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· 综述 ·

肿瘤微环境中免疫细胞在口腔鳞状细胞癌发生发展中作用的研究进展

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【摘要】 口腔鳞状细胞癌（oral squamous cell carcinoma，OSCC）是头颈部最常见的恶性肿瘤，其强侵袭性、高淋巴结转移的特点是患者预后差的主要原因。肿瘤微环境（tumor microenvironment，TME）是肿瘤细胞生存的特殊微环境。肿瘤相关免疫细胞（tumor-associated immune cell，TAIC）是TME主要的基质细胞。一方面，TAIC调控与OSCC相关的增殖、侵袭、上皮-间充质转化（epithelial mesenchymal transformation，EMT）和抗肿瘤免疫。肿瘤相关巨噬细胞（tumor-associated macrophages，TAMs）中的促肿瘤型M2-TAMs通过MIF/NLRP3/IL-1β分子轴促进OSCC的侵袭转移；肿瘤相关中性粒细胞（tumor-associated neutrophils，TANs）中的促肿瘤型N2-TANs通过JAK2/STAT3通路促进OSCC细胞的增殖和EMT；髓源性抑制细胞（myeloid-derived suppressor cells，MDSCs）分泌白细胞介素（interleukin，IL）-6、IL-10和转化生长因子（transforming growth factor，TGF）-β促进OSCC进展；而T淋巴细胞可分泌IL-17促进炎症进展，也可分泌IL-10和TGF-β抑制炎症介导的肿瘤免疫反应；自然杀伤（natural killer，NK）细胞识别并攻击肿瘤细胞进而抑制OSCC的进展。另一方面，TAIC之间的相互作用也调控OSCC的进展。M2-TAMs分泌IL-10和程序性死亡配体（programmed death-ligand，PD-L）-1促进T淋巴细胞的凋亡调控OSCC的侵袭转移；N2-TANs分泌血凝素样氧化低密度脂蛋白受体-1和精氨酸酶-1抑制T淋巴细胞的增殖和细胞毒性；MDSCs通过抑制程序性细胞死亡受体（programmed cell death，PD）-1/PD-L1信号传导抑制$CD8^+$ T淋巴细胞的增殖和抗肿瘤效应；同时，MDSCs也可降低CD3-zeta链的表达和干扰素-γ（interferon-γ，IFN-γ）的分泌抑制T淋巴细胞增殖；而肿瘤浸润淋巴细胞（tumor-infiltrating lymphocytes，TILs）与NK细胞的数量在OSCC进展中呈正相关关系。因此，靶向调控OSCC中TAIC及其相关的信号通路，精准靶向TAIC之间的相互作用将有望提高免疫治疗疗效从而抑制OSCC进展。笔者对近年来TME中TAIC及其相互作用对OSCC进展的影响进行综述，探讨其在OSCC早期诊断和治疗中的应用前景。

【关键词】 肿瘤微环境；　肿瘤相关免疫细胞；　肿瘤相关巨噬细胞；　肿瘤相关中性粒细胞；　髓源性抑制细胞；　T淋巴细胞；　自然杀伤细胞；　口腔鳞状细胞癌；　基质细胞；　肿瘤免疫

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Research progress on the role of immune cells in the tumor microenvironment in the development and progression of oral squamous cell carcinoma

