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调节性T细胞作为抗癌治疗的潜在靶点

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摘　要

免疫逃避是大多数人类恶性肿瘤的特征，并通过各种机制诱导。免疫抑制细胞，包括调节性T细胞(Regulatory T cells, Tregs)和髓源性抑制细胞(myeloid-derived suppressor cell, MDSCs)，是帮助肿瘤逃避免疫监视的关键介质。此篇综述讨论了Treg在癌症进展中的作用、当前靶向Treg的治疗策略以及临床应用前景。

关键词

调节性T细胞，免疫治疗，肿瘤微环境

Regulatory T Cells as Potential Therapeutic Targets for Anticancer Therapy

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Abstract

Immune evasion characterizes most human malignancies and is induced by various mechanisms. Immunosuppressor cells, including Regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), are key mediators that help tumors evade immune surveillance. This review discusses the role of Tregs in cancer progression, current Treg-targeting therapeutic strategies, and clinical prospects.

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Keywords

Regulatory T Cells, Immunotherapy, Tumor Microenvironment

1. Treg 功能及分型

调节性 T 细胞(Tregs)是 $CD4^+$T 细胞的免疫抑制亚群，具有强大的抑制活性和限制免疫激活和维持体内平衡的功能。Tregs 可以被招募并持续存在于肿瘤微环境(tumor microenvironment, TME)中，作为有效抗肿瘤免疫的强大屏障[1] [2]。此外，Treg 细胞还直接和间接地促进肿瘤血管生成，以确保氧气和营养物质输送到肿瘤。目前 Treg 细胞的高浸润对癌症患者的预后的影响仍然存在争议；大家普遍认为肿瘤中浸润的 Treg 数量增加与不良预后相关。而在某些情况下，例如，在结肠直肠癌(Colorectal Cancer, CRC)患者中[3]，一些患者 $FOXP3^+$T 细胞高浸润浸润往往预示着更好的预后。这是因为目前对于 Treg 细胞的定义没有一个统一的说法，或者使用 FOXP3 作为 Treg 细胞的唯一标记。

根据 $CD4^+FOXP3^+$T 细胞的作用目前可分为三个亚群[4] [5] [6]：1) $CD45RA^+FOXP3^{lo}CD25^{lo}$ 原始 Treg 细胞(nTreg)；2) $CD45RA^-FOXP3^{hi}CD25^{hi}$ 效应 Treg 细胞(eTreg)；3) $CD45RA^-FOXP3^{lo}CD25^{lo}$ 非 Treg 细胞(non-Treg)。其中，eTreg 在肿瘤中丰富存在且具有高度抑制功能，而在 TME 中几乎检测不到 nTreg 和 non-Treg 细胞[6]，这表明 eTreg 才是造成癌症患者不良预后的罪魁祸首[7]。另外研究者已经发现 CRC 患者存在两种 Treg 细胞亚群的浸润，其中有一部分是属于 $FOXP3^+non^-$Treg 细胞浸润，那么这部分结肠癌患者就会有较好预后[3]，而如果是有抑制能力的 eTreg 亚群大量浸润结直肠癌，则会导致预后不良。

2. Treg 介导的免疫抑制机制

在肿瘤免疫中，Tregs 会损害健康个体对癌症的免疫监视，并削弱荷瘤宿主的抗肿瘤免疫反应，加速了肿瘤细胞的免疫逃逸，从而导致各种癌症的肿瘤发展和进展。Tregs 表面上表达的许多分子对于引发针对肿瘤的免疫反应至关重要。

2.1. Treg 和抗原提呈细胞(Antigen Presenting Cell, APC)的相互作用

Treg 细胞表达的细胞毒性 T 淋巴细胞抗原 4(CTLA-4)与 APC 上的 CD80 (B7-1)或 CD86 (B7-2)配体结合，从而将抑制信号传递给效应 T 细胞(effector T cells, Teff)，抑制了 Teff 的毒性功能和增殖[8]；它还可降低 APCs 和 Teff 的活性，并通过 Fas/Fas 配体、穿孔素和颗粒酶 B 信号通路可直接杀死这些细胞[5]。同时，CTLA-4 和 APC 上的 CD80/86 之间的相互作用促进了吲哚胺 2,3-二氧酶(indoleamine 2,3-dioxygenase, IDO)的分泌[5]，这是驱动色氨酸代谢的犬尿氨酸途径中的关键酶，可导致色氨酸减少和犬尿氨酸的积累，抑制 T 细胞的活化并诱导 Tregs 的产生[9]。

