疫治疗的主要障碍。食药菌多糖辅助放疗、化疗, 减少 MDSCs 的抑制作用, 降低毒副作用, 也是发挥食药菌多糖功效的重要途径。

4.1 食药菌多糖靶向 MDSCs 增强化疗疗效

化疗是一种非特异杀伤肿瘤细胞的治疗方法, 在这个治疗的过程中会促进免疫抑制

细胞 MDSCs、TAM 等大量增殖, 引起免疫抑制^[57]。吉西他滨(gemcitabine, GEM)是多种癌症(如胰腺癌、卵巢癌和非小细胞肺癌等)的临床治疗的化疗药物, 存在多种副作用, 包括骨髓抑制^[58]。陈菲菲等报道了微粒型灵芝孢子粉 β-葡聚糖 PGSG 联合 GEM 重塑 LLC (Lewis lung cancer)小鼠肿瘤微环境免疫。GEM 反复化疗引起小鼠免疫抑制, PGSG 显著降低肿瘤与脾脏组织免疫抑制细胞 MDSC (CD11b⁺Gr-1-PE⁺) 和 M-MDSC (CD11b⁺Ly6G⁻Ly6C^{high})、M2 巨噬细胞(F4/80⁺CD206⁺)和 Treg 细胞的数量和比例, 促进 Th1 (CD4⁺IFN-γ⁺ T 细胞)与 CTL (CD8⁺IFN-γ⁺ T 细胞)数量显著提升, 实现抑瘤增效和激活免疫应答^[59]。Sun 等发现 LNT 联合 GEM 治疗膀胱癌移植荷瘤小鼠, 相比单一 GEM 组, 不仅增强抑瘤, 而且明显提升 CD4⁺ T 细胞、CD8⁺ T 细胞和活化的巨噬细胞的比例, 下调免疫抑制细胞 Treg 细胞和 MDSCs 的比例, 上调 IFN-γ 和 IL-2 的表达, 下调免疫抑制因子 IL-10 和 TGF-β 的表达, 解除免疫抑制, 增强小鼠的免疫应答^[44], 为 LNT 在临床上应用于放化疗免疫增强剂提供解释。

紫杉醇作为一种广谱的天然抗癌药物, 已广泛应用于卵巢癌、乳腺癌、肺癌等癌症的治疗, 其最为常见的不良反应包括骨髓抑制、过敏反应和神经毒性^[60]。王小红等研究探讨了竹荪多糖 ZSP1 与多西紫杉醇在肺癌治疗中的协同效应及机制, 与对照组和紫杉醇组相比, ZSP1 联合紫杉醇组抑瘤率增加, 且体内外周血中 MDSCs 数量显著下调; 并发现 ZSP1 对 TLR4 缺陷小鼠无效, 推测其受体为 TLR4^[61]。本课题组近期研究灰树花糖蛋白联合紫杉醇治疗 4T1 荷瘤小鼠, 结果发现灰树花糖蛋白联合紫杉醇用药组的抑瘤率显著下降, 脾脏指数下调, 外周血中 CD8⁺ T 细胞的比例显著上升。因此,

靶向抑制 MDSCs, 解除因化疗药物所引起的免疫抑制, 增强机体抗肿瘤免疫应答是增强部分化疗药物疗效的潜在策略和研究方向。

4.2 食药菌多糖靶向 MDSCs 增强免疫治疗疗效

作为肿瘤治疗的新手段, 肿瘤免疫治疗为多种实体瘤及恶性肿瘤提供了有效的治疗方案, 但单一免疫治疗难以维持长期的抗肿瘤免疫反应^[62]。在侵袭性乳腺肿瘤小鼠模型中, MDSCs 的缺失被证明可以增强抗 PD-1 和抗 CTLA-4 治疗的疗效, 肿瘤完全消退, 转移减少^[63]。食药菌生物活性多糖, 其中大部分属于 β -葡聚糖, β -葡聚糖是最广为人知的强大免疫刺激剂, 对良恶性肿瘤都有非常强大的拮抗作用^[64]。Li 等发现阿魏菇多糖 PFPS 可增强治疗性人乳头瘤病毒树突状细胞疫苗 (HPV-DC vaccine) 抗肿瘤效果, 疗效与 MDSCs 比例降低、 $CD4^+$ T 和 $CD8^+$ T 细胞活性升高及诱导 HPV 特异性 $CD8^+$ T 细胞反应显著相关^[65]。目前, 食药菌多糖联合肿瘤免疫治疗的研究较少, 但相关研究策略提示我们这可能是未来肿瘤治疗的趋势和很好的方向。

5 讨论与展望

MDSCs 被肿瘤分泌的趋化因子招募至肿瘤组织, 与肿瘤微环境的癌细胞、不同类型免疫细胞的聚集与交流, 免疫细胞活性物质的分泌与传递, 相关级联信号的产生与交联, 均在织就着这个微观世界里的庞大网络。MDSCs 与肿瘤微环境相互交流、肿瘤微环境的免疫抑制状态和 MDSCs 本身的免疫抑制能力都变得更加强大, 阻碍免疫疗法发挥效应。利用 MDSCs 在肿瘤微环境中的可塑性, 诱导 MDSCs 分化成非免疫抑制细胞, 是免疫治疗肿瘤的策略和途