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【Abstract】 Oral squamous cell carcinoma (OSCC), the most common type of head and neck malignancy, has a poor prognosis owing to its high invasiveness and high rate of cervical lymph node metastasis. The tumor microenvironment (TME) is a complex microenvironment that is essential for tumor cell survival. Tumor-associated immune cell (TAIC), the main stromal cell of TME, regulates the proliferation, invasion, epithelial-mesenchymal transformation (EMT), and anti-tumor immunity of OSCC. M2-tumor-associated macrophages (TAMs) promote the invasion and metastasis of OSCC through the macrophage migration inhibitory factor/NOD-like receptor family pyrin domain containing 3/interleukin (IL)-1β axis, while N2-tumor-associated neutrophils (TANs) regulate the proliferation and EMT of OSCC through the Janus kinase 2/signal transducer and activator of transcription 3 pathway. Meanwhile, myeloid-derived suppressor cells (MDSCs) accelerate the progression of OSCC by secreting IL-6, IL-10, and transforming growth factor (TGF)-β; T cells promote inflammation by secreting IL-17 and inhibit inflammation-mediated tumor immune response by secreting IL-10 and TGF-β; and natural killer (NK) cells recognize and attack OSCC cells to inhibit OSCC progression. TAIC interaction network also regulates OSCC progression. M2-TAMs regulate the invasion and metastasis of OSCC by promoting T cell apoptosis through the secretion of IL-10 and programmed death-ligand (PD-L) -1, while N2-TANs inhibit T cell proliferation and cytotoxicity by secreting LOX-1 and arginase-1. MDSCs inhibit the proliferation and anti-tumor effects of $CD8^+$ T cells through the inactivation of programmed cell death (PD)-1/PD-L1 signaling. Additionally, MDSCs inhibit the proliferation of T cells by decreasing the expression of the CD3-zeta chain and interferon-γ (IFN-γ). Moreover, tumor-infiltrating lymphocytes and NK cells were found to be positively correlated in OSCC progression. Therefore, target regulation, related signaling pathways, and the interaction network of TAIC may serve as promising therapeutic targets in the immunotherapy of OSCC. In this review, we summarize the recent research on the effects of TAIC and their interaction network in the TME in the progression of OSCC and explore its application in the early diagnosis and treatment of OSCC.

【Key words】 tumor microenvironment; tumor-associated immune cells; tumor-associated macrophages; tumor-associated neutrophils; myeloid-derived suppressor cells; T lymphocytes; natural killer cells; oral squamous cell carcinoma; stromal cells; tumor immunity

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口腔鳞状细胞癌(oral squamous cell carcinoma,OSCC)占头颈部鳞状细胞癌(head and neck squamous cell carcinoma,HNSCC)的90%,5年生存率低至50%[1]。2020年数据统计每年全球约30万新发病例和10万死亡病例[2]。OSCC侵袭性强、颈淋巴结转移率高,患者预后差。肿瘤微环境(tumor microenvironment,TME)包括非细胞成分和细胞成分,非细胞成分包括细胞外基质、生物活性因子、细胞外囊泡等;细胞成分包括肿瘤细胞和基质细胞[3]。TME中基质细胞主要有肿瘤相关免疫细胞(tumor-associated immune cell,TAIC)、血管内皮细胞、成纤维细胞和脂肪细胞。一方面,基质细胞通过改变肿瘤细胞的基因型和表型介导OSCC的恶性进展促进转移[4-5]。另一方面,基质细胞还可通过细胞间的直接或间接作用调节TME。多项研究指出TAIC是影响OSCC进展的重要因素,具体机制尚不明确[6]。因此,探究TAIC在OSCC进展中的作用对改善患者的预后具有积极意义。

TAIC包括肿瘤相关巨噬细胞(tumor-associated macrophages,TAMs)、肿瘤相关中性粒细胞(tumor-associated neutrophils,TANs)、髓源性抑制细胞(myeloid- derived suppressor cells,MDSCs)、T淋巴细胞、自然杀伤(natural killer,NK)细胞等。本文基于中国知网、万方数据知识服务平台、维普网、CINAHL、Embase、PubMed、Web of Science、Cochrane Library数据库,主题词与自由词结合并辅以人工进行中英文检索。中文检索词为“口腔鳞状细胞癌、口腔癌、头颈部鳞状细胞癌、肿瘤相关免疫细胞、免疫细胞、肿瘤相关巨噬细胞、肿瘤相关中性粒细胞、髓源性抑制细胞、T淋巴细胞、自然杀伤细胞”,英文检索词为“Oral squamous cell carcinoma, Oral cancer, Head and neck squamous cell carcinoma, TAIC, Immune cells, TAMs, TANs, MDSCs, T cells, NK cells”。文献排除标准:研究类型不明确、样本

