



· 综 述 ·

头颈部鳞状细胞癌免疫微环境及其作用机制的最新研究进展及展望

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[摘要] 头颈部恶性肿瘤 (head and neck cancer, HNC) 作为一类常见的恶性肿瘤, 至今仍有较高的发病率和死亡率。在HNC中, 头颈部鳞状细胞癌 (head and neck squamous-cell carcinoma, HNSCC) 是最常见的病理学类型。肿瘤微环境 (tumor microenvironment, TME) 是指肿瘤细胞周围的成分, 主要包括免疫细胞、基质细胞、细胞外基质 (extracellular matrix, ECM)、血管和淋巴管及其驱动分子。一些针对TME的肿瘤治疗策略已在临床上广泛应用, 并产生了显著的治疗效果。更深层次地探索TME中各组分之间的相互作用机制具有重要意义。本文综述了HNSCC的TME中细胞毒性T淋巴细胞 (cytotoxicity T lymphocyte, CTL)、CD4⁺ T 淋巴细胞、调节性T细胞 (regulatory T cell, Treg)、髓样来源抑制细胞 (marrow-derived myeloid cell, MDSC)、自然杀伤 (natural killer, NK) 细胞、肿瘤相关巨噬细胞 (tumor-associated macrophage, TAM) 的最新研究进展。本文中总结的研究主要聚焦于如何恢复抗肿瘤细胞活性, 以及如何消除Treg等免疫抑制细胞的免疫抑制作用, 旨在为研究更有效的HNSCC治疗方法提供新思路。

[关键词] 肿瘤微环境; 头颈部鳞状细胞癌; 免疫细胞; 免疫治疗

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[Abstract] Head and neck cancer (HNC) remains a significant cause of morbidity and mortality. The most prevalent pathology among HNC is head and neck squamous cell carcinoma (HNSCC). The tumor microenvironment (TME) encompasses the components surrounding tumor cells, including immune cells, stromal cells, extracellular matrix (ECM), blood and lymph vessels. Strategies targeting the TME have yielded significant outcomes. Thus, further exploration of the interactions between TME components is crucial. This review discussed recent advances in cytotoxic T lymphocytes (CTL), CD4⁺ T lymphocytes, regulatory T cells (Treg), myeloid-derived suppressor cells (MDSC), natural killer (NK) cells and tumor-associated macrophages (TAM) in HNSCC TME. The article summarized herein primarily focused on restoring the activity of anti-tumor cells and eliminating the immunosuppressive effects of Treg and so on, to provide new insights for more effective HNSCC therapy.

[Key words] Tumor microenvironment; Head and neck squamous cell carcinoma; Immune cells; Immunotherapy

头颈部恶性肿瘤 (head and neck cancer, HNC) 作为一类常见的恶性肿瘤, 至今仍有较高的发病率和死亡率^[1]。头颈部鳞状细胞 (head and neck squamous-cell carcinoma, HNSCC) 是 HNC 最常见的病理学类型, 在中国的发病率为 135.1/10万, 主要包括口腔癌、下咽癌和喉癌

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等。HNSCC局部复发率高, 淋巴结转移率高, 患者总生存率较低^[2-3]。烟草和乙醇滥用以及人类乳头状瘤病毒感染是HNSCC最常见的病因^[4-5]。目前, HNSCC的常规治疗方法主要有手术、化疗和放疗, 但总体效果仍不理想^[6], 因此, 针对HNSCC, 目前仍然需要更加有效的治疗方法。

