

肿瘤胞外酸性微环境与缺氧交互调控 肿瘤细胞的研究进展

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摘要 胞外酸性微环境是肿瘤微环境的重要特征之一, 胞外酸性微环境主要是由肿瘤细胞的代谢重编程引起的。胞外酸性微环境在多种肿瘤中存在, 对肿瘤细胞的发生、发展及治疗的影响已成为近年来研究的主要焦点。胞外酸性微环境可促进肿瘤细胞增殖、侵袭、血管生成、免疫抑制及耐药性。开发专门针对胞外酸性微环境的新治疗方法至关重要。该研究通过靶向乳酸代谢抑制乳酸的形成, 调节胞外酸性微环境pH值的平衡, 以及设计pH敏感化学键及缺氧敏感纳米材料等方法来治疗肿瘤, 这是一种新型的治疗策略。

关键词 胞外酸性微环境; 肿瘤的进展; 缺氧; 耐药性; 免疫抑制; 肿瘤治疗

Research Progress on the Interaction between Extracellular Acidic Microenvironment and Hypoxia in Regulating Tumor Cells

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Abstract The extracellular acidic microenvironment is one of the important characteristics of the tumor microenvironment, which is mainly caused by metabolic reprogramming of tumor cells. The extracellular acidic microenvironment exists in various tumors, and its impact on the occurrence, development, and treatment of tumor cells has become a major focus of research in recent years. The extracellular acidic microenvironment can promote tumor cell proliferation, invasion, angiogenesis, immune suppression, and drug resistance. It is crucial to develop new therapeutic methods specifically targeting the extracellular acidic microenvironment. This study proposes a novel therapeutic strategy for treating tumors by targeting lactate metabolism to inhibit lactate formation, regulating the balance of extracellular acidic microenvironment pH, and designing pH sensitive chemical bonds and hypoxia sensitive nanomaterials.

Keywords extracellular acidic microenvironment; the progression of tumors; hypoxia; drug resistance; immune suppression; tumor treatment

肿瘤细胞胞外酸性微环境是一种常见的表型, 在多种肿瘤中普遍存在。胞外酸性微环境是由代谢转变使细胞外乳酸和质子积累, 导致胞外酸性微环境中的pH值降低^[1]。胞外酸性微环境在其初期起到抑癌作用, 随着持续酸化, 肿瘤细胞适应酸性微环

境, 导致肿瘤细胞增殖、迁移、侵袭及肿瘤新生血管形成^[2]。胞外酸性微环境还会损害周围健康细胞和免疫细胞功能, 削弱免疫细胞活性, 降低其识别和杀死肿瘤细胞的能力^[3]。随着肿瘤快速生长、异常血管形成和肿瘤细胞代谢改变, 氧气供应和营养无

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法得到满足,导致缺氧,缺氧会进一步加剧胞外酸性微环境中pH值降低,并使胞外酸性微环境中乳酸增加,增加的乳酸通过稳定缺氧诱导因子-1 α (hypoxia-inducible factor-1 α , HIF-1 α)促进新生血管形成,改变肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAFs)的特性,促进肿瘤进展^[4]。在缺氧状态下,细胞内会激活一系列机制,促使HIF-1 α 产生,HIF-1 α 通过调节血管内皮生长因子(vascular endothelial growth factor, VEGF)和葡萄糖转运蛋白1(glucose transporter type 1, GLUT1)的表达来促进肿瘤细胞的存活和适应,提高肿瘤细胞对化疗药物的耐受性^[5]。目前,围绕胞外酸性微环境开展的治疗肿瘤策略正成为研究的热点,主要通过减少乳酸的生成和纳米药物递送,使pH值降低,进而治疗肿瘤。纳米药物递送是一种新型治疗方法,主要通过设计微米和纳米级材料和载体来实现有效的药物递送,确保靶向和降低全身毒性^[6]。

