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述评 EDITORIAL

恶性肿瘤缺氧酸性微环境对免疫治疗影响机制的研究进展

李伟东, 孙学英

背景资料

肿瘤免疫治疗面临的最大障碍就是低应答率和高抵抗率, 肿瘤微环境可能是影响这两大问题的关键因素. 因此, 研究肿瘤微环境, 尤其是缺氧酸性微环境, 对免疫反应的调控和影响, 是提高肿瘤免疫治疗效果的方向.

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Mechanisms by which tumor hypoxic and acidic microenvironments affect immunotherapy

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Abstract

Cancer immunotherapy has become one of the areas in which major medical breakthroughs are being witnessed. The recent promising progress in activating therapeutic anti-tumor immunity, such as checkpoint blockade and chimeric antigen receptor T-cell immunotherapy therapy, has made us closer to, but there is still a long way to reach, the final goal in the battle against cancer, since cancer cells utilize different mechanisms to escape from immune attack, leading to limited efficacy of immunotherapies in treating malignant tumors. Tumor tissues consist of cancer cells, blood vessels, lymphatic capillaries, fibroblasts, inflammatory cells and various types of extracellular matrixes, which compose tumor microenvironments. Tumor microenvironments not only support the growth and metastasis of cancer cells, but also affect the recognition and killing of cancer cells by immune cells and their ability to migrate and regulate the activation of effector molecules, thus influencing the therapeutic effects of immunotherapies. Tumor hypoxic microenvironments are caused by abnormal blood supply networks and outweighing demands of oxygen by fast dividing cancer cells. Hypoxia can also, together with abnormal metabolism of cancer cells, lead to sequential tumor acidic microenvironments. Hypoxic and acidic microenvironments are frequently

同行评议者

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observed in almost all solid tumors, and adapted and exploited by cancer cells for their survival and invasion. Hypoxic and acidic microenvironments can also result in the diversity and instability of gene mutations and the activation of cellular signaling pathways and survival factors, and have been regarded as one of the major causes of the resistance to various therapies including immunotherapy. The present article summarizes the recent progress in the understanding of the mechanisms by which tumor hypoxic and acidic microenvironments influence immunotherapy, and analyzes the potential strategies for coping with these obstacles to combating cancer. We hope it can provide some new clues for clinicians and scientists engaged in the research areas of tumor microenvironments and immunotherapy.

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Key Words: Tumor hypoxic microenvironment; Tumor acidic microenvironment; Immunotherapy

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摘要

近年来, 以免疫检查点阻断单克隆抗体和抗原受体T细胞免疫疗法细胞治疗为代表的免疫疗法在治疗恶性肿瘤方面取得突破性进展. 然而, 肿瘤通过各种不同的机制逃避免疫系统的识别和杀伤, 导致免疫治疗效果仍不理想. 由癌细胞、血管、淋巴、成纤维细胞、炎症细胞以及多种细胞外基质有机构成的肿瘤组织微环境不仅支持癌细胞的生长和转移, 也影响免疫细胞识别和杀伤癌细胞以及迁移的功能, 调控免疫效应分子的活化, 从而影响免疫治疗的效果. 实体肿瘤内异常血管网络和快速生长的癌细胞对氧过量需求导致肿瘤组织缺氧, 并加剧由于癌细胞异常代谢导致肿瘤组织的酸性微环境. 缺氧酸性微环境是肿瘤微环境最重要的组成部分, 癌细胞适应和利用这些微环境, 导致基因变异的多样性和不稳定性, 激活多种信号通路和生存因子, 造成肿瘤对包括免疫治疗在内的多种治疗方法的耐受和抵抗. 本文针对近年来肿瘤缺氧酸性微环境对免疫治疗影响机制的研究进展进行述评, 希望给从事癌症微环境和免疫治疗的临床基础科研人员提供新的思路.

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关键词: 肿瘤缺氧微环境; 肿瘤酸性微环境; 免疫治疗

核心提要: 以免疫检查点阻断单克隆抗体和抗原受体T细胞免疫疗法细胞治疗为代表的免疫治疗取得重大突破, 已经被应用于多种恶性肿瘤的临床治疗. 然而, 肿瘤特异微环境影响了免疫治疗的效果. 深入了解肿瘤缺氧酸性微环境对免疫治疗的影响, 研究癌细胞逃避免疫监视和攻击的机制, 有助于探索新的思路和方法, 提高肿瘤免疫治疗的疗效.