肿瘤微环境 (tumor microenvironment, TME) 是指肿瘤细胞周围的成分^[7], 主要包括免疫细胞、基质细胞、细胞外基质 (extracellular matrix, ECM)、血管和淋巴管及其驱动分子^[8-9]。越来越多的证据表明, 头颈部鳞状细胞癌的发生不仅与遗传及表观遗传的改变有关, 还与肿瘤细胞同其所处TME中各组分之间复杂的相互作用关系密切^[10]。因此, 开发基于调节TME的HNSCC治疗新策略是必要且可行的。目前针对TME的治疗方法, 特别是免疫检查点阻滞已经取得了显著的治疗效果, 其中又以针对程序性死亡 [蛋白] -1 (programmed death-1, PD-1) 的单克隆抗体为典型代表^[11-12], 这也让HNSCC的治疗研究展现了新的希望。然而, 目前的治疗方式并非对所有的HNSCC患者都有效^[13], 因此, HNSCC的治疗需要效果更好、适用性更广的治疗措施。

鉴于HNSCC总体治疗效果不佳的现状, 又考虑到调节TME的广阔应用前景且目前取得的成果仍然不理想, 在本篇综述中, 我们讨论了HNSCC的TME中有关主要免疫细胞作用机制的最新研究进展, 并特别关注TME中免疫细胞是如何被抑制的, 以及免疫抑制细胞是如何发挥作用的, 旨在发现能够恢复免疫细胞活性以及消除免疫抑制细胞作用的关键环节, 开发出新的调控TME的治疗策略, 以求更有效地治疗HNSCC。

1 细胞毒性T淋巴细胞 (cytotoxicity T lymphocyte, CTL) 领域新进展

CTL在抗肿瘤免疫反应中起着关键作用, 但在肿瘤发生、发展过程中经常处于耗尽和被限制的状态。CTL可通过表面的T细胞受体 (T cell

receptor, TCR) 特异性识别肿瘤细胞产生的肿瘤特异性抗原和肿瘤相关抗原^[14], 进而分泌穿孔素和颗粒酶直接杀伤肿瘤细胞^[15-16]。研究^[17]表明, CTL穿孔素和颗粒酶水平的升高与HNSCC患者更好的预后相关。

TME中各组分之间的相互作用最终会导致HNSCC中CTL的功能障碍^[18], 恢复CTL抗肿瘤免疫活性对于HNSCC的治疗至关重要^[19]。目前, 医学研究已经发现了HNSCC中导致CTL抗肿瘤免疫反应缺陷的部分机制, 其中免疫检查点相关的研究受到广泛关注。在HNSCC免疫细胞表面检测到了PD-1、程序性死亡 [蛋白] 配体-1 (programmed death ligand-1, PD-L1)、T细胞免疫球蛋白及黏蛋白结构域分子3 (T cell immunoglobulin and mucin domain-3, TIM-3)、淋巴细胞活化基因3 (lymphocyte-activation gene 3, LAG-3)、细胞毒性T淋巴细胞相关抗原4 (cytotoxic T lymphocyte associated antigen-4, CTLA-4)、T细胞免疫球蛋白和基于酪氨酸的免疫受体抑制基序 (T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain, TIGIT)、糖皮质激素诱导的肿瘤坏死因子受体 (glucocorticoid-induced tumor necrosis factor receptor, GITR) 家族相关基因等免疫检查点的广泛表达^[11, 20]。免疫检查点的主要功能是防止免疫反应过度激活, 保护正常组织, 而在HNSCC中, 它是诱导免疫抑制微环境、抑制CTL肿瘤杀伤能力、促进肿瘤细胞增殖的关键因素。因此, HNSCC中免疫检查点抑制剂的使用有望逆转CTL的免疫抑制状态, 增强CTL的杀伤活性, 目前针对HNSCC相关免疫检查点抑制剂疗效、安全性的研究也已经广泛开展起来。除免疫检查点以外, 一项体外研究^[21]证实, HNSCC的TME中间质细胞产生的一种氨基酸氧化酶IL4I1可以通过其分解代谢产物H₂O₂抑制CTL在内的T细胞的增殖。另一项研究^[22]证明, HNSCC的TME中组胺和组胺受体H1含量经常增加并可导致CTL功能障碍。最新研究表明, 鼻咽癌细胞中