1 胞外酸性微环境形成机制

胞外酸性微环境形成是利用葡萄糖转运蛋白(glucose transporters, GLUTs)增加葡萄糖摄取,葡萄糖在细胞质中经历代谢过程转化为丙酮酸,产生ATP和NADPH^[7]。乳酸脱氢酶(lactate dehydrogenase, LDH)催化丙酮酸转化为乳酸,单羧酸盐转运蛋白促进乳酸从细胞中排出到胞外^[8],导致胞外乳酸积聚,积聚的乳酸引起胞外酸性微环境中pH值降低^[9]。肿瘤细胞代谢重编程不仅会产生乳酸,还会产生其他酸性代谢物如质子和二氧化碳,细胞内产生的质子通过液泡V-ATP酶(vacuolar ATPase, V-ATP)、Na⁺/H⁺交换酶(sodium hydrogen exchanger, NHE)、单羧酸转运蛋白和碳酸酐酶^[10],把质子排出到细胞外,使胞外质子浓度升高,导致pH值降低。细胞代谢产生的二氧化碳随质子扩散到胞外,与水结合形成碳酸,碳酸又会解离出氢离子和碳酸根离子,氢离子增多会使酸性增强,导致pH值降低。胞外酸性微环境形成的另一个重要标志是缺氧,肿瘤细胞通过上调缺氧诱导因子HIF-1 α 的表达来适应缺氧微环境,HIF-1 α 上调糖酵解和戊糖磷酸途径相关基因的表达,促进酸性代谢产物产生^[11]。通过多种途径的综合作用,使胞外酸性微环境酸化,影响细胞的正常生理功能以及细胞内外物质交换。

2 胞外酸性微环境对肿瘤发生、发展的影响

酸性微环境是肿瘤微环境的基本特征,提供了驱动肿瘤恶性进展的能量来源。在肿瘤发展中,酸性微环境扮演重要角色,酸性微环境通过调节细胞内多种酶活性,促进肿瘤细胞增殖,还会影响肿瘤细胞表面黏附分子,调节黏附分子的表达和功能,导致肿瘤细胞活性降低,使得肿瘤细胞间连接变松散,为肿瘤细胞转移提供条件,进而影响预后生存期。酸性微环境通过影响药物摄取及分布,改变药物代谢等,影响耐药性。

2.1 胞外酸性微环境促进肿瘤细胞增殖、转移及血管生成

胞外酸性微环境是驱动肿瘤细胞侵袭和转移的诱因^[12],主要通过胞外酸化和缺氧导致肿瘤细胞增殖、迁移、侵袭及血管生成。缺氧诱导上皮-间充质转化(epithelial-mesenchymal transition, EMT)使肿瘤细胞发生侵袭、转移,还会增强VEGF和其他促血管生成因子表达水平,这些因子刺激内皮细胞增殖、迁移并形成新的血管,为肿瘤的生长和进一步转移提供营养和氧气,促进肿瘤的持续发展和恶化^[13]。缺氧状态下,HIF-1 α 被激活,激活不同信号通路,Wnt/ β -catenin、TGF- β /SMAD、PI3K/Akt/mTOR,这些信号通路促使肿瘤细胞适应缺氧环境为肿瘤细胞侵袭创造条件^[14]。胞外酸性微环境激活一些基质金属酶(matrix metalloproteinases, MMPs),这些酶可以降解细胞外基质(extracellular matrix, ECM),破坏肿瘤细胞周围的物理屏障,方便肿瘤细胞向周围组织侵袭并进入血管、淋巴管等,进而实现转移。在黑色素瘤中,pH降低促进蛋白水解酶和促血管因子分泌,增加黑色素瘤细胞侵袭和肺转移的形成^[15]。细胞外酸化还激活转移性小鼠黑色素瘤中磷脂酶D、ERK1/2、p38MAPK和NF- κ B信号通路,诱导肿瘤细胞中MMP9的表达^[16]。ROFSTAD等^[17]表明,在胞外酸性pH下,黑色素瘤细胞分泌大量蛋白酶、血管生成因子和白细胞介素-8(interleukin-8, IL-8),促进黑色素瘤细胞增殖、迁移、血管形成。胞外酸性微环境还可影响CAF的功能,CAF是肿瘤微环境中最主要的成分之一。CAF在ECM重塑和缺氧中起重要作用,CAF分泌胶原蛋白、纤连蛋白等,参与构建新的细胞外基质结构,实现对其重塑,为肿瘤迁移创造条件^[18]。CAF在缺氧条件下,分泌VEGF等因子,

