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微观力学信号与生物技术在肿瘤治疗中的研究进展

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摘要 目前, 恶性肿瘤仍然是全球主要的死亡原因之一。现代癌症的治疗方法包括手术、化疗、放疗、激素治疗、免疫治疗和营养补充治疗等。然而, 由于肿瘤的多样性、异质性和不稳定性, 当前肿瘤诊疗领域仍缺乏高精度的调控手段。在微观层面上, 生物力学信号对肿瘤细胞的生长行为以及对肿瘤治疗的调控作用, 为研究肿瘤的发生发展和实现精准医疗提供了新的方向。大多数国内外研究主要聚焦于生物化学因素的作用, 却忽视了力学在生物技术领域的重大突破。该文将对恶性肿瘤的多层面、多尺度力学特征以及肿瘤生物技术治疗的研究进展进行综述。

关键词 力学; 固体应力; 流体应力; 基质刚度; 生物技术治疗

The Progress of Microscopic Mechanical Signals and Biotechnology in Tumors

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Abstract At present, malignant tumors continue to be one of the primary causes of death globally. Modern cancer treatments encompass surgery, chemotherapy, radiotherapy, hormone therapy, immunotherapy, and nutritional supplement therapy. However, owing to the diversity, heterogeneity, and instability of tumors, there is currently no high-precision regulatory approach for tumor diagnosis and treatment. On the microscopic level, biomechanical signals play a role in regulating tumor cell growth behavior and tumor treatment, offering a novel direction for research into the occurrence and development of tumors, as well as precision medicine. Most domestic and foreign studies primarily concentrate on the effects of biochemical factors, neglecting the significant breakthroughs in biomechanics within the realm of biotechnology. This review summarizes the multilevel and multiscale mechanical characteristics of malignant tumors and the advancements in biotechnology-based tumor treatment research.

Keywords mechanics; solid stress; fluid stress; matrix stiffness; biotechnology treatment

癌症是21世纪最为致命的疾病之一, 是导致死亡和发病的主要原因之一。尽管世界各国都对癌症的基础研究和临床诊疗给予了高度重视, 但当前的癌症治愈率依然偏低。由于肿瘤的多样性、异质性和不稳定性限制了传统诊断和治疗方法的临床应用, 癌症的治疗仍然面临巨大挑战。在目前的形势下, 主要的焦点是探索针对肿瘤细胞的精准高效干预手段来治疗癌症。力学干预有望成为一种经济且高效的肿瘤治疗新途径。

生物力学是从微观至宏观的多尺度层面探究力学与人体健康之间的关联[1-2]。肿瘤细胞及其所处的微环境展现出独特的机械力学属性, 这些属性

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在肿瘤的发生、发展、侵袭及转移过程中无处不在, 是癌症进展中不可或缺的驱动因素。机械力经由机械感受器的转导, 进而影响细胞的增殖、分化等生理过程[3]。细胞增殖、基质沉积及交联作用的增强会导致基质刚度提升, 从而在肿瘤及其周围组织内产生固体应力, 压迫血管和淋巴管, 致使肿瘤内部液体压力上升[4]。同时, 高度渗透的血管以及固体应力对血管和淋巴管的异常压迫, 会引起肿瘤内部间质液压力升高, 以及肿瘤边缘间质液流动速度的加剧[5]。这些力学因素, 包括固体应力、剪切应力及基质刚度, 既可独立作用, 又可相互协同, 共同对肿瘤的恶性进展、转移以及对肿瘤治疗的疗效产生影响。随着对肿瘤力学特性研究的不断深入, 力学疗法逐渐崭露头角, 成为肿瘤治疗的新途径, 即通过利用机械力对肿瘤细胞进行干预, 以抑制肿瘤的生长和转移, 例如通过调控细胞外基质的物理特性, 来控制纳米粒子在肿瘤微环境中的扩散[6]。

在癌症的发生、发展、诊断及治疗过程中, 微观力学发挥着至关重要的作用。它通过影响肿瘤细胞的力学特性、肿瘤微环境的力学因素, 以及肿瘤细胞与微环境间的相互作用等, 对肿瘤的发生和发展产生深远影响。因此, 本文综述了肿瘤细胞与肿瘤微环境相互作用的力学机制, 并阐述了在微观层面上, 如何通过调控微观力学刺激, 来激活肿瘤治疗, 进而提升肿瘤治疗的疗效。