量过小、数据模糊不清、国内外重复发表或影响因子较低以及无法获得全文的文献。文献检索及结果报告遵循PRISMA指南。本文就TAIC及其相互作用对OSCC进展的研究进行综述。

1　TAMs

TAMs在免疫代谢、组织稳态和抗炎抗感染中发挥关键作用[7]。TAMs分为抗肿瘤的巨噬细胞（M1-TAMs）和促肿瘤的巨噬细胞（M2-TAMs）两个功能类别[8]。干扰素-γ（interferon-γ，IFN-γ）和脂多糖（lipopolysaccharide，LPS）诱导TAMs分化为M1-TAMs，M1-TAMs分泌白细胞介素（interleukin，IL）-12、IL-6、肿瘤坏死因子（tumor necrosis factor，TNF）-α和C-X-C基序趋化因子配体（C-X-C motif chemokine ligand，CXCL）-10等促进抗肿瘤免疫；相反，TAMs被IL-4和IL-13诱导分化为M2-TAMs，M2-TAMs分泌转化生长因子（transforming growth factor，TGF）-β和IL-10等促进炎症反应。Wang等[9]研究发现M2-TAMs通过激活MIF/NLRP3/IL-1β分子轴促进OSCC的侵袭转移。与正常口腔黏膜相比，25例OSCC组织中M2-TAMs的数量明显增多，且与OSCC浸润深度、癌灶大小、淋巴结转移等临床特征正相关[10]。随着M2-TAMs数量的增加，患者生存率下降，表明M2-TAMs与OSCC的预后密切相关，且有望用作OSCC诊断及预后的重要指标[11]。一方面，M2-TAMs产生基质金属蛋白酶（matrix metalloproteinases，MMPs）破坏基底膜促进OSCC的侵袭转移，李玮柏等[12]研究发现M2-TAMs分泌IL-6并与肿瘤细胞表面的IL-6受体结合，通过上调白血病抑制因子的表达促进OSCC的侵袭转移。另一方面，M2-TAMs产生血管内皮生长因子（vascular endothelial growth factor，VEGF）促进血管新生为OSCC的生长提供营养，为血行转移提供通道[13]。目前，大量研究报道了M2-TAMs在OSCC进展中的作用机制，尚缺少M1-TAMs在OSCC进展中的研究，需要进一步探索。

2　TANs

中性粒细胞占人类白细胞总数的50%～70%，是参与炎症相关肿瘤进展的主要免疫细胞之一[14-15]。TANs通过选择素、整合素和趋化因子被募集到炎症部位。IFN-β诱导形成抗肿瘤N1型TANs（N1-TANs），N1-TANs参与先天性和适应性免疫的激活，促使高水平活性氧（reactive oxygen species，ROS）的产生和肿瘤细胞端粒DNA的损伤，并发挥细胞毒性抑制肿瘤的侵袭转移[16]；相反，TGF-β诱导形成促肿瘤N2型TANs（N2-TANs），N2-TANs产生趋化因子、CCL2、HGF和TNF-α等促进肿瘤增殖并抑制免疫反应，N2-TANs还可分泌MMP-8和MMP-9激活VEGF促进血管新生[17-18]。研究发现TANs浸润程度与OSCC预后呈负相关，表明TANs参与调控OSCC的进展[19]。Hu等[20]研究发现N2-TANs激活JAK2/STAT3信号通路上调靶基因E2F1的表达介导增殖和上皮-间充质转化（epithelial mesenchymal transformation，EMT）促进OSCC的侵袭转移。

中性粒细胞是口腔黏膜的屏障，维持口腔微环境稳态。口腔黏膜屏障受损造成微生物稳态失调诱导炎症反应，LPS和IL-17促进DNA和髓过氧化物酶的分泌诱导中性粒细胞胞外陷阱（neutrophil extracellular traps，NETs）的形成[21]。最新研究发现PI3K/PKB通路参与诱导OSCC中NETs形成促进OSCC进展[22]。此外，NETs通过加速凝血酶和纤维蛋白的生成促进肿瘤内高凝血状态的形成，增加N2-TANs的浸润促进OSCC的转移[23]；同时N2-TANs释放弹性蛋白酶刺激肿瘤细胞发生EMT促进肿瘤的侵袭转移[24]。截止目前，TANs的生物学功能及其在OSCC微环境中的作用尚未得到充分阐述，需进一步学习TANs相关炎症信号对OSCC的TME的功能调控。