李伟东, 孙学英. 恶性肿瘤缺氧酸性微环境对免疫治疗影响机制的研究进展. 世界华人消化杂志 2017; 25(21): 1934-1944 URL: http://www.wjgnet.com/1009-3079/full/v25/i21/1934.htm DOI: http://dx.doi.org/10.11569/wcjd.v25.i21.1934

研发前沿

实体肿瘤特有的缺氧酸性微环境负向调节免疫反应的激活和应答, 影响了肿瘤免疫治疗的效果. 研究缺氧酸性微环境对免疫效应细胞的调控机制、干预其对免疫反应的抑制作用, 将可能成为提高免疫治疗效果的新方法.

0 引言

早在19世纪, 美国医生威廉姆•科莱(William B. Coley)基于临床观察, 首次进行了病菌感染刺激免疫系统治疗癌症的临床试验, 并于1893年发表了利用溶血性链球菌感染导致丹毒治疗10例骨癌的临床分析[1]. 这是最早关于恶性肿瘤免疫治疗的报道, 尽管这一疗法被广泛质疑. 半个多世纪后, 1949年Burnet提出了肿瘤免疫耐受假说, 1957年Klein等[2]在小鼠发现了肿瘤特异性抗原, 1967年Burnet[3]进一步完善了肿瘤免疫监视理论, 开始了现代肿瘤免疫研究的新纪元.

经典有效抗肿瘤免疫反应主要通过4个步骤而产生[4]: 第1步, 肿瘤特异性抗原或相关抗原由肿瘤细胞直接呈递, 或被抗原呈递细胞[如树突状细胞(dendritic cell, DC)]捕获、加工和呈递; 第2步, 树突状细胞在合适的活化成熟信号调控下分化并迁移到淋巴结, 将肿瘤抗原呈递给幼稚T细胞使之分化为成熟的细胞毒性T细胞(cytotoxic T lymphocyte, CTL). 如果没有合适的成熟信号, 抗原呈递可能导致T细胞无能或产生抑制效应T细胞的调节性T细胞(regulatory T cell, Treg); 第3步, 具有识别和消除肿瘤细胞功能的CTL在淋巴结内扩增到

创新盘点
本文系统阐述了肿瘤缺氧酸性微环境如何影响机体针对肿瘤细胞的免疫反应及免疫治疗的效果.

足够数量; 最后, 活化的CTL离开淋巴结, 浸润入肿瘤组织, 并持续足够长时间杀死癌细胞[4]. 在近半个世纪里, 临床和基础医学研究者们进行了多种激活机体免疫系统识别和杀灭癌细胞的基础和临床研究. 例如, 以白介素(interleukin, IL)-2为代表的多种细胞因子的临床应用, 以淋巴因子激活的杀伤细胞为代表的细胞治疗, 以树突状细胞为代表的多种抗癌疫苗等[5]. 然而这些方法在临床试验中并未取得显著效果, 与传统癌症治疗手段相比较, 并未展示出太多的优势, 仅能作为临床治疗癌症的辅助方法. 直到近年来, 肿瘤免疫治疗才取得突破性进展. 细胞毒性T淋巴细胞相关抗原4(cytotoxic T lymphocyte antigen-4, CTLA-4)阻断抗体在多种恶性肿瘤患者身上显示出长期显著的疗效[6,7]; 2011年Ipilimumab(anti-CTLA-4 mAb)被批准上市. 细胞程序死亡蛋白1(programmed cell death protein 1, PD-1)阻断抗体在治疗多种癌症中展示出更好的疗效[8]; 两种anti-PD-1 mAb(单克隆抗体)Pembrolizuma和Ninolumab于2014年被批准上市. 以上这两种单克隆抗体针对关键肿瘤免疫抑制机制, 可以促进CTL的活化并延长其活性, 被称为免疫检查点阻断或抑制剂. 另外一种新的治疗方法嵌合抗原受体T细胞免疫疗法(chimeric antigen receptor T-cell immunotherapy, CAR-T)在治疗B细胞恶性肿瘤中达到惊人的效果, 最显著的是针对CD19抗原的CAR-T细胞治疗B细胞急性淋巴细胞白血病获得了90%完全缓解率[9,10]. CAR-T免疫治疗是利用基因转染方法使T细胞表达CAR蛋白质受体, 进而可以识别癌细胞表面的特定抗原. CAR-T细胞在实验室培养扩增后输入到癌症患者体内, 杀死具有相应特异性抗原的癌细胞[9,10]. 随着美国食品和药物管理局批准PD-1和CTLA-4阻断抗体上市, 以及CAR-T细胞疗法的扩展和深入, 免疫治疗已经从试验台走向临床, 成为继手术治疗、化疗、放疗和分子靶向治疗后又一有效的癌症治疗方法, 并且可能成为未来治愈恶性肿瘤的最有效方法[11]. 然而, 临床试验数据深度分析发现, 尽管免疫治疗提高了许多晚期恶性肿瘤患者的存活率, 但是免疫治疗无应答的发生率也较高, 特别是常见恶性肿瘤(乳腺癌、结肠癌和前列腺癌)的免疫应答率更低[12], 这表明我们对癌细胞逃避免疫监视和杀伤的机制尚未能完全了解.