1 原发肿瘤的微观力学信号

原发肿瘤的微观力学信号是一个复杂且多层面的研究领域, 这些信号能够激活癌细胞和基质细胞(包括内皮细胞、上皮细胞、间充质细胞和免疫细胞)中的大量机械反应途径[7]。它涉及肿瘤细胞及其微环境在力学层面上的相互作用与变化。这些信号在癌症的发生、发展、诊断和治疗过程中, 持续受到微观力的大小和持续时间的深刻影响。因此, 我们的研究聚焦于固体应力、流体应力以及基质刚度这三个方面, 以揭示它们是如何改变肿瘤细胞的增殖、存活、力的产生、可变形性、迁移及侵袭能力的。图1揭示了微观力学的特征。例如: 基于固体应力、流体应力和基质刚度的差异, 可以设计特定的力学干预手段, 如使用机械力刺激或改变细胞外基质的物理特性, 来调控肿瘤细胞的生物学行为。通过监测肿瘤微环境中力学特性的变化, 可以更早地发现肿瘤的存在, 甚至在肿瘤尚未形成明显肿块之前提前发现肿瘤的存在。通过测量和分析微观力学信号, 可以为每位患者制定个性化的治疗方案, 从而更准确地打击肿瘤细胞, 减少对正常组织的损伤[8-9]。以下是对原发肿瘤微观力学信号的深入探讨。

1.1 固体应力

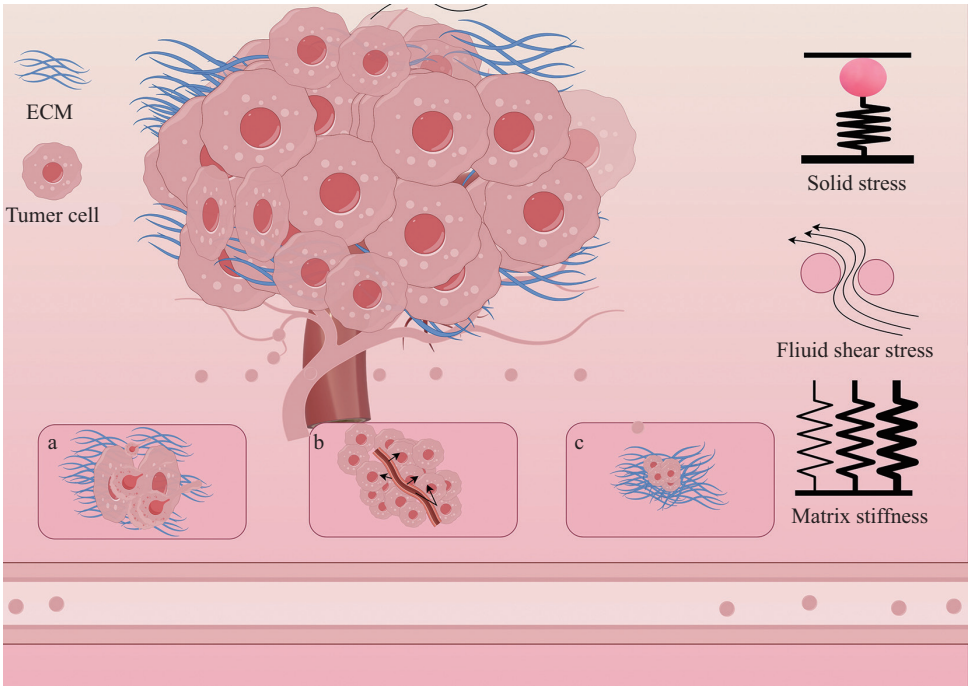
固体应力(或称固体应激)指的是由细胞外基质(extracellular matrix, ECM)及细胞生长和重塑过程中产生并传递的机械力。它通过细胞−细胞及细胞−基质的相互作用, 对肿瘤细胞施加物理力或压力, 能够破坏原发性肿瘤的组织结构, 并压迫血液和淋巴管[10]。固体应力主要分为两类: 外部施加的应力, 源于周围健康组织与肿瘤固体成分间的相互作用力; 生长诱导的应力, 它储存在肿瘤的细胞和基质成分中, 能够改变肿瘤微环境的结构组成。癌细胞的增殖和成纤维细胞的活化会导致ECM变形, 进而引起胶原纤维的拉伸、透明质酸的压缩以及正常细胞的变形[11-12]。ECM蛋白沉积会增加组织张力和肿瘤内固体应力, 从而导致缺氧增加并阻碍免疫细胞如T细胞、B细胞向肿瘤区域迁移和浸润, 导致免疫抑制[13]。固体应力对肿瘤的生长和转移有影响, 包括直接压缩癌细胞、压迫血管和淋巴管以及诱导上皮−间充质转化。研究表明, 生长诱导的固体应力和外部施加的固体应力是叠加的, 它们以两种方式分别影响癌细胞的生长导致不同的后果: 一是固体应力在肿瘤内部积聚, 直接压缩癌细胞或压迫血管和淋巴管, 在大脑中, 固体应力施加在周围脑组织上导致神经元丢失和神经功能障碍[14-16]; 二是固体应力在肿瘤内部形成压缩环境, 在乳房中, 肿瘤生长过程中积累的压应力压缩诱导乳腺癌细胞迁移和细胞骨架重塑[17-18]。当固体应力激活转化生长因子-β(transforming growth factor beta, TGF-β)信号通路时, 会诱导上皮发生上皮−间充质转化(epithelial-mesenchymal transition, EMT)。EMT使肿瘤细胞失去细胞间连接和极性, 这与肿瘤的侵袭、转移和不良预后密切相关[19-21]。此外, 固体应力还能通过整合素和肌动蛋白重排肿瘤细胞的骨架物理连接, 并通过机械转导过程将外部力学信号转化为细胞内的生化信号。这些信号进一步激活与肿瘤侵袭和转移相关的基因表达[22]。故而, 固体应力通过力学干预影响细胞行为, 改变肿瘤血管的通透性, 进而影响药物递送。