促进血管形成,改善缺氧状态。在乳腺肿瘤中, CAFs变为细长和棘状,分泌I型胶原蛋白,增强基质黏附并通过信号转导,诱导细胞发生形态改变,促使其向间充质表型转化,产生具有增加硬度和排列胶原纤维的ECM,促进肿瘤细胞侵袭和迁移^[19]。CAFs在肝脏肿瘤细胞和胰腺肿瘤细胞外酸性微环境中能促进肿瘤生长,导致预后较差^[20]。胞外酸性微环境和缺氧对肿瘤细胞影响显著,可推动肿瘤细胞增殖、增强其转移能力,并利于血管形成,整体上促进肿瘤的发展。

2.2 胞外酸性微环境对免疫抑制的影响

免疫抑制是导致肿瘤发生、进展、转移和免疫治疗耐药性的重要因素^[21-22]。研究证实,胞外酸性微环境可阻碍免疫细胞迁移,影响免疫细胞代谢^[23]。同时胞外酸性微环境会改变一些免疫细胞表面受体的表达和功能,阻碍其精准识别肿瘤细胞,使免疫细胞抗肿瘤能力下降,利于肿瘤细胞逃避免疫监视与清除,进而促进肿瘤发展^[24]。缺氧也会损害自然杀伤(natural killer, NK)细胞的免疫特性,转化生长因子 $\beta 1$ (transforming growth factor- β , TGF- $\beta 1$)通过肿瘤细胞缺氧产生的外泌体转移到NK细胞,降低NK细胞活性,导致肺癌NKG2D受体脱敏和免疫抑制^[25]。HIF- α 主要与肿瘤微环境中浸润的一类巨噬细胞的M2型极化和先天淋巴细胞(innate lymphoid cells, ILCs)介导的免疫抑制有关^[26], YE等^[27]证实在胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDCA)中,缺氧通过诱导2型先天淋巴细胞(ILC2s)产生ILCregs来促进免疫抑制形成。GARCIA等^[28]表明,在PDAC自发小鼠模型中, M2型巨噬细胞和调节性T细胞(regulatory T cells, Tregs)的募集增加,在促进肿瘤微环境的免疫抑制中发挥重要作用。胞外酸性微环境形成主要是由乳酸积累导致的,研究证实,积聚的乳酸阻碍T细胞的功能,降低其增殖能力,因为T细胞在识别抗原后,需要增殖来扩大免疫反应,影响免疫应答。乳酸还会影响毒性T淋巴细胞的分化和活性,使其免疫功能受到抑制^[29]。乳酸水平升高,通过相关信号通路促进肿瘤相关巨噬细胞向M2表型极化,使M2表型标志物上调,降低诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)水平,诱导脑肿瘤发生免疫逃逸^[30]。

2.3 胞外酸性微环境导致耐药性

随着医学领域的发展,治疗肿瘤的方法越来越多,耐药性变得越来越普遍,耐药性已成为治疗癌症

的主要障碍。耐药细胞可能会导致基质金属蛋白酶高表达,降解细胞外基质,为转移提供条件^[31]。最近,研究发现胞外酸性微环境在耐药性中的研究引起广泛关注。酸性微环境通过降低化疗药物在细胞内外的浓度来降低其药效,引起肿瘤细胞耐药性^[32]。胞外酸性微环境通过影响弱碱性化疗药物解离后在细胞内摄取的情况,影响药物对肿瘤细胞等的杀伤作用,导致耐药性发生。酸性微环境阻止弱碱性药物到达其细胞内靶点,进而降低其对肿瘤细胞的毒性^[33]。在化疗中,许多药物在酸性条件下失去稳定性,导致药物活性和治疗效果降低。在放射治疗中,酸性环境可以增强某些肿瘤细胞对辐射的抵抗力,因为损伤的DNA修复机制在低pH值条件下更有效^[34]。BRAF V600E突变黑色素瘤细胞在酸性条件下也表现出对维罗非尼的耐药性。酸性微环境还导致黑色素瘤细胞对依托泊苷的抵抗力增强,依托泊甙是一种靶向活跃分裂细胞的化合物。这种类型的药物可能影响酸中毒诱导的细胞增殖,会导致耐药,并可能导致肿瘤复发^[35]。黑色素瘤细胞利用衰老产生具有干细胞样特性的肿瘤起始细胞,并获得化疗耐药性^[35]。体内实验表明,缺氧增加肿瘤细胞对药物毒性的耐受性, HIF-1 α 在癌细胞中诱导多药耐药相关蛋白1(multidrug resistance-associated protein 1, MRP1)表达,增强肿瘤耐药性。缺氧诱导因子HIF-1 α 上调通过激活COX-2途径,促进前列腺素合成,激活抗凋亡通路等机制,可增强肝癌细胞对索拉非尼的耐药性^[36]。