肿瘤微环境(tumor microenvironment, TME)对免疫系统的激活和应答起着至关重要的作用. 完整的肿瘤组织不仅包括癌细胞, 还包括其周围的微血管、淋巴管、成纤维细胞、炎症细胞以及细胞外基质等多种成分, 同时也包括多种细胞间质以及浸润其中的生物分子, 所有的这些总和称之为肿瘤微环境[13]. TME作为癌细胞赖以生存和发展的环境, 具有低氧、低pH等特殊的理化特点, 不仅在肿瘤进展和转移中起关键作用, 对于肿瘤的治疗效果也有明显的影响[14,15]. 因此, 研究TME对免疫治疗的调控作用, 阐明部分恶性肿瘤对免疫治疗效果欠佳的机制和原因, 有助于提高免疫治疗的应答率和治疗效果. 缺氧是所有实体肿瘤的共有特征, 缺氧癌细胞内多种细胞通路被激活以适应周围环境[15]. 缺氧也加剧了癌细胞代谢的异常造成肿瘤组织酸性环境. 缺氧酸性微环境介导肿瘤对常规化疗和放疗的耐药[16], 在免疫治疗耐药中也起到非常重要的作用[17,18]. 本文就TME, 重点是缺氧酸性微环境对免疫治疗的影响机制综述如下.

1 缺氧微环境对免疫系统及免疫治疗的影响

缺氧是TME中最主要、最普遍的现象[15]. 肿瘤缺氧微环境形成原因包括癌细胞的高代谢和快速增殖导致氧消耗量超过氧供应、肿瘤周围微血管结构及血液供应异常、肿瘤慢性消耗及放化疗导致的机体贫血、化疗初期癌细胞线粒体损伤等[19]. 总体来说, 缺氧微环境可以促进癌细胞转移和浸润, 是导致治疗耐受的关键因素之一, 也是对抗肿瘤免疫反应产生抵抗的重要因素, 主要体现在以下几个方面:

1.1 缺氧微环境对T淋巴细胞的活化和功能的影响 在体外缺氧可能增加T细胞毒性, 但在大多数体内缺氧微环境中T细胞功能被抑制[20]. T细胞可通过细胞本身缺氧诱导PI3K/mTOR通路激活缺氧诱导因子(hypoxia-inducible factor-1α, HIF-1α)而不依靠外在的缺氧微环境激活[21]. 由T细胞受体激活的T细胞通过蛋白激酶C和Ca^{2+}/钙调神经磷酸酶, 在转化生长因子-β(transforming growth factor-β, TGF-β)和/或IL-6作用下, 促进HIF-1α mRNA的合成[22]. 在pO_2为2.5%时激活的$CD8^+$T细胞比在pO_2为20%时激活的细胞更易裂解[23]. $CD8^+$T细胞中VHL