最新研究显示, 微纳米力学测试技术、生物力

学模型以及力学−生物学耦合模型等新型测量技术，将作为更为精确且高效的手段，用于测量固体应力，并开辟肿瘤治疗的新途径。因此，固体应力通过多种方式影响肿瘤的生长机制，这些机制相互交织、共同作用，使得固体应力成为肿瘤生长和转移过程中一个至关重要的因素，不容被忽视。

1.2 流体应力

流体剪切应力(fluid shear stress, FSS)是流体流动时对其所接触的周围物质施加的应力。在肿瘤微环境中，这种剪切应力主要源自异常通透性的肿瘤血管导致的血浆泄漏、淋巴引流不足以及肿瘤组织内部的液体流动[4,14]。多项研究已证实，肿瘤微环境内FSS的升高对肿瘤细胞的迁移和侵袭具有显著的促进作用。流体剪切应力对肿瘤相关的信号通路如表1所示。在特定范围内，FSS能够刺激上调一系列细胞因子或机械敏感分子，如胰岛素样生长因子-2(insulin-like growth factor 2, IGF-2)、血管内皮生长因子(vascular endothelial growth factor, VEGF)



异常细胞增殖，使周围的ECM发生位移、固体应力积累、实体瘤血管渗漏，肿瘤僵硬增加。a: 被致密ECM包围的实体瘤。由于肿瘤细胞异常增殖导致细胞过度拥挤，使ECM移位并导致固体应力的积累; b: 实体瘤中的血管渗漏会导致血浆渗漏，再加上缺乏功能性淋巴管，导致大部分肿瘤的IFP升高; c: 基质刚度的三个主要因素: (1) 基质沉积; (2) 基质收缩; (3) 基质交联。

Abnormal cell proliferation causes displacement of the surrounding ECM, accumulation of solid stress, vascular leakage in solid tumors, and increased tumor stiffness. a: solid tumors surrounded by dense ECM. Due to abnormal proliferation of tumor cells, cells become overly crowded, causing ECM displacement and accumulation of solid stress; b: vascular leakage in solid tumors leads to plasma leakage, and combined with the lack of functional lymphatic vessels, results in elevated IFP in most tumors; c: three main factors of matrix stiffness: (1) matrix deposition; (2) matrix contraction; (3) matrix cross-linking.