3　MDSCs

MDSCs是具有免疫抑制功能的髓系细胞群，分泌IL-6、IL-10、TGF-β和ROS等因子，通过上调一氧化氮合酶和精氨酸酶-1的表达抑制T淋巴细胞的功能。MDSCs通过降低CD3-zeta链的表达和IFN-γ的分泌抑制T淋巴细胞增殖；MDSCs分泌IL-6、IL-1β、IL-23和前列腺素E2（prostaglandin E2，PGE2）并激活一氧化氮合酶和环加氧酶2酶活性促进辅助T细胞17（T helper cell，Th17）细胞分化，促进OSCC进展[25]。此外，IL-6可抑制T细胞增殖并削弱肿瘤的免疫反应[26]。研究表明[27]OSCC细胞可诱导健康供体的MDSCs转化为免疫抑制表型的肿瘤相关MDSCs。体外3D培养模型结果表明OSCC患者外周血中MDSCs的数量与OSCC临床分期、病理分级、淋巴结转移和预后不良正相关。MDSCs可增强OSCC的增殖、侵袭和转移，而凋亡能力不受影响，MDSCs通过逃避免疫监视、介导

EMT和血管生成促进OSCC的进展[28]。抑制CD39/CD73腺苷信号通路可抑制MDSCs的数量和功能，从而恢复OSCC的抗肿瘤免疫能力[29]。近来研究发现牙龈卟啉单胞菌引发的炎症上调MDSCs的数量，通过促进CXCL2、CCL2、IL-6和IL-8的分泌募集MDSCs促进OSCC的恶性进展[30]。

4　T淋巴细胞

T淋巴细胞按其分化抗原分为$CD4^+$ T细胞和$CD8^+$ T细胞[31]。$CD4^+$ T细胞是适应性免疫的主要组成部分，在宿主对病原体反应的激活和调节过程中起着重要作用。$CD4^+$ T细胞在细胞因子的影响下可分化为辅助性T细胞（T helper cell，Th）1、2、17和调节性T细胞（regulatory T cell，Treg）等亚群，其中Th17分泌IL-17和IL-21促进炎症进展，而Treg分泌IL-10和TGF-β抑制$CD8^+$ T细胞和NK细胞的抗肿瘤免疫功能，Th17和Treg之间的平衡对维持免疫稳态至关重要[32]。Th17/Treg比值与OSCC肿瘤大小、淋巴结转移和临床分期显著正相关[33]。$CD8^+$ T细胞主要包括细胞毒性T细胞（cytotoxicity T lymphocytes，CTLs）、肿瘤浸润淋巴细胞（tumor-infiltrating lymphocytes，TILs）以及其他亚群。CTLs分泌IFN-γ、TNF和颗粒酶抑制肿瘤进展；TILs在口腔癌前病变中显著增加，是口腔癌前病变中介导抗肿瘤效应的关键。在OSCC侵袭的最前沿检测到大量的$CD8^+$ T细胞的聚集，且患者总生存期与$CD8^+$ T细胞密度成正比，表明$CD8^+$ T细胞可作为抑制OSCC进展的重要防线和预后指标[34]。此外，CXCL14可诱导TILs聚集进而抑制OSCC的进展，TILs数量与OSCC肿瘤大小、增殖能力和侵袭程度负相关[35]。EMT引起的肿瘤表型改变可以抑制OSCC中$CD8^+$ T细胞的抗炎功能，减弱机体抗肿瘤免疫反应，导致免疫逃逸和预后不良[36-38]。因此，干预T淋巴细胞的功能将有望抑制OSCC的发展。目前，关于T淋巴细胞的功能机制研究多集中在细胞水平，临床研究较少，证据强度较弱。因此，开展基于临床及公共数据库的大样本量研究具有重要意义。