基因缺失使HIF-1和HIF-2共同激活并延迟其分化为效应细胞, 但可通过增强粒酶B的表达增加CTL的细胞毒性[24], 其原因在于HIF-1可直接或间接调节穿孔素和多种粒酶[25]. 在重度缺氧(pO_2≤1%)条件下, T细胞的增殖受到抑制, 反过来可通过下调KV1.3钾通道活性来满足T细胞扩张的需求[26]. 缺氧可以抑制$CD4^+$和$CD8^+$T细胞的效应物[如干扰素γ(interferon γ, IFN-γ)]和增殖细胞因子(如IL-2)的产生[27]. 虽然HIF-1过表达对细胞因子的分泌没有影响, 但敲除VHL可增加来自$CD8^+$ T细胞的Th1型细胞因子, 表明HIF-2对此可能有直接或间接作用[25].

缺氧导致的其他继发性代谢改变也具有免疫抑制功能. 缺氧可导致癌细胞胞外腺苷积累, 而游离腺苷可以抑制效应T细胞和自然杀伤(natural killer, NK)细胞的增殖和细胞毒性[28]; 同时缺氧还可以通过HIF-1α诱导ATP水解$FoxP3^+$ Tregs上的外核苷酸酶CD39和CD73来促进腺苷的积累[29]. 缺氧还通过诱导NO合酶促进活性氮物质[30], 而后者的硝化影响T细胞受体识别同源MHC(抗原复合物)和T细胞活化的能力[31].

此外, 缺氧还可以诱导T细胞共刺激和共抑制受体的表达[17]. 在小鼠肿瘤模型中, 肿瘤内缺氧以HIF-1依赖性的方式增加肿瘤浸润性$CD8^+$T细胞表面的共刺激受体CD137的表达[32]. CD137上调可刺激肿瘤细胞的增殖及侵袭能力, 然而自发性乳腺癌却对anti-CD137的免疫治疗抵抗[33]. 通过HIF-1α依赖的缺氧诱导信号通路可诱导肿瘤细胞和骨髓来源的抑制细胞(myeloid derived suppressor cell, MDSC)过表达PD-L1[34]. 过表达PD-L1的肿瘤及其周围基质可通过PD-1与缺氧诱导的抑制T细胞的途径协同抑制T细胞的功能[35].

1.2 缺氧微环境对NK和自然杀伤T细胞的影响 目前对缺氧调节NK和自然杀伤T细胞(natural killer T cell, NK-T)的研究比T细胞少. 有研究[36]发现缺氧可以通过多种方式影响两种细胞的功能. Yamada等[37]研究发现, 激活受体NK细胞活化性受体(natural-killer group 2D, NKG2D)在NK细胞对抗肿瘤的应答反应中起关键作用, 缺氧通过HIF-1α依赖性机制诱导肿瘤细胞NKG2D配体可溶性MHC Ⅰ类分子相关蛋白A(MHC Class Ⅰ Polypeptide-Related Sequence A, MICA)的下调. 缺氧还可通过肿瘤微泡传送的TGF-β降低NKG2D的表达[38]; 同时这些微泡可导致CD107a下调[39], CD107a是经miRNA-23a传递的由NK细胞释放的细胞毒性颗粒的关键组分[40]. Sceneay等[41]发现NK细胞在TME中丧失了细胞毒性, 失去了阻止肿瘤细胞集聚的能力, 从而有助于肿瘤细胞形成转移前生长区. Baginska等[42]发现缺氧通过粒酶B诱导自噬来降解缺氧时NK介导的癌细胞裂解, 还可通过选择性降解突触连接蛋白-43负调节NK细胞对肿瘤的免疫监视. HIF-2α通过多种途径诱导NK-T细胞的免疫抑制. Zhang等[43]使用HIF-2α条件性敲除的小鼠发现HIF-2下调其Fas配体的表达、诱导其腺苷A2A受体的表达抑制NK-T细胞的功能. 尽管逆转缺氧诱导的NK和NK-T细胞功能障碍的潜在机制目前仍不明了, 但是Sarkar等[44]发现外源性IL-2的治疗可以逆转缺氧诱导的NK功能障碍.