图1 微观力学特征

Fig.1 Microscopic mechanical features

表1 流体剪切应力影响肿瘤相关信号通路

Table 1 Fluid shear stress affects tumor-related signaling pathways

信号通路 Signaling pathways	机械敏感分子 Mechanosensitive molecules	功能 Function	参考文献 References
PI3K/AKT, c-Jun, NF-κB	IGF-2/VEGF/Cav-1	Promote the proliferation and metastasis of tumor cells	[23-24]
PI2-K, p3, JNK	IGF-1R/VEGF	Enhance the synthesis and in vitro invasion of chondrosarcoma cells	[25-26]
Smad1/5/p38MAPK, RhoA-YAP1	Caspase-8/LC3B-I	Promote autophagy of tumor cells	[28]
Ang1/Ang2-Tie2	PDGF/VEGF	Stimulate angiogenesis	[32,34]
ROCK-LIMK-YAP1		Enhance tumor cell metastasis	[35]

和小窝蛋白-1(caveolin-1, Cav-1), 并激活PI3K/AKT、c-Jun和NF-κB通路, 从而推动肿瘤细胞的增殖和转移[23-24]。最新研究发现, 低FSS(2 dyn/cm^2)通过激活胰岛素样生长因子-1受体(insulin-like growth factor 1 receptor, IGF-1R)和VEGF, 靶向PI3K、p38或JNK信号通路, 最终增强了软骨肉瘤细胞的合成及其体外侵袭能力[25-26]。当剪切应力超过一定阈值时, FSS可促进肿瘤细胞的自噬过程, 而剪切诱导的自噬是部分肿瘤细胞凋亡的原因, 流体剪切应力通过Piezo1介导的Ca^{2+}内流和钙蛋白酶的激活增强了悬浮肿瘤细胞对TRAIL介导的细胞凋亡的敏感性[27]。FSS可以激活Smad1/5/p38MAPK信号通路, 促进caspase-8或LC3B-II的裂解, 进一步促进肿瘤细胞凋亡或自噬[28]。流体剪切应力诱导肝癌干细胞增殖, 并通过RhoA-YAP1自噬途径增强球体形成能力和迁移能力[29]。同时, 由于循环系统由不同幅度的FSS组成导致不同的结果, 0.1~2.0 dyn/cm^{2}的FSS已被证实可促进肿瘤相关的血管生成和淋巴管生成, 从而增强癌细胞的移动性和侵袭性, 而在生理条件下5.0 dyn/cm^{2}的FSS受到抗CD3/CD28抗体的刺激时可以促进T细胞的活化[30-31]。血小板衍生生长因子(platelet-derived growth factor, PDGF)和血管内皮生长因子通过VEGF或Ang1/Ang2-Tie2途径, 以自分泌或旁分泌方式刺激血管生成, 导致血管系统重编程, 以募集内皮细胞形成新血管[32-34]。由于血管生成, 高渗透性的未成熟肿瘤血管导致肿瘤间质液压力(interstitial fluid pressure, IFP)升高, 在肿瘤边缘产生陡峭的压力梯度, 推动血流通过间质进入瘤周淋巴管, 导致淋巴管的扩张和增生[15]。此外, 淋巴管系统中的FSS(0.05 dyn/cm^2)促进YAP1/TAZ易位到细胞核, 通过激活ROCK-LIMK-YAP1信号轴导致细胞运动发生变化以增强其转移潜力[35]。深入研究FSS对肿瘤的影响机制可能为肿瘤治疗提供新的思路和方法。然而, 流体应力对肿瘤细胞及其微环境也存在一定的弊端。FSS会对肿瘤细胞产生直接的机械损伤, 导致细胞膜的破裂、细胞骨架的破坏以及细胞内部结构的紊乱等。此外, FSS还可能使肿瘤细胞对传统的化疗和放疗产生耐药性, 进而干扰药物的输送和分布, 从而降低治疗效果。