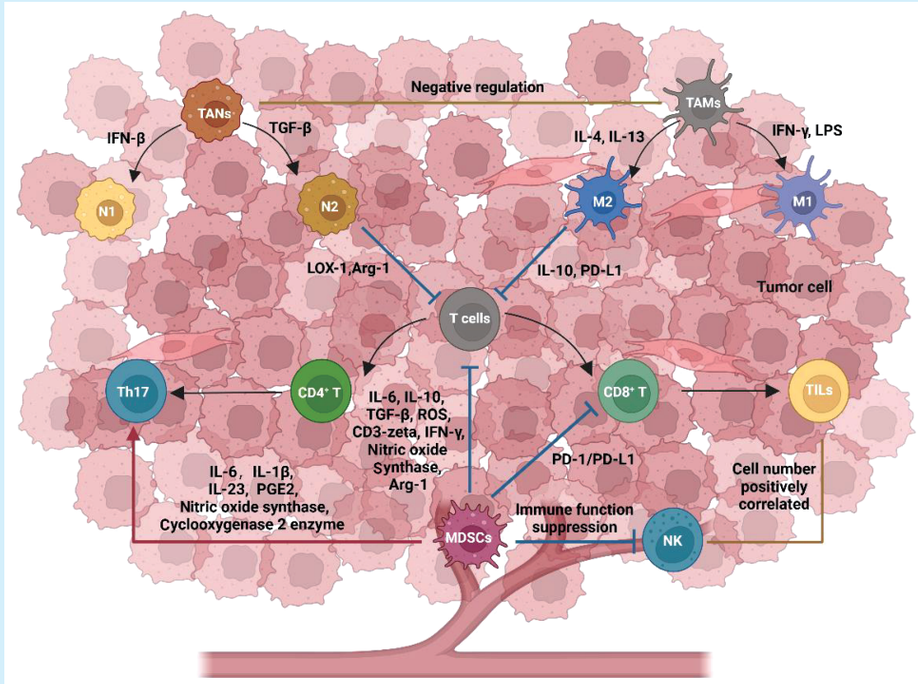
5　NK细胞

NK细胞属于固有淋巴细胞。NK细胞可抑制$CD8^+$ T细胞增殖，同时利用激活和抑制的种系编码受体识别肿瘤细胞，在激活后识别并发挥细胞毒性攻击局部和播散的肿瘤细胞抑制肿瘤进展，在肿瘤免疫监测中发挥重要作用[39]。Gupta等[40]研究发现OSCC中NK细胞数量与机体T淋巴细胞免疫应答呈正相关，证明NK细胞的浸润是抗肿瘤免疫的关键。OSCC中NK细胞的瘤内密度较低，且NK细胞浸润程度越低患者的总体生存期越短，证明NK细胞可能成为评价OSCC患者预后的潜在指标及免疫治疗疗效评估的效应细胞[41-42]。NK细胞精确靶向OSCC细胞的实验模型和临床试验已经开展应用[43]，为进一步研究NK细胞在肿瘤免疫浸润过程的调控机制和抗肿瘤作用提供了多维度的分析基础和可靠的临床证据。

6　TAIC之间的相互作用

TAIC除a了与OSCC细胞进行通讯交互，还可通过TAIC之间的相互作用调控OSCC的进展（图1）。OSCC中TILs与NK细胞数量正相关，共同调节OSCC的生长转移[44]。HNSCC的临床模型研究发现靶向调控CXCR1和CXCR2可减少MDSCs的募集，通过增强NK细胞的免疫功能抑制HNSCC的进展[45]。