肿瘤细胞固有三联基序蛋白21 (tripartite-motif protein 21, TRIM21) 的高表达可通过抑制放疗诱导的 I 型干扰素信号转导通路来抑制CTL的抗肿瘤活性^[23]。因此, 通过调节氨基酸分解代谢的酶或组胺受体的表达以及抗组胺治疗等有助于恢复CTL有效的抗肿瘤免疫。

2 CD4⁺T淋巴细胞抗肿瘤及功能下调机制

CD4⁺T淋巴细胞可以分为许多类型, 除经典的辅助性T细胞Th1和Th2外, 还包括Th9、Th17、Th22和调节性T细胞 (regulatory T cell, Treg)^[24]。CD4⁺T淋巴细胞作为一种重要的适应性免疫细胞, 在抗肿瘤免疫应答和增强CTL杀伤肿瘤能力方面也发挥着不可或缺的作用^[25-26]。

一项针对63例HNSCC患者的生存分析显示, CD4⁺T淋巴细胞高浸润可改善患者总生存期和无病生存期^[27]。最新的研究发现, 在HNSCC的TME中, 一种共表达PD-1和ICOS的CD4⁺T辅助性细胞亚型 (DP CD4⁺ Th) 呈高度激活状态, 且定量PCR分析结果显示, DP CD4⁺ Th能够高表达CXCL9和CXCL10, 这两种趋化因子可与肿瘤反应性CD8⁺T细胞表面的CXCR3结合, 从而将更多CD8⁺T细胞招募进TME内, 这提示DP CD4⁺Th可能在HNSCC中招募表达CXCR3的CD8⁺T细胞, 提高HNSCC的TME中的抗肿瘤免疫反应^[28]。

虽然CD4⁺T细胞在HNSCC中具有抗肿瘤作用, 但HNSCC的TME中尚存在各种机制导致CD4⁺T细胞功能受到抑制。LAG-3作为可表达在CD4⁺T细胞表面的免疫抑制性受体, 可以影响CD4⁺T细胞对CTL功能的促进作用, 最终降低CTL的抗肿瘤反应。Katabathula等^[29]最近发现一种新的免疫检查点蛋白VSIR, 并证明其与口腔鳞状细胞癌 (oral squamous cell carcinoma, OSCC) 患者较差的总生存率有关, 他们还证实由信号转导及转录激活蛋白3 (signal transducer and activator of transcription 3, STAT3) 激活介导的VSIR过表达与CD4⁺Th细胞浸润减少有关。此

外, HNSCC中饱和脂肪酸通过抑制STING-INF信号转导通路能够抑制Th的浸润^[30]。这些研究表明, 通过调节LAG-3、VSIR等免疫检查点及其相关通路, 有望逆转HNSCC的TME中的免疫抑制状态, 但距离临床应用还有很长的路要走。

3 调节性T细胞功能机制及潜在治疗价值

Treg是CD4⁺T细胞的重要细胞亚群, 也是不可或缺的免疫调节细胞, 在促肿瘤效应和免疫抑制反应中发挥着关键作用^[31]。在HNSCC中检测到了Treg的高度浸润^[32], 且HNSCC患者外周血中Treg的升高可导致免疫抑制状态, 被认为是预后较差的征象^[33]。因此, 更好地了解Treg在HNSCC中的作用机制对于更有效地治疗HNSCC至关重要。

在HNSCC的TME中, Treg可以通过多种不同的途径被激活。一项研究^[34]阐明了HNSCC中白细胞介素 (interleukin, IL) -33与Treg的关系, 结果发现, IL-33可通过诱导IL-10和转化生长因子 (transforming growth factor, TGF) - β 1的表达促进Treg增殖, 并增强Treg的免疫抑制功能。除IL-33以外, LAG-3也被证明是一种促进Treg激活的因素^[35]。此外, 鼻咽癌细胞产生的外泌体能以剂量依赖性的方式促进Treg增殖, 并增强Treg的免疫抑制功能^[36]。上述结果为HNSCC治疗提供了新思路, 即通过阻断Treg激活因素来逆转Treg介导的免疫抑制状态。