3 胞外酸性微环境在肿瘤治疗中的现状

恶性肿瘤是人类死亡的主要原因。随着研究不断深入,肿瘤治疗方法越来越多,近年来,肿瘤微环境中的酸性微环境和缺氧微环境是生物学和医学领域研究的热点,尤其在肿瘤中的研究备受关注。基于乳酸盐靶向治疗与纳米药物递送治疗,在肿瘤治疗中发挥重要作用。

3.1 靶向乳酸盐

在癌症治疗领域,乳酸盐代谢调节剂的开发和应用正成为研究热点,胞外酸性微环境中乳酸的积聚导致血管生成、侵袭、转移和免疫逃逸^[37]。因此,减少乳酸的形成可以改善肿瘤微环境,进而对肿瘤治疗发挥重要作用。研究发现,二氯乙酸(dichloroacetic acid, DCA)是一种免疫治疗的药物,通过抑制丙酮酸脱氢酶激酶(pyruvate dehydrogenase kinase,

PDK)的活性,抑制乳酸引起的免疫抑制作用。DCA还可以降低巨噬细胞中精氨酸酶I(arginase I, Arg1)的表达水平,促进CD8⁺ T细胞的增殖,是一种新的免疫治疗方法^[37]。二甲双胍是一种广泛用于治疗2型糖尿病的药物,通过抑制肝脏糖异生,间接减少乳酸的产生。此外,二甲双胍具有抗炎作用,这可能与它对乳酸稳态的影响有关^[38]。碳酸氢钠通过中和过量乳酸并恢复pH平衡,在治疗乳酸酸中毒中起着重要作用^[39]。乳酸脱氢酶A(lactate dehydrogenase A, LDHA)可以减少肿瘤细胞产生的乳酸,调节pH值,增强免疫细胞对肿瘤的浸润和杀伤能力^[40]。丙酮脱氢酶(propane dehydrogenation, PDH)是将丙酮酸转化为乙酰辅酶A的关键酶,可以促进丙酮酸的氧化磷酸化,减少乳酸的产生^[41]。在临床应用中,目前还没有专门针对肿瘤乳酸代谢的药物。随着研究不断深入,乳酸盐在肿瘤微环境中的作用对临床肿瘤患者的治疗和预后具有深远的意义。针对乳酸盐代谢的干预策略可能为癌症治疗提供新的途径^[42]。

3.2 pH靶向药

除了乳酸代谢外,靶向胞外酸性微环境中的pH为肿瘤治疗提供了另一种潜在的治疗方法。当前临床正在研究多种治疗方法^[43]。其中一种方法为缓冲剂碳酸氢钠,已证明具有中和肿瘤胞外酸性pH的能力,目前正在多种肿瘤的I/II期临床试验(NCT03420480)中进行评估^[44]。另一类pH靶向药物碳酸酐酶CAIX抑制剂,这是一种在肿瘤中过表达的酶,可提高pH调节并提高缺氧环境中细胞的存活率^[45]。SLC-0111等药物已进入临床试验(NCT02215850)阶段,以评估其抑制CAIX活性和增强肿瘤对治疗敏感性的疗效^[46]。质子泵抑制剂,包括奥美拉唑和兰索拉唑,通过抑制质子泵提高pH值,已经在多个临床试验中进行了评估,旨在提高化疗药物在乳腺和胃恶性肿瘤中的疗效^[47]。V-ATPase抑制剂埃索美拉唑已被批准用于临床,并已用于癌症研究^[48]。MCT1抑制剂AZD3965正在进行临床试验(NCT01791595)^[49]。总之,缓冲剂、CAIX抑制剂、质子泵抑制剂对pH的调节目前正在用于临床研究。持续的pH调节可以增强免疫记忆,有助于预防肿瘤转移。在免疫检查点阻断后立即给予pH调节剂会抑制酸性微环境的重建。尽管,靶向pH正常化有望带来好处,但由于肿瘤的多样性、酶抑制剂的异质性会影响其有效性,还需进行大量研究。