CD155和程序性死亡配体（programmed death-ligand，PD-L）-1在MDSCs中高表达，阻断CD155/TIGIT可通过抑制MDSCs的功能调控靶向程序性细胞死亡受体（programmed cell death，PD）-1/PD-L1信号传导，增加$CD8^+$ T淋巴细胞促进抗肿瘤效应和抗PD-L1疗效，表明MDSCs可通过抑制PD-1/PD-L1信号传导抑制$CD8^+$ T淋巴细胞增殖[46]。MDSCs也可通过降低CD3-zeta链的表达和IFN-γ的分泌抑制T淋巴细胞的增殖，同时激活一氧化氮合酶和环加氧酶2酶活性促进Th17细胞分化[25]。Essa等[47]研究发现OSCC中TAMs与TANs呈负调控关系，但相关机制有待进一步研究。此外，N2-TANs通过分泌血凝素样氧化低密度脂蛋白受体-1和精氨酸酶-1抑制T淋巴细胞的增殖和细胞毒性促进头颈癌的进展[48]。M2-TAMs通过分泌IL-10和PD-L1抑制T淋巴细胞的增殖调控OSCC的侵袭转移[49-50]。然而，MDSCs、NK细胞与TAMs、TANs是否通过细胞间相互作用调控OSCC的进展尚不明确。有研究报道了TAIC在其他肿瘤中的相互作用。MDSCs通过分泌IL-10抑制NK细胞的增殖，降低抗肿瘤活性促进结肠癌进展[51]。缺氧下调STAT3活性促进MDSCs分化为M2-TAMs[52]。M2-TAMs分泌TGF-β介导Treg募集从而抑制$CD8^+$T细胞分泌IFN-γ，而IFN-γ可增强M2-TAMs代谢适应性和线粒体完整



TAMs (M2-TAMs) and TANs (N2-TANs) are negatively correlated during OSCC progression. N2-TANs and M2-TAMs inhibit T cell proliferation by secreting LOX-1 and Arg-1 and IL-10 and PD-L1, respectively. MDSCs induce $CD4^+$ T cell differentiation into Th17 by secreting IL-6, IL-1β, IL-23, PGE2, nitric oxide synthase, and cyclooxygenase 2; inhibit T cell proliferation by secreting IL-6, IL-10, TGF-β, ROS, CD3-zeta, IFN-γ, nitric oxide synthase, and Arg-1; and inhibit NK cell and $CD8^+$ T cell function. TILs and NK cells are positively correlated during OSCC progression and increase the proliferation and metastasis of OSCC.

IFN-β: interferon-β; IFN-γ: interferon-γ; TAMs: tumor-associated macrophages; Th17: T helper cell; TGF-β: transforming growth factor-β; TANs: tumor-associated neutrophils; IL: interleukin; PD-L1: programmed death-ligand 1; PD-1: programmed cell death 1; ROS: reactive oxygen species; PGE2: prostaglandin E2; LOX-1: lectin-like oxidized low-density lipoprotein receptor-1; Arg-1: arginase-1; T cells: T lymphocytes; TILs: tumor-infiltrating lymphocytes; OSCC: oral squamous cell carcinoma; NK cells: natural killer cells; IFN-γ: interferon-γ; MDSCs: myeloid-derived suppressor cells