事实上, 目前已有一些研究致力于调节HNSCC中的Treg, 开发新的治疗方法, 以提高抗HNSCC的效果。例如, 在HNSCC中, 抑制补体C3a、C5a的受体可导致Treg扩增, 进而促进肿瘤生长, 而抗Treg治疗联合补体C3a、C5a受体的阻滞可有效地逆转其促肿瘤生长的效应^[37]。抑制PI3K δ 可诱导Treg减少, 增强HNSCC的抗肿瘤免疫应答, 虽然这种措施可引起非恶性器官的免疫相关性不良反应, 但通过替代给药方案可以克服这一缺陷^[38]。神经蛋白酶-1 (neuroprotease1, NRP1) 可在Treg表面大量表达, 是调节Treg功能的关键分子, NRP1⁺Treg的高浸润与HNSCC患

者的不良预后相关, 抑制NRP1有望产生更有效的抗肿瘤反应^[39]。研究^[40]显示, 阻断CCR6-CCL20轴可有效地抑制Treg在HNSCC中的浸润, 抑制肿瘤生长, 并能提高放疗敏感性。敲除鼻咽癌细胞的CD70可通过抑制Treg的发育和功能来减轻免疫抑制^[41]。由此可见, HNSCC中存在多种调节Treg功能的机制, 且通过调节Treg治疗HNSCC的策略是十分有前景的。

4 髓样来源抑制细胞 (marrow-derived myeloid cell, MDSC) 促肿瘤机制及上游调节机制

作为髓系调节细胞之一, MDSC在肿瘤等病理环境下可以表现出强烈的免疫抑制特性。在HNSCC中, MDSC的积累与肿瘤进展及细胞毒性抑制呈正相关, 并能够导致肿瘤转移率增加以及不良预后^[42-43]。因此, 针对MDSC的HNSCC治疗措施同样具有重要的临床转化价值, 目前也正处于研究阶段。

针对MDSC的研究, 一方面集中在MDSC对HNSCC的TME中抗肿瘤免疫细胞抑制机制的探索。在HNSCC中, 磷酸化的STAT3可与MDSC中精氨酸酶-1 (arginase 1, ARG1) 启动子元件结合, 并上调ARG1的表达, 从而促进L-精氨酸的代谢, 最终抑制T淋巴细胞的抗肿瘤免疫反应^[44]。病理性激活中性粒细胞中髓样来源抑制细胞 (pathologically activated neutrophils-bone marrow-derived myeloid cell, PMN-MDSC) 已被证实可在OSCC小鼠模型中抑制自然杀伤 (natural killer, NK) 细胞的功能, 且HNSCC患者具有高水平的肿瘤浸润性PMN-MDSC^[45]。有研究^[46]发现, 肿瘤源性细胞外囊泡通过其内容物miR-21增强MDSC的免疫抑制作用, 而这一过程需要囊泡表面膜蛋白90K的辅助。以上针对MDSC免疫抑制机制的研究, 为选择性阻断HNSCC中MDSC的免疫抑制作用提供了重要线索。

另一方面, MDSC的研究也关注了影响MDSC在HNSCC中浸润的上游机制。研究^[47]发现, 肿瘤细胞可以诱导小鼠垂体释放 α -促黑素细

胞激素 (α -melanocyte-stimulating hormone, α -MSH), α -MSH与骨髓祖细胞表面受体MC5R结合, 除发挥免疫抑制作用外, 还能促进MDSC增多。拮抗 α -MSH的配体MC5R, 可有效地减少MDSC的肿瘤浸润。并且, 研究^[48]还发现HNSCC患者血清中 α -MSH浓度与循环血液中MDSC的含量密切相关, 进一步说明了拮抗MC5R对于HNSCC治疗的潜在价值。此外, 曲美替尼 (trametinib) 作为一种MEK1/2激酶抑制剂, 经验证可下调肿瘤衍生集落刺激因子-1的表达, 从而导致HNSCC小鼠模型中MDSC的减少。*NFE2L2*基因突变可增加PMN-MDSC的浸润并进一步引起放疗抵抗, 而谷氨酰胺酶抑制剂CB-839可有效地逆转这一效应^[49]。因此, 通过调节上游机制减少MDSC在HNSCC中的浸润同样具有潜在的应用价值。