1.3 缺氧微环境对免疫抑制性细胞的影响 肿瘤组织缺氧区域可以招募MDSC、肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)和Tregs等免疫抑制细胞[18]. HIF-1α与PD-L1近端启动子中的缺氧反应元素(hypoxia-response element, HRE)结合选择性上调MDSC上的PD-L1, 因此阻断PD-L1可使MDSC减少分泌IL-6和IL-10以增强其介导的T细胞活化[45]. 在缺氧应激和TGF-β存在的情况下, $CD4^+$T细胞通过HIF-1与*Foxp3*启动子区域HRE结合上调Foxp3诱导Tregs的分化[46]. 但在没有TGF-β的情况下, HIF-1可促进FoxP3的降解, 诱导RORγt将T细胞转变成Th17表型, 并上调存活因子延长Th17细胞的存活时间[47]. 在HIF-1稳定表达的Tregs中, Foxp3限制性VHL缺失使得Tregs倾向于Th1样表型, 这些Tregs通过HIF-1与*IFNγ*启动子HRE的结合诱导IFN-γ高水平表达[48]. 在肿瘤组织中缺氧通过影响微环境内的细胞因子吸引Tregs. Facciabene等[49]报道缺氧可增加卵巢癌细胞CCL28的表达和分泌, 而CCL28是Tregs的诱导物, 对$CD8^+$T细胞具有免疫抑制功能. TAM对肿瘤的存活、扩增、侵袭和转移有重要的作用, 维持肿瘤对机体免疫耐受[50]. 缺氧通过HIF-1诱导产生VEGF、SDFα、IL-8和G-CSF, 将未成熟骨髓细胞动员和募集到TME, 促进转化为TAM和MDSC[51]. 高表达HIF-1α可诱导NO合酶表达,

■应用要点
进一步研究肿瘤微环境和肿瘤免疫反应的关系将成为提高免疫治疗效果的关键, 在此基础上研究新的药物和方法具有广阔的应用前景.

同行评价
本文针对近年来研究热点—肿瘤缺氧酸性微环境对免疫治疗影响机制进行述评, 总结了国内外对此问题研究的全新进展, 并针对肿瘤微环境提高疗效和克服治疗耐受机制的研究提出展望. 论文内容充实, 总结较全面, 学术水平较高.

HIF-2α则会诱导精氨酸酶的表达[52], 促进TAM的分化; 此外TAM还可诱导基质金属蛋白酶(matrix metalloproteinase, MMP)-7在肿瘤缺氧区域的表达[53], MMP-7可激活其他MMPs, 如前MMP-2和前MMP9, 来促进肿瘤的细胞生长和浸润[54].

1.4 缺氧对T细胞迁移浸润的影响 缺氧诱导同源框蛋白质NANOG直接调节TGF-β1以帮助Tregs和TAM在肿瘤组织的浸润[55]. 实体肿瘤的血管化程度较低区域存在持续而严重的缺氧, 这种状态缺乏支持T细胞黏附并浸润到肿瘤中所必需的蛋白质, 因此目前各种治疗的着眼点在于如何使异常的血管正常化[56]. T细胞共抑制受体CTLA-4和PD-1的组合可以治愈大部分患有黑素瘤的动物模型[57]. 抗CTLA-4和PD-1单克隆抗体用于黑素瘤和非小细胞肺癌(仅anti-PD-1 mAb)的临床治疗, 两者的反应率达到54%; 联合应用可提高90%的转移性黑色素瘤的两年生存率[58]. 但是免疫检查点抑制剂对许多实体瘤, 如去势耐药性前列腺癌、胰腺癌和部分结直肠癌并没有作用. 因此, 研究如何将缺氧的负面影响最小化以提高免疫治疗的敏感性至关重要[59].