2.2. CD39 介导的腺苷产生

CD39 是一种在 Treg 细胞表面过表达的外核苷酸酶，有助于三磷酸腺苷(ATP)转化为腺苷。因为 Treg 细胞对氧化应激比 Teff 更敏感，所以氧化应激诱导 Treg 细胞凋亡，而凋亡的 Treg 细胞释放出大量的 ATP [10]。随后，ATP 被 CD39 和 CD73 代谢为腺苷[10]，腺苷向 APC 发出负信号从而减弱 Teff 的活化[6] [10]。

腺苷与树突状细胞(dendritic cell; DC)、Teff 和自然杀伤细胞(natural killer cell; NK)上表达的 A2A 受体(A2AR)或 A2B 受体(A2BR)结合会导致免疫抑制，从而增加 Treg 细胞的增殖和免疫抑制能力[8] [11]。

2.3. IL-2 消耗

白细胞介素 2 受体亚基-α (CD25)在 Treg 上组成型表达，它以更高的亲和力与 IL-2 结合，导致周围环境中 IL-2 耗尽，从而限制了 Teff 的增殖及活化[12] [13]。总之，Tregs 诱导的免疫抑制可由 Treg 细胞表面表达的受体或酶介导，包括 CTLA-4、CD39 和 IL-2R。另外，Tregs 产生可溶性抑制分子 TGF-β、IL-10 和 IL-35。而 TGF-β 可降低 Teff 的细胞毒功能[5]。

2.4. 神经纤毛蛋白-1 (Nrp1)神经免疫信号蛋白 4A (Sema4a)轴和转录因子

Nrp1-Sema4a 轴是肿瘤内 Tregs 稳定性和抑制功能所需的关键途径，对于维持肿瘤中 Tregs 的免疫抑制能力至关重要[14]。有研究表明 Sema4A 过表达可通过抑制口腔鳞状细胞癌的血管生成、侵袭和迁移来限制肿瘤进展，增加信号通路和靶点[15]；而 Nrp1 是 Sema4A 和其他配体的细胞表面受体，所以 Nrp1 的特异性缺失可阻断 Sema4A 对 Treg 细胞扩增和功能的影响[16]。转录因子 Helios 是另一个与肿瘤浸润性 Tregs 稳定性有关的靶标。在晚期胃癌中，Helios 表达可以是独立的预后因素[17]。Tregs 中的 Helios 缺陷显示选择性地促进肿瘤内 Tregs 转化为 TME 内的 Teff，从而导致体内抗肿瘤免疫反应增强[18] [19]。进一步阐明肿瘤内 Treg 特异性抑制机制将有助于指导治疗方法以更高的特异性靶向癌症中的 Tregs。

3. 靶向 Treg 策略

TME 中大量 Treg 细胞的存在和 $CD8^+$T 细胞与 Treg 细胞的低比例与预后不良相关，这表明 Treg 细胞抑制肿瘤抗原特异性 T 细胞反应[20]。因此，Treg 细胞的消耗或者对 Treg 细胞功能的控制可能是有希望的措施。虽然没有开发出专门针对 Treg 的药物，但有几种潜在的治疗方法直接或间接控制 Treg 细胞的抑制。

3.1. 靶向 CD25 和 CTLA-4

已知 Treg 高表达 CD25，那么针对 CD25 的抗体作为 Treg 耗竭的一种手段也是很好的方法。具有相同特征的抗人 CD25 (RG6292)抗体的临床前评估证明了有效的 Tregs 消耗，而没有显着的免疫相关毒性[21]。Fc 优化的抗 CD25 抗体有效地消耗了肿瘤浸润性 Treg，增加了效应与 Treg 的比率，并与抗 PD-1 抗体协同根除肿瘤[22]。达克珠单抗(Daclizumab)是一种抗 CD25 抗体，可有效耗尽外周循环中的所有 Treg。两种阻断 CTLA-4 功能的单克隆抗体易普利姆玛(IgG1)和曲美木单抗(IgG2)，通过增强 Teff 介导的免疫反应，在一部分晚期实体恶性肿瘤患者中显示出持久的临床活性。小鼠研究表明，抗 CTLA-4 单抗还可以通过 Fc 依赖性机制选择性地消耗瘤内 $Foxp3^+$Tregs，增加 CD8/Tregs 比率并促进肿瘤排斥[23]。