5 NK细胞免疫抑制状态研究新进展

NK细胞作为参与固有免疫应答的重要细胞类型, 以其细胞毒性闻名^[50]。从杀伤肿瘤细胞的方式来看, NK细胞与CTL都可通过分泌穿孔素和颗粒酶直接杀伤肿瘤细胞^[51]。NK细胞和CTL也有明显的区别, 当肿瘤细胞下调其表面MHC-I的表达时, $CD8^+$ T淋巴细胞则很难识别肿瘤细胞因此难以有效地杀死肿瘤细胞, 而NK细胞却可以被激活^[52]。因此, NK细胞在HNSCC治疗方面同样具有很高的开发价值。

在HNSCC中, NK细胞往往会受到各种机制的抑制。NKG2A为一种抑制性NK细胞受体, 在大多数HNSCC肿瘤浸润的NK细胞中表达^[53]。而NKG2D为NK细胞激动性受体, 研究^[54]发现, 含有NKG2D配体的肿瘤源性外泌体可以下调NK细胞表面的NKG2D表达, 这与HNSCC的TME免疫抑制特性相关。在HNSCC肿瘤细胞表面可以检测到HLA-G和HLA-E等非经典HLA的高表达, 这类分子同样可使NK细胞功能受到抑制^[55-56]。尚有研究^[57]表明, HNSCC肿瘤细胞MHC-I和PD-L1上调能够增强肿瘤细胞对NK细胞和T细胞的抑制, 并促进肿瘤淋巴结转

移,且伴有淋巴结转移的HNSCC患者,具有更高的MHC-I和PD-L1转录水平。探索NK细胞在HNSCC的TME中的抑制机制,将为进一步针对这些机制进行调节,消除NK细胞的免疫抑制状态,增强其肿瘤杀伤能力奠定基础。

事实上,多项研究^[58-59]已经发现了NK细胞在HNSCC治疗中的潜在价值。在HNSCC中,染色质修饰蛋白/荷电多泡体蛋白CHMP2A可介导含有主要组织相容性复合体I类多肽相关序列A和B(major histocompatibility complex class I polypeptide-related sequence A and B, MICA/B)和肿瘤坏死因子相关凋亡诱导配体(tumor necrosis factor-related apoptosis-inducing ligand, TRAIL)的细胞外囊泡的分泌,从而诱导NK细胞凋亡,并增强肿瘤细胞对NK细胞的抵抗,靶向CHMP2A有望恢复NK细胞介导的抗肿瘤免疫反应^[58]。放疗联合顺铂治疗可上调NK细胞活化配体ULBP2和黏附分子ICAM-1、ICAM-2和ICAM-3的表达,协同增强NK细胞在HNSCC中的免疫治疗效果^[59]。HNSCC中CD8⁺T淋巴细胞和NK细胞可特征性地表达自然杀伤细胞颗粒蛋白7(natural killer cell granule protein-7, NKG7),NKG7与免疫细胞的细胞毒性和免疫检查点阻滞疗效密切相关,上调CD8⁺T淋巴细胞和NK细胞中NKG7的表达在HNSCC治疗中具有广阔的应用前景^[60]。另外,一项针对二甲双胍用药的HNSCC患者的研究^[61]显示,二甲双胍可通过磷酸化的STAT1抑制CXCL1的产生,增强NK细胞的细胞毒性和抗肿瘤能力。另一项研究^[62]发现,伊立替康的一种活性代谢物SN-38能够促进NK细胞介导的HNSCC肿瘤细胞凋亡。