1.5 缺氧在肿瘤异质性形成中的作用 肿瘤异质性是恶性肿瘤的特征之一. 肿瘤细胞在生长过程中, 经过多次分裂增殖, 其子细胞呈现出分子生物学或基因方面的多样性, 从而使肿瘤细胞在生长速度、侵袭能力、对药物的敏感性等各方面产生差异[60]. 缺氧微环境是肿瘤异质性形成的关键因素, 可维持肿瘤细胞具有干细胞特性, 并驱动肿瘤细胞从增殖性向侵袭性表型的转换[61]. 缺氧通过HIF调控OCT4、SOX2和NANOG等因子的过表达维持肿瘤细胞的干细胞表型[62]. Jögi等[63]发现在缺氧条件下培养神经母细胞瘤细胞可诱导神经嵴祖细胞表达基因增加, 以及神经元标记基因减少. McCord等[64]报道缺氧胶质母细胞瘤细胞中$CD133^+$干细胞样细胞的比例增加, 并且可诱导诸如OCT4和SOX2等胚胎标志物, 这可能与HIF-2β的选择性增加相关. 在缺氧的肺腺癌细胞中使用Notch抑制剂可诱导细胞死亡, 表明缺氧可激活Notch通路[65]; Notch通路可促进角质形成细胞和某些神经干细胞分化, 表明缺氧可能会诱导并保持肿瘤细胞的干细胞表型[66]. 缺氧通过HIF介导对肿瘤细胞分化的影响, $CD133^+$神经胶质瘤干细胞靶向敲除HIF-1α和HIF-2α可以降低细胞的存活、成瘤率和血管生成的能力[67]. Yeung等[68]使用三维细胞培养技术证明缺氧抑制结肠癌细胞的分化并维持其干细胞样表型在缺氧条件下, HIF-1α可以积累并诱导肿瘤细胞的上皮-间质转化, 有利于肿瘤组织侵袭、转移扩散以及周围基质的免疫抑制[69].

1.6 缺氧在对CTL抵抗中的作用 目前, 大多数肿瘤免疫治疗策略的最终目标是诱导并增强CTL效应[70], 而缺氧可以通过多种途径诱导对CTL的抵抗. 缺氧癌细胞HIF-1α的核移位、STAT3的磷酸化和VEGF的分泌等机制抑制特异性CTL介导的细胞裂解[71]. 研究[71]表明, 沉默STAT3可抑制HIF-1α的表达及Akt磷酸化的下调, 促进缺氧条件下CTL的杀伤靶细胞能力. 研究还发现, 缺氧诱导的肿瘤细胞对CTL抵抗是通过过表达金属蛋白酶ADAM10和其相关的HIF-1α途径实现的. ADAM10是缺氧诱导的从肿瘤细胞表面触发免疫效应物的细胞溶解作用的配体(MICA)脱落所需的. HIF-1α和ADAM10的表达增加与MICA水平降低之间有密切的关系, 他们共同影响对CTL介导的细胞裂解的耐药[72].

另外, 缺氧诱导的细胞自噬在肿瘤对免疫细胞介导细胞毒性的抵抗中起重要作用. 最近的研究[73]表明, 缺氧诱导的自噬是NK细胞和CTL介导的先天和适应性抗肿瘤免疫的重要调节剂. 缺氧肺癌细胞可以通过自噬逃避CTL介导的裂解, 抑制自噬可以恢复其对CTL介导细胞裂解的敏感性, 这与磷酸化STAT3的低氧依赖性诱导的减少相关. 缺氧细胞通过泛素蛋白酶系统和SQSTM1/p62降低磷酸化STAT3水平抑制自噬并修复CTL介导的细胞杀伤作用[74]. 缺氧肿瘤细胞还可通过激活自噬逃避NK细胞介导的免疫监视, 因为缺氧细胞自噬激活时粒酶B会选择性降解, 从而抑制NK介导的靶细胞凋亡[75].

转录组学研究[76]发现, *PTPN1*、*HOXA1*和*TP53I11*是缺氧细胞中miR-210的靶基因, 而降低miRNA-210可恢复对CTL介导细胞裂解的敏感性; 相反, 沉默上述靶基因可显著降低肿瘤细胞对CTL介导细胞裂解的敏感性. 肾透明细胞癌细胞*VHL*基因出现突变并抵抗NK介导的杀伤作用[77]. 靶向沉默1,4,5-三磷酸肌醇Ⅰ型受体(由内质网释放钙介导的细胞内离子通道,

在应激诱导的细胞凋亡中起作用)可以消除NK细胞介导786-O肾细胞自噬的能力[78].