径。根据癌症类型和阶段, 研究清晰 MDSCs 发挥相关抑制作用的信号路径, 研发相关药物或结合现有的免疫疗法, 阻滞 MDSCs 形成, 缓解或者解除肿瘤微环境的抑制状态, 激活杀伤性免疫细胞, 尤其是 $CD8^+$ T 细胞的识别杀伤, 将会极大推动免疫疗法的进展。目前, 临床研究 MDSCs 抑制剂为直接使用或联合免疫检查点, 如靶向抑制 MDSCs 消耗氨基酸的精氨酸抑制剂^[66]、VEGFR 抑制剂^[67]和 DNMT1 抑制剂^[68]等, MDSCs 直接或间接抑制剂与免疫检查点用药 (如 PD-1 抑制剂和 CTLA-4 抑制剂的联合免疫治疗) 在对多种类型癌症中展开^[69-70]。

食药菌作为传统中药一直被用于治疗癌症和许多慢性炎症疾病。尽管食药菌多糖可以缓解肿瘤生长和修复免疫系统, 但确切的机制仍然大多数不清楚。癌症的免疫逃逸机制表明, MDSCs 是寻找治疗肿瘤的重要药物开发靶点。近年在小鼠体内外实验中发现, 香菇多糖和灵芝多糖等可以抑制 MDSCs 的免疫抑制功能, 且抑制肿瘤的生长 (图 2)。MDSCs 是免疫治疗和化疗的障碍, 食药菌多糖抑制 MDSCs 功能的报道逐渐增多, 与化疗和免疫治疗药物联用的研究也已开始, 但这些数据和结果需要在临床试验中进行评价。因此, 可利用食用菌多糖毒副作用极小甚至无毒副作用、可作为化疗和放疗的降毒剂、缓解疼痛、免疫调节、抗肿瘤活性、显著提高癌症患者的生存质量等特点^[71], 研发相关的 MDSCs 药物, 以及通过药物联合使用或药物与其他免疫疗法联合应用, 以期获得更好的治疗效果。我国食药菌资源丰富, 种类繁多。食药菌真菌多糖在预防治疗癌症方面具有广阔的开发及应用前景, 研究食药菌真菌多糖并进一步地研发相关的抗肿瘤药物, 是开发新药的重要途径之一。

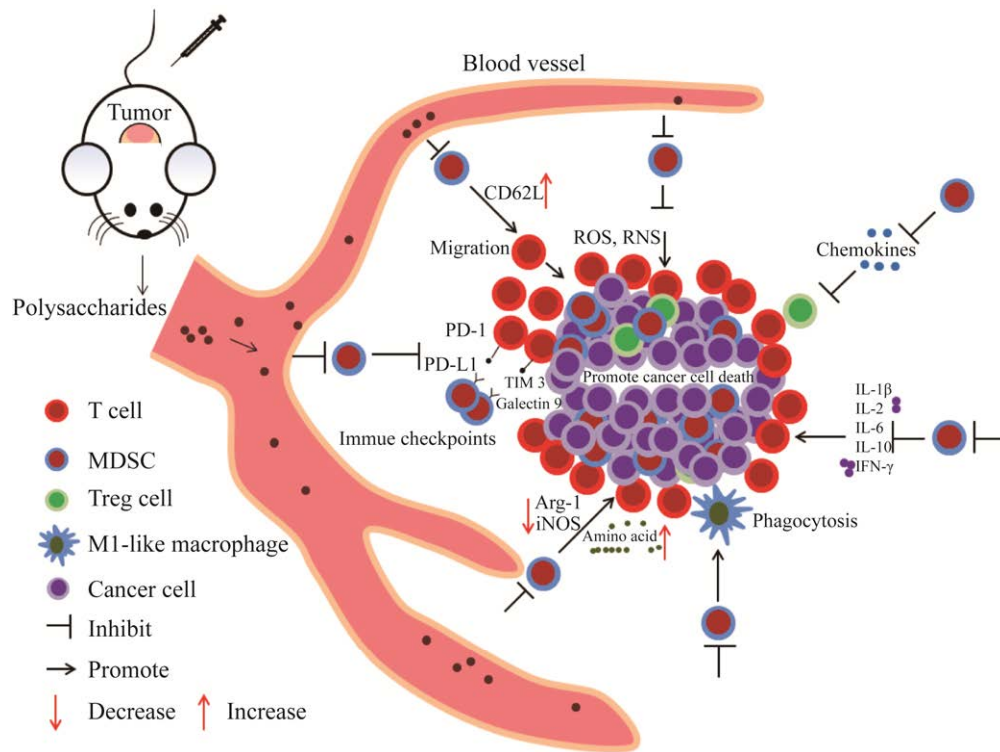


图 2 食药菌多糖介导 MDSCs 抑制作用的潜在途径

Figure 2 Potential pathway of MDSCs inhibition mediated by edible and medicinal fungal polysaccharides.

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