6 肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)功能及相关治疗策略研究

巨噬细胞主要可分为两种类型,即经典激活的M1型和替代激活的M2型^[63]。在肿瘤发生、发展过程中,外周血中的单核细胞可以在肿瘤细胞或基质细胞分泌的CCL2等趋化因子的作用下,被募集到肿瘤组织中,这些免疫细胞功能类

似于M2型巨噬细胞,通常被称为TAM^[64]。

在HNSCC中,TAM能够促进肿瘤生长、侵袭和转移。在体外培养的HNSCC肿瘤细胞系中,M2样TAM产生的CCL18能够诱导上皮-间质转化(epithelial-mesenchymal transition, EMT),增强肿瘤细胞干性,促进肿瘤转移^[65]。HNSCC中的TAM还能产生表皮生长因子(epidermal growth factor, EGF)并激活表皮生长因子受体(epidermal growth factor receptor, EGFR)/细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)1/2信号转导通路,促进EMT和肿瘤转移^[66]。另有研究^[67]发现TAM与OSCC的EMT与患者较差的总生存情况相关。在OSCC中,TAM可与TGF- β 1结合,TGF- β 1可激活T β R II/Smad3信号转导通路,诱导TAM分泌更多VEGF以促进血管生成,促进肿瘤细胞的转移^[68]。以上研究说明,通过调节TAM作用机制中的关键组分如CCL18、EGFR/ERK1/2信号转导通路、TGF- β 1/T β R II/Smad3信号转导通路有望抑制TAM的促肿瘤作用,增强HNSCC的治疗效果。

事实上,目前的许多研究都集中在TAM相关的治疗策略上。例如,铁死亡的驱动因子SOCS1和抑制因子FTH1可影响HNSCC的TME中M1型和M2型巨噬细胞的浸润,通过靶向SOCS1和FTH1治疗HNSCC具有广阔的治疗前景^[69]。另外,在HNSCC中检测到了STAT3诱导的TAM的增加,特异性抑制TAM的STAT3可以增强HNSCC的放疗效果^[70]。

7 总结与展望

CTL在抗肿瘤免疫反应中起着关键作用,能够直接杀伤HNSCC肿瘤细胞,TME中各成分之间的相互作用最终会导致HNSCC中CTL的功能障碍。研究CTL的抑制机制以寻求解除抑制的方法对HNSCC治疗十分关键。CD4⁺T淋巴细胞在抗肿瘤免疫应答方面也发挥着重要作用,调节LAG-3、VSIR等免疫检查点及其相关信号转导通路,有望逆转CD4⁺T细胞的抑制状态,有利于HNSCC

的治疗。Treg是HNSCC的TME中重要的免疫调节细胞, 具有显著的促肿瘤效应, 在HNSCC中可以通过各种途径被激活。已有一些研究致力于调节HNSCC中的Treg, 以开发新的治疗方法。MDSC在HNSCC中具有强烈的免疫抑制特性, 本文主要关注MDSC抑制抗肿瘤免疫细胞的机制和HNSCC中影响MDSC在TME中浸润的机制, 以便寻找调节MDSC的新靶点, 消除HNSCC过强的免疫抑制。NK细胞是HNSCC中参与固有免疫应答的重要细胞类型, HNSCC肿瘤细胞能够通过NKG2A、NKG2D、非经典HLA等途径抑制NK细胞的功能, 导致肿瘤细胞难以被有效清除, 但NK细胞在HNSCC治疗方面同样具有很高的开发价值。TAM能够促进肿瘤生长、侵袭和转移, 目前的许多研究开始关注TAM相关的治疗策略。增强免疫细胞如CTL、NK细胞的抗肿瘤活性, 逆转免疫细胞的抑制状态; 免疫抑制细胞如Treg、MDSC具有免疫抑制作用, 减少这类细胞在TME中的浸润等都有望成为未来HNSCC治疗的有效策略。总而言之, 近年来针对肿瘤的治疗已有了巨大的发展和创新, 而越来越多的证据也表明针对TME的免疫治疗极具有发展前景。我们相信, 随着科技的发展, 肿瘤治疗将会向更加有效、安全的方向发展。

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