1.3 基质刚度

基质刚度被视为癌症进展的关键因素, 在肿瘤的发生与发展过程中扮演着举足轻重的角色。基质硬化这一现象, 主要是由癌症细胞和基质细胞对ECM的积累、收缩以及交联作用共同引起的。作为组织的固有材料特性, 刚度与固体或流体机械应力有所不同, 它主要聚焦于细胞外基质的机械力如何影响细胞行为和组织功能上[36]。基质变硬的一个核心原因是ECM的沉积与交联程度增加。当癌症相关成纤维细胞(cancer-associated fibroblasts, CAF)被TGF-β和PDGF等因子激活后, 它们会获得CAF表型[37-38]。CAF主要负责胶原蛋白的产生, 这些胶原蛋白的增加会提升基质硬度, 并诱导基质收缩。随着基质硬度的不断上升, 这会触发Src的激活以及YES相关蛋白(Yes-associated protein, YAP)与转录增强相关结构域蛋白(transcription-enhancing domain-related domain proteins, TEADs)的结合。而活跃的YAP则会促进ANLN和DIAPH3的表达, 同时稳定肌动球蛋白, 这进一步加剧了基质的硬化, 形成了一个促进恶性肿瘤增殖和侵袭的正反馈回路[39-41]。此外YAP是对外部机械力和刚度敏感的研究最充分的机械传感器之一, 它以刚度依赖性方式抑制效应T细胞的代谢重编程[42]。基于三维(3D)胶原的体外培养研究表明, ECM刚度的提升在触发侵袭性伪足组装和ECM降解方面起到了积极作用, 从而诱导了肿瘤的侵袭和转移[43]。此外, 硬度的增加还能促进免疫细胞的浸润。有研究发现, 浸润性巨噬细胞的数量与浸润性肿瘤基质的硬度之间, 以及这些巨噬细胞的数量与人类乳腺肿瘤浸润性前沿细胞中TGF-β信号转导的强度之间, 均存在显著的正相关, 这在更具侵袭性的肿瘤亚型中相关性最强[44-47]。

2 微观力学调节癌症的治疗策略

疾病进展往往伴随着细胞和组织的生化组成及其生物物理性质的显著变化。尽管许多肿瘤治疗研究已聚焦于遗传和生化过程, 但物理因素却常被忽视。机械治疗因其无创性、对癌细胞的选择性以及副作用小等潜在优势, 正受到越来越多的关注。基于微观力学的研究成果, 科学家们正致力于开发针对肿瘤的新型治疗方法。例如, 通过精准调控机械刚度的变化, 或设计特定的纳米粒子以实现肿瘤靶向递送, 从而提高抗癌效果[48-49]。此外, 利用纳米颗粒在磁场和外力的作用下产生的机械力, 或减轻对肿瘤组织施加的固体应力和剪切力, 以破坏肿瘤细胞的力学平衡, 进而抑制其生长和转移[50-52]。这

些新型治疗方法的开发, 为肿瘤治疗领域提供了新的思路和策略。

因此, 微观力学在生物技术领域对肿瘤的作用是多维度的。以下是通过针对机械微环境对肿瘤实施靶向治疗, 并基于免疫治疗、超声照射以及微磁力等手段, 来深入探索癌症的力学治疗方法。

2.1 免疫肿瘤靶向治疗

机械免疫工程是一种利用生物力学线索(如刚度和外力)对肿瘤实施靶向治疗的方法。肿瘤常采用免疫抑制途径(即免疫检查点)来逃避抗肿瘤免疫, 尤其是T细胞介导的细胞毒性[53-54]。T细胞的迁移特性和形态可直接受到环境中各种生物物理线索的影响, 其中基质刚度是最为关键的机械参数之一。