3.2. 阻断趋化因子和趋化因子受体

阻断趋化因子和趋化因子受体相互作用会减弱 Treg 细胞在 TME 中的积累，从而增加抗肿瘤免疫反应。莫加木单抗(mogamulizumab)，抗 CCR4 抗体，在 III 期 MAVORIC 研究中，已被证明可以消耗 Tregs 并可作为晚期蕈样肉芽肿和 Sézary 综合征的一种有价值的治疗方法[24]。另外抗 CCR8 抗体可能发挥特定的抗肿瘤作用[25]，已有关于 CCR8 的临床前研究表明，靶向小鼠 CCR8 特异性抗体的单一疗法显著抑制肿瘤生长，可降低肿瘤 Treg 频率并同时增加 $CD8^+$T 细胞频率[25] [26] [27]。

3.3. 针对 Treg 上的免疫检查点

OX40，GITR，和 LAG-3，主要由 Treg 细胞表达，也可以作为 Treg 细胞耗竭和功能操作的候选者。

抗 OX40 抗体，Ivuxolimab，在 I 期试验中，56%的患者实现了疾病控制[28]且不良事件少。GITR 是一种 TNF 受体，抗人 GITR 抗体 TRX518 可减少循环和瘤内 Tregs，并在晚期黑色素瘤患者中表现出明显的临床疗效[29]。ICOS 信号通路赋予 Tregs 增加的生成、增殖和存活能力[30]。在急性髓系白血病中[31]，可在其微环境中发现 $ICOS^{+}$Tregs 的积累。在临床前研究中，ICOS 激动剂单克隆抗体已显示可增强抑制性检查点阻断的作用[32]。相比之下，拮抗性抗 ICOS 抗体不仅可以抑制表达 ICOS 的淋巴肿瘤细胞，还可抑制免疫抑制性 Tregs [32]。在 I/II 期试验中评估了两种激动剂抗体和一种拮抗剂。但其安全性和联合策略尚未明确。最近的研究表明，LAG-3 阻断可以防止 Treg 招募，可促进 DCs 在黑色素瘤治疗中的功能[33]。

ATOR-1015 是一种人类 CTLA-4 和 OX40 双特异性抗体，可诱导 T 细胞活化和 Treg 细胞耗竭，并提高几种同基因肿瘤模型的存活率。预计 ATOR-1015 与抗 PD-1/PD-L1 疗法联合使用时会产生协同效应。临床前数据表明，ATOR-1015 的进一步临床应用和首次人体试验已经启动(NCT03782467) [34]。

3.4. TGF-β 受体激酶抑制剂

目前也有针对 Treg 衍生的细胞因子的策略，即 TGF-β。TGF-β 信号传导通过促进转移、刺激血管生成和提高免疫力来推动肿瘤的发展。促进转移，刺激血管生成。并抑制先天性和适应性抗肿瘤免疫力[35]，且通过有助于 T 细胞排除[36]来减弱对 PD-L1 抑制的治疗反应。因此，TGF-β 信号抑制和 ICI 的组合在几种实体瘤中显示出前景[37] [38] [39] [40]。

3.5. 其他特异性的策略

目前也有很多新型的特异靶向 Tregs 的方法，如 tDCs 相关疗法[41]、FoxP3 相关方法[42] (TCR 模拟抗体和下一代反义寡核苷酸 FoxP3 抑制剂)、近红外光免疫疗法[43] (NIR-PIT)，多特异性抗体疗法[44]以及转录组学和基于计算的筛选以识别优先的 Treg 细胞靶标[45] [46]等。

4. 小结与展望

治疗耐药性仍然是治疗几种晚期恶性肿瘤的主要挑战。人们普遍认为，宿主免疫反应具有消除肿瘤细胞的潜力，但由于 TME 中存在免疫抑制因子，其功效可能受到限制。Treg 不仅在肿瘤免疫逃避中发挥核心作用，而且由于个体间 TME 的固有异质性，在不同肿瘤类型中观察到不同程度的 Treg 浸润。就表型和功能而言，瘤内人类 Treg 种群的异质性仍然是识别 TME 中特定 Treg 靶标的障碍是肿瘤免疫治疗成功的根本障碍。因此，通过了解 Treg 分化、募集、扩增和免疫抑制的机制，能准确开发消耗 Treg 亚群的治疗策略，以在不引起严重不良免疫反应的情况下增加抗肿瘤免疫反应。

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