2 酸性微环境对免疫功能及治疗的影响

目前对酸性微环境对免疫功能和治疗影响的研究非常少, 大部分研究者认为微环境pH的降低是由缺氧带来的“副产品”, 因此仅在研究缺氧时对酸性微环境的作用有所关注. 酸性微环境可诱导细胞外基质重塑而增加肿瘤的侵袭性和转移性[79], 延迟细胞对致癌物的代谢, 抑制细胞对致癌物导致DNA损伤的修复[80]. 机体内的酸性微环境也被认为可以抑制免疫功能[81], 最典型的例子是乳酸性酸中毒是败血症的强阴性预后指标. 酸性微环境也可以影响免疫系统的其他组成部分, 包括DC、MDSC或巨噬细胞[82], 但具体作用及其机制目前尚不明确.

缺氧诱导的肿瘤酸性微环境是T细胞发挥功能的强大障碍, 轻至中度的缺氧对T细胞功能没有显著的影响, 重度缺氧及乳酸强烈抑制T细胞的活化、增殖和细胞毒性[82]. Wargurg效应导致乳酸聚集, 缺氧驱动碳酸酐酶和质子转运蛋白的功能, 二者结合会引起肿瘤细胞外部环境pH降低[83]. 众所周知, 活化的T细胞内pH的变化会被及时缓冲, 因此酸性微环境对T细胞的影响主要通过细胞外pH的变化而起作用[84]. 细胞外pH = 6.7时, 由IL-2诱导的T细胞增殖会停止, 而缺氧肿瘤细胞的胞外pH可以低至5.8-6.5, 此时淋巴细胞实际上处于凋亡状态, 而肿瘤细胞可以耐受并继续生长[85]. 在体外实验中, 酸性pH可以降低T细胞分泌IFN-γ和TNF-α, 表明酸性微环境可广泛阻断促炎细胞因子的产生[86]. 另外, 特定酸感受体家族可以将细胞外酸度的变化转变为细胞内的信号. 酸性微环境可以促进G-蛋白, T细胞抑制性受体及T细胞死亡相关基因-8的表达; 后者在淋巴细胞中介导c-myc的翻译与表达[87].

根据治疗性药物的分子和结构特征, 以及其在TME中的分布, 可以推测酸性微环境对其作用的影响[88]. 细胞内外pH差异所形成的pH梯度、组织液的高压和低氧压力阻碍了许多化疗药物的功能. 单克隆抗体的治疗活性取决于其是否和肿瘤细胞或免疫细胞表达的靶抗原直接或间接作用, 进而调节T细胞功能增强免疫应答. 单克隆抗体受pH影响的程度取决于本身的生化和物理性质, 以及其所处的物理化学环境. 一般认为, 弱酸环境(pH = 6-7)是mAb的最佳存在环境. 实体肿瘤组织内细胞外的酸性环境可能会降低mAb的治疗效果, 因为微环境过于偏酸会导致mAb降解最终降低其活性[89]. 利用碳酸氢盐中和黑色素瘤细胞的酸性微环境, 发现酸性微环境有明显的免疫抑制作用, 改善酸性微环境可以增加检查点抑制(anti-PD-1和anti-CTLA4)及过继性细胞治疗的持久反应率[90]. 这为抗肿瘤免疫治疗提供了一个新的方向, 即通过提高TME的pH来逆转免疫治疗抵抗, 进而提高免疫治疗的效果.

3 结论

近年来以免疫检查点阻断单克隆抗体和CAR-T细胞治疗为代表的免疫疗法在治疗恶性肿瘤方面取得突破性进展, 显示出广阔的应用前景. 几乎所有的实体肿瘤都存在缺氧微环境以及伴随的酸性环境. 由于癌细胞本身基因变异的多样性和不稳定性, 使得针对TME提高疗效和克服治疗耐受机制的研究成为最有希望的方向之一. 尽管关于TME对免疫治疗的影响和调控机制的研究仍在不断深入中, 但肿瘤缺氧酸性微环境对免疫治疗的负向调节不容忽视. 因此, 调控缺氧状态下免疫细胞对肿瘤细胞的应答, 提高T细胞、NK细胞和NK-T细胞的活性, 减低免疫抑制细胞的活性, 以及提高TME pH值, 将可能成为提高免疫治疗应答、增强免疫治疗效果的新方法.

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• 消息 •

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