SAITAKIS团队[55]设计了一种采用不同刚度值聚丙烯酰胺凝胶水凝胶, 探究了刚度值在0.5 kPa至100 kPa范围内对预刺激的人$CD4^+$ T细胞的影响。肿瘤免疫治疗机械力相关策略和治疗机械靶点如表2所示。研究发现, 随着刚度的增加, T细胞增殖能力得到增强。这为癌症免疫疗法等应用中底物刚度的选择提供了参考, 以实现T细胞的最佳扩增, 从而增强免疫细胞的抗肿瘤能力。在调节抗肿瘤免疫中, ECM受体的整合素家族发挥着关键作用。一系列整合素阻断剂可与细胞程序性死亡–配体1(programmed cell death-ligand 1, PD-L1)抑制剂[56-57]和白细胞介素2(interleukin 2, IL-2)[58]的免疫治疗产生协同作用。因此, 肿瘤内靶向基质已成为一种改变肿瘤内免疫环境和提高疗效的方法。此外, ECM严重阻碍了药物向肿瘤组织深处的渗透, 导致了无法有效诱导肿瘤细胞发生免疫源性死亡(immunogenic cell death, ICD), 从而限制了肿瘤的治疗效果。为此, LUO团队[59]开发了一种新型纳米药物, 通过合成两种基于树状聚合物的纳米药物P-DAS和P-Epi, 实现了对ECM的重塑。P-DAS能够重编程CAFs, 抑制胶原蛋白合成和能量代谢, 减少ECM的沉积, 为P-Epi的深层渗透创造了条件。P-Epi在ECM重塑后能有效穿透肿瘤组织, 诱导癌细胞凋亡, 显著抑制肿瘤增殖, 并诱导ICD效应。PANG等[60]的最新研究发现, PIEZO1作为一种免疫力学调节剂, 可通过激活上调转录因子GRHL3, 诱导E3泛素连接酶(RING finger protein 114, RNF114)的表达。RNF114与丝状肌动蛋白结合, 导致其下调和重排, 进而降低T细胞中的牵引力, 从而提高癌症免疫治疗的效果。PIEZO1是T细胞上的机械力感受器, 可介导T细胞牵张力的变化, 进而影响T细胞毒性。它被视为促进T细胞激活的机械传感器[61-62]。另一种策略依赖于光机械致动器[63], 其中包含的纳米颗粒能够吸收红外光并在光照下收缩。粒子的快速收缩可产生皮牛顿级的力, 通过pMHC分子传递来激活T细胞。这种方法通过提高对T细胞的特异性来提高疗效并降低非特异性激活导致的自身免疫反应。综上所述, 机械免疫工程将发展成为一种与生化免疫工程相辅相成的重要方法, 旨在提高患者对免疫治疗的反应率。

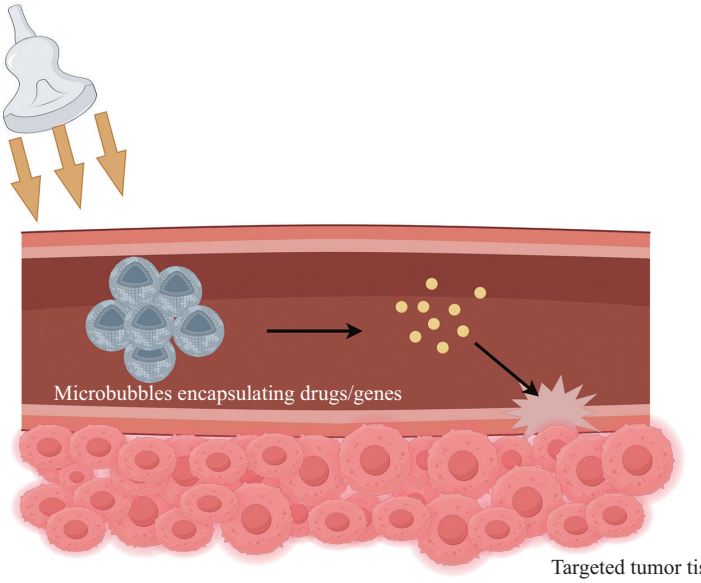
2.2 微磁力肿瘤靶向治疗

近年来, 微磁力靶向治疗作为一种操纵细胞命运的新策略, 其在抗肿瘤治疗中得到了积极开发[64-65]。这种方法通过磁性材料与磁场的耦合, 产生转化的生物物理细胞刺激(如机械力), 直接作用于肿瘤细胞, 造成肿瘤细胞损伤或诱导凋亡。该方法具有精度高、穿透深、时空可控等优势, 能够实现对肿瘤细胞的精准打击[66-68]。机械力的大小与磁性颗粒的尺寸密切相关, 而磁性颗粒的尺寸又会影响对癌细胞的机械破坏效率。大颗粒的磁性材料虽然能产生