Figure 1　Interaction network of immune cells in OSCC

图1　OSCC中免疫细胞的相互作用关系

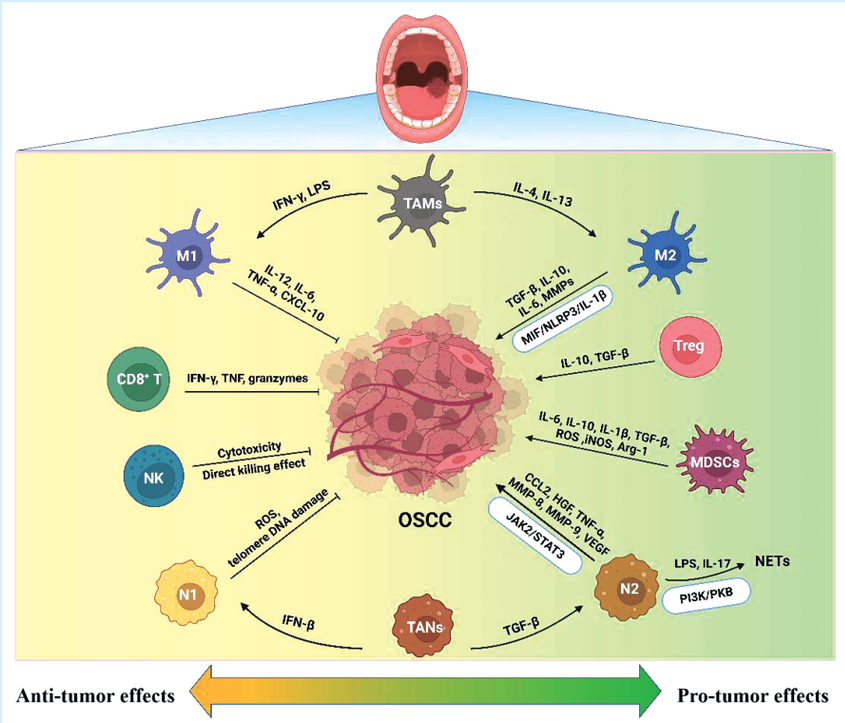
性[53]。Krneta等[54]从小鼠乳腺癌中分离M2-TAMs和NK细胞并进行体外共培养，发现M2-TAMs可显著抑制NK细胞活性。尿路膀胱上皮癌中，N2-TANs分泌PGE2促进肿瘤细胞表达吲哚胺-2，3-双加氧酶1抑制T淋巴细胞免疫功能[55]。N2-TANs分泌抑瘤素M促进M2-TAMs的形成介导乳腺癌的生长转移[56]。因此，功能调控TANs将有望诱导促瘤的M2-TAMs向抗瘤M1-TAMs转化，从而达到抑制肿瘤进展的目的。然而，MDSCs、NK细胞与TAMs、TANs细胞间相互作用是否参与调控OSCC的进展有待进一步的研究。

7　总结与展望

一方面，TAIC通过分泌促肿瘤细胞因子、介导血管新生、诱导免疫抑制等促进OSCC的增殖、侵袭和转移；另一方面，TAIC也可分泌抗肿瘤细胞因子、介导细胞毒性等发挥抗肿瘤免疫效应（图2）。各类TAIC在OSCC中的作用见表1。

此外，不同TAIC之间也可通过分泌细胞因子介导TAIC的细胞毒性、诱导异种TAIC的募集、促进TAIC的分化等参与免疫促进或抑制，调控OSCC的进展。通过对TAIC的功能调控将有望实现促瘤TME向抑瘤TME的转化。通过免疫抑制剂逆转Treg介导的免疫抑制的免疫疗法已用于OSCC的临床治疗[57]。免疫检查点抑制剂（immune checkpoint inhibitor，ICI）联合放化疗、溶瘤治疗等治疗策略可通过提高TAIC的抗炎活性改善HNSCC患者的预后[58-59]。口腔扁平苔藓、白斑等口腔癌前病变中PD-1和PD-L1的表达显著升高[60-61]，因此，以PD-1/PD-L1为免疫靶点的ICI将有望抑制OSCC的生长。

由于TME的复杂性以及细胞失活、扩增不足、寿命短等原因，从患者的外周血和肿瘤中分离出特定的免疫细胞难度较大。因此，目前尚缺乏TAIC之间相互作用及其功能分布对调控OSCC进展的研究，免疫联合治疗策略也只停留在理论阶段，尚未在OSCC临床治疗实践中运用。临床运用中，由于个体的特异性等原因，并非所有的OSCC患者都能从免疫治疗中获益；因此，丰富TAIC的生物标志