4 与纳米材料结合治疗癌症

随着生物医学技术的发展,纳米技术为药物输送提供了新型治疗策略,纳米医学是一个多学科的研究领域。主要通过设计微米和纳米级材料和载体来实现药物递送、精确靶向治疗且无毒性^[50]。纳米技术在肿瘤治疗中的应用显示出巨大潜力,特别是在靶向肿瘤微环境的纳米载体设计方面^[51]。常规化疗药物通常面临药物不易到达核心肿瘤区域、药物在正常组织中的非特异性分布以及肿瘤微环境引起的耐药性等问题^[52]。纳米载体通过靶向肿瘤微环境的缺氧和酸性特性,能精确定位肿瘤部位并释放药物,从而提高输送效率,降低对正常组织的损伤。

4.1 缺氧敏感纳米材料

缺氧通常会导致肿瘤内形成缺氧区,缺氧会促进肿瘤的侵袭和转移,以及肿瘤血管形成,诱导肿瘤细胞耐药性^[53]。缺氧敏感纳米载体利用肿瘤微环境中氧浓度的差异来进行特定的药物释放或通过感知低氧水平来增强治疗效果^[54]。一些纳米粒子被设计成在缺氧条件下分解或释放活性药物,确保在肿瘤的缺氧区内有效递送药物。研究证实,超顺氧化铁纳米颗粒可以用作药物载体,将化疗药物精确地输送到缺氧区域^[55]。超顺磁性氧化铁纳米粒子可以携带氧气并在到达缺氧区域时释放氧气,以改善局部缺氧状态,从而增强放射治疗效果^[56]。另一种策略是通过纳米载体直接增加肿瘤的局部缺氧供应,提高肿瘤对放化疗的敏感性^[57]。携带过氧化氢酶的纳米载体可以催化过氧化氢分解为产生氧气,缓解肿瘤的缺氧状态,增强放射治疗的效果。该策略增强了药物的效果,同时提高了放射治疗的敏感性^[58]。

4.2 pH纳米递送材料

肿瘤微环境中的微酸条件已成为设计新治疗策略的关键目标。设计的温和酸性响应纳米颗粒,如CaCO₃和MnO₂,可以通过消耗肿瘤细胞外基质中的H⁺来调节酸性肿瘤微环境。纳米颗粒可以在正常生理pH下保持稳定,在低pH条件下触发药物释放。开发响应肿瘤微环境酸性的纳米药物递送系统,既可以提高治疗靶向性和效率,又可以减少对正常组织的副作用,为癌症治疗提供新的策略^[59]。pH敏感纳米粒子可以在正常pH下包封疏水性药物,并在肿瘤部位的微酸性pH条件下触发药物释放。pH响应纳米载体设计用于延长血液循环,促进肿瘤部位的药物积聚,防止在达到目标之前过早释放pH响应。

纳米材料主要包括有机纳米材料、无机纳米材料和复合纳米材料。在酸性微环境下, 药物和聚合物之间或聚合物内部不稳定键的形成是pH响应有机纳米材料的关键设计策略, 通过破坏酸不稳定键, 使药物在酸性pH环境下被递送到肿瘤组织并释放^[60]。开发响应肿瘤微环境酸性的纳米药物递送系统, 既可以提高治疗靶向性和效率, 又可以减少对正常组织的副作用, 为癌症治疗提供新的策略。

5 展望

肿瘤微环境作为肿瘤的治疗靶点, 已受到广泛关注, 肿瘤微环境可以导致肿瘤细胞维持增殖信号转导、抵抗细胞死亡、诱导血管生成、激活细胞侵袭、触发促肿瘤炎症。胞外酸性微环境是肿瘤微环境与肿瘤进展相关的一种微环境。研究证实, 胞外酸性微环境影响肿瘤增殖、侵袭、血管形成及免疫抑制功能及耐药性。胞外酸性微环境成为近年来研究的热点, 通过了解胞外酸性微环境在肿瘤发生及发展的作用, 可为开发新的抗肿瘤治疗策略提供新的见解。肿瘤胞外酸性微环境已成为设计新治疗策略的关键目标, 是一个快速增长的领域, 为肿瘤治疗提供一种新型靶点。

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