表2 肿瘤免疫治疗机械力相关策略和治疗机械靶点

Table 2 Mechanical force-related strategies and therapeutic mechanical targets in tumor immunotherapy

治疗策略 Treatment strategies	治疗机械靶点 Therapeutic mechanistic targets	治疗效果 Therapeutic effect	参考文献 References
Increase matrix stiffness	$CD4^+$ T cells	Enhance the anti-tumor ability of immune cells	[55]
Integrin blockers can work synergistically with the PD-L1 inhibitor IL-2	Intratumoral targeting of the stroma	Alter intratumoral immune complement and efficacy	[56-58]
Nanopharmaceuticals based on dendritic polymethyl ether methacrylate	ECM	Treatment of fibroprolife rative tumors	[59]
Piezo1 antagonists	T cells	Enhance cancer immunot herapy	[60]
Optomechanical actuators	Antigen-presenting cells	Control the activation of T cells	[63]



静脉内注射微泡, 使用低频超声辐照刺激后, 肿瘤脉管系统中的微泡会发生空化, 导致内皮细胞连接处破裂。药物分子更容易渗透到肿瘤组织增加局部药物浓度。

The intravenous injection of microbubbles, after stimulation with low-frequency ultrasound irradiation, causes cavitation in the tumor vasculature, leading to rupture at the endothelial cell junctions. Drug molecules are more readily penetrated into the tumor tissue to increase the local drug concentration.

图2 超声靶向微泡破坏技术示意图

Fig.2 The schematic diagram of ultrasound-targeted microbubble destruction technology

强磁力, 但给药方式受限且存在生物代谢障碍; 而小颗粒的磁性材料则因含磁感应物质不足, 难以产生足够的机械力来杀伤肿瘤细胞[69-71]。在磁原应用中磁性纳米粒子(magnetic nanoparticle, MNP)的最佳尺寸范围通常为20~25 nm, 这一平衡区间可兼顾磁响应强度与生物相容性/组织穿透性等关键参数[72]。20 nm磁铁矿MNP已被证明可以通过施加每粒子0.2至38.9 pN的机械力来激活细胞内信号转导。CHEN团队[73]设计了有效靶向线粒体的超小尺寸磁性纳米材料(20 nm锌掺杂铁氧体纳米方块)。在旋转磁场下该纳米材料能组装成纳米尺寸的“磁力刀”, 产生约12 pN的剪切力作用于线粒体, 破坏脑肿瘤细胞的生长。微磁力治疗充分结合了可修饰微纳米材料的靶向性, 同时发挥了外加磁场进行远程无创操纵的优越性。利用磁性材料和磁性调节系统产生磁机械力, 可以实现不同模式的刺激反应, 促进纳米药物对肿瘤组织的精准靶向[74-75]。例如, MA研究团队[76]开发了一种模块化设计的工程细菌, 借助磁性纳米材料的磁热效应启动裂解蛋白的表达, 实现细菌的裂解以及抗CD47纳米抗体的释放, 从而实现对肿瘤的精准治疗。又如, ZHANG等[77]制备了透明质酸(hyaluronic acid, HA)表面修饰的聚乙烯亚胺(PEI)-PLGA载体, 共载Fe_3O_4纳米粒子和奥拉帕尼(一种抗癌药物)。由于HA能够主动靶向三阴性乳腺癌细胞表面过表达的CD44受体, 该机械平台通过不完全旋转产生磁机械力, 与奥拉帕尼协同破坏癌细胞。微磁力肿瘤靶向治疗具有广阔的应用前景。然而, 要实现该技术的临床转化, 还面临一系列挑战, 包括提高磁性材料的生物相容性、优化靶向策略、完善磁场控制系统等。