Immune cells exhibit anti-tumor and pro-tumor effects during OSCC progression. M1-TAMs, $CD8^+$ T cells, NK cells, and N1-TANs display anti-tumor effects in OSCC by secreting pro-inflammatory cytokines and antibody-mediated cytotoxicity. However, M2-TAMs, Treg cells, MDSCs, and N2-TANs exhibit pro-tumor effects by secreting anti-inflammatory cytokines, promoting angiogenesis and EMT. IFN-γ: interferon-γ; LPS: lipopolysaccharide; TAMs: tumor-associated macrophages; IL: interleukin; TGF-β: transforming growth factor-β; TNF-α: tumor necrosis factor-α; CXCL: serum CXC chemokine ligand-10; MMP: matrix metalloproteinase; MIF: macrophage migration inhibitory factor; NLRP3: Nod-like receptor protein 3; T cells: T lymphocytes; Treg: regulatory T cell; NK cells: natural killer cells; ROS: reactive oxygen species; iNOS: inducible NOS; Arg-1: arginase-1; MDSCs: myeloid-derived suppressor cells; OSCC: oral squamous cell carcinoma; CCL2: C-C motif chemokine ligand 2; HGF: hepatocyte growth factor; VEGF: vascular endothelial growth factor; JAK2: Janus kinase 2; STAT3: signal transducer and activator of transcription 3; TANs: tumor-associated neutrophils; PI3K: phosphoinositide 3-kinase; PKB: protein kinase B; NETs: neutrophil extracellular traps

Figure 2　Roles of tumor-associated immune cells in OSCC progression

图2　肿瘤相关免疫细胞在OSCC发生发展中的作用

表1　肿瘤相关免疫细胞在OSCC进展中的作用

Table 1　Roles of tumor-associated immune cells in OSCC progression

Immune cells	Roles in the development of OSCC	References
TAMs	● Activation of the MIF/NLRP3/IL-1β signaling thereby induces metastasis and invasion	[9]
	● TAMs were correlated with infiltration depth and lymph node metastasis	[10][11]
	● TAMs-derived IL-6 upregulates leukemia inhibitory factor expression by binding to IL-6 receptors on tumor cells	[12]
	● Promote metastasis, invasion, and vasculogenesis through VEGF regulation	[13]
	● Promote tumor proliferation and EMT by up-regulating the target genes of JAK2/STAT3 signaling	[20]
TANs	● NETs enhance procoagulant activity by increasing thrombin and fibrin generation	[23]
MDSCs	● MDSCs secrete IL-6, IL-1β, IL-23 and PGE2 and activate nitric oxide synthase and cyclooxygenase 2 enzymes to promote the differentiation of Th17 cells	[25]
	● The number of MDSCs was positively correlated with pathological grade, lymph node metastasis, and poor prognosis	[28]
	● STAT3 signal induces the monocyte differentiation into MDSCs in TME through the CD39/CD73-adenosine signal pathway	[29]
	● *Porphyromonas gingivalis* increases MDSCs during infection to promote OSCC progression by enhancing CXCL2, CCL2, IL-6, and IL-8 secretion	[30]
T cells	● Th17/Treg ratio significantly correlates with tumor size, lymph node metastasis, and clinical stage	[32][33]
	● Migration of TILs was increased through CXCL14-depended manner	[35]
NK cells	● NK cells influence antitumor cytotoxic T cells generation to inhibit OSCC proliferation	[39]
	● A low density of NK cells in OSCC was associated with later clinical staging of OSCC	[41][42]

TAMs: tumor-associated macrophages; TANs: tumor-associated neutrophils; MDSCs: myeloid-derived suppressor cells; T cells: T lymphocytes; NK cells: natural killer cells; OSCC: oral squamous cell carcinoma; Th17: T helper cell; Treg: regulatory T cell; TILs: tumor-infiltrating lymphocytes; VEGF: vascular endothelial growth factor; IL: interleukin; CXCL: serum CXC chemokine ligand; CCL2: C-C motif chemokine ligand 2

物、制定个体化的免疫治疗将有助于提高免疫治疗的效果并促进精准治疗的形成。随着单细胞组学和生信分析的发展，开展基于临床样本的空间组学揭露TAIC的异质性并构建TAIC的功能调控网络、开展基于公共数据库的大样本量研究确定免疫细胞新的功能亚型是未来研究的重点。因此，研究TAIC的功能调控及其相互作用将有望为OSCC的治疗提供新思路新方向。

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