2.3 超声肿瘤靶向治疗

超声靶向治疗作为一种具有潜力的癌症治疗辅助手段, 能够利用其深层组织穿透能力和可聚焦的能量源, 产生多种生物物理效应, 如热效应、空化效应和机械效应等, 这些效应共同作用, 使肿瘤细胞与正常细胞之间的物理相互作用发生结构或功能上的改变[78-80]。这些改变进一步影响了肿瘤组织的微环境。在此背景下, 超声靶向微泡破坏技术(ultrasound-targeted microbubble destruction, UTMD)的应用日益广泛。该技术以微泡的壳或核为载体, 包裹药物或基因等物质, 并通过低频超声刺激体内微泡发生空化破裂, 图2展示了技术示意图。在此过程中, 产生的机械能(如流体流动、剪切应力、冲击波和微射流)会引发空化效应或声波化, 从而增强癌症治疗效果[81-84]。空化效应会对周围的细胞膜与血管壁施加剪切力, 导致它们的通透性增大并形成孔

隙, 进而增强细胞膜的通透性, 促进基因及药物的递送[85]。HUANG团队[86]提出了一种新策略, 他们利用HYD-NDs(一种以全氟己烷为核心、*O*-羧甲基壳聚糖为涂层材料设计的纳米药物载体)联合UTMD技术, 实现了肼屈嗪的快速释放。这一过程上调了GSDME的表达, 诱导了焦化作用, 从而精准调控了肿瘤细胞内的药物释放和焦亡过程。其中, UTMD产生的超声效应增加了局部微血管和细胞膜的通透性, 提高了物质的摄入率, 进而提升了治疗效果。ZHOU等[87]则将miR-21-5p抑制剂通过UTMD技术转染到肺癌细胞中。体内外实验结果表明, 联合UTMD技术可以显著提高基因转染效率, 并诱导肺癌细胞凋亡。UTMD技术能够实现治疗物质的定点释放, 并高效杀伤肿瘤细胞。超声波在软组织中能够产生压缩和剪切力。为探究这些力激活细胞过程的具体机制, ZAMFIROV团队[88]发现低强度聚焦超声可以激活机械敏感的RET信号通路, 诱导结肠隐窝细胞中的RET磷酸化, 使用长达数小时的超声处理, 会影响细胞表型如增殖和干性等。此外, 超声介导的机械力激活Piezo1, 使钙离子在细胞内被吸收, 钙激活的钙蛋白酶通过线粒体依赖性途径触发细胞凋亡[89]。利用超声波的机械效应产生一系列生物反应, 包括操纵中枢神经系统、靶向破坏组织和调节内源性免疫系统等, 这些新兴应用具有巨大的潜力[90]。

3 总结和展望

近几十年来, 随着生物力学研究深入到细胞分子水平, 微观力学领域也取得了不断发展, 为医学界带来了一系列新的认知和方法。研究者们开始进行深入的定量化研究, 并建立了相应的生物力学模型。肿瘤从发生、发展到最终转移, 是一个高度调控且极为复杂的病理学过程。在此过程中, 从多尺度角度探究微观力学的产生及其对肿瘤细胞及肿瘤细胞微环境的影响, 旨在为肿瘤的诊断和治疗提供指导。通过高靶向性的免疫治疗、微磁力靶向治疗以及超声靶向微泡破坏等技术手段, 我们可以实现对肿瘤细胞的精准杀伤, 并抑制肿瘤的生长和扩散。然而, 到目前为止, 对肿瘤微环境中力学问题的研究仍面临诸多挑战。由于肿瘤微环境以及生物体的复杂性, 难以在体内开展定量化实验以研究单一力学因素对肿瘤的影响, 因此肿瘤的机械力学分析仍处于起步阶段。目前, 已有基于几种机械力的策略针对肿瘤细胞的机械感觉机制来选择性杀伤, 但我们对肿瘤细胞中感知机械信号的分子元件及其下游效应通路尚未完全了解, 因此在向临床转化的过程中仍需要更多、更深入的探索。此外, 机械生物工程协同联合治疗与传统抗癌治疗相结合, 为弥补其局限性提供了一个有前途的策略。未来, 随着多学科交叉融合以及新型治疗技术的不断研发与进步, 微观力学在肿瘤治疗中的应用前景将越来越广阔, 并将在人类的健康事业中发挥重要作用。

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