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·综述·

细胞力学与细胞外基质力学在肿瘤治疗中的研究进展

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【摘要】 在肿瘤进展的过程中，肿瘤微环境的力学性质扮演着关键角色。细胞硬度与细胞外基质硬度作为核心的力学指标，通过调控细胞骨架重构、信号传导通路的激活以及代谢调节等多途径，参与肿瘤发展的调控过程。研究表明，多种实体瘤的组织硬度明显高于其相应的正常组织，而其细胞硬度却更低，口腔鳞状细胞癌的力学性质亦符合该变化，并且在肿瘤进展中具有重要调控作用。本综述回顾了肿瘤细胞及其细胞外基质硬度的分子构成与调控机制，概述当前主流的硬度检测技术，包括原子力显微镜、微流控技术和实时形变细胞仪等，重点探讨这些技术在肿瘤研究中的应用与局限性。着重分析力学性质在调控肿瘤生长增殖、侵袭转移、血管生成及淋巴管生成、耐药性以及免疫逃逸等关键过程中的作用。基于生物力学特征的肿瘤治疗策略主要包括：①通过细胞骨架调节剂或胆固醇耗竭剂靶向调控肿瘤细胞硬度以增强免疫应答；②利用基质重塑酶抑制剂、基质成分调节剂或受体阻断剂降低细胞外基质硬度以改善药物递送效率，以及结合免疫治疗或光热疗法的联合治疗以增强疗效；③使用药理学或遗传手段增强免疫细胞的机械适应性和抗肿瘤活性。本综述为创新抗肿瘤治疗策略的制定奠定坚实的理论基础，对口腔鳞状细胞癌未来的临床治疗提供新的思路和方法。

【关键词】 肿瘤；　肿瘤细胞；　肿瘤微环境；　肿瘤治疗；　细胞外基质；　硬度；　细胞力学；　细胞外基质力学；　生物力学；　免疫治疗
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Research progress on cell mechanics and extracellular matrix mechanics in tumor therapy

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【Abstract】 During tumor progression, the mechanical properties of the tumor microenvironment play a pivotal regulatory role. As core mechanical indicators, cellular stiffness and extracellular matrix stiffness profoundly influence tumor development through multiple pathways, including cytoskeletal remodeling, activation of signaling pathways, and metabolic regulation. Studies have demonstrated that the tissue stiffness of various solid tumors is significantly higher than that of corresponding normal tissues, while their cellular stiffness exhibits the opposite trend. This mechanical characteristic is also observed in oral squamous cell carcinoma and exerts crucial regulatory effects during tumor progression. This review systematically summarizes the molecular composition and regulatory mechanisms underlying the stiffness of tumor cells and extracellular matrix (ECM). Mainstream stiffness detection technologies such as atomic force microscopy, microfluidic deformation, and real-time deformability cytometry are outlined, with particular emphasis on their applications and limitations in oncology research. This review comprehensively analyzes how mechanical properties regu-

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late key processes in tumor progression, including growth, proliferation, invasion, metastasis, angiogenesis, lymphangiogenesis, drug resistance, and immune escape. This review synthesizes biomechanics-based therapeutic strategies, including: ① targeting the regulation of tumor cell stiffness through cytoskeletal modulators and cholesterol-depleting agents to enhance immune responses; ② reducing ECM stiffness by matrix remodeling enzyme inhibitors, ECM component modulators, or receptor antagonists to improve drug delivery efficiency, and combining with immunotherapy or photothermal therapy for enhanced therapeutic effects; ③ enhancing the mechanical adaptability and anti-tumor activity of immune cells through pharmacological or genetic approaches. This review establishes a robust conceptual framework for developing novel anti-tumor therapeutic strategies and provides insights for future clinical management of oral squamous cell carcinoma.

【Key words】 tumor; tumor cell; tumor microenvironment; tumor therapy; extracellular matrix; stiffness; cell mechanics; extracellular matrix mechanics; biomechanics; immunotherapy

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肿瘤发展是一个复杂的生物学过程，其形成和演变不仅受到遗传和表观遗传变异的调控，还与肿瘤微环境密切相关。近年研究揭示，肿瘤微环境的力学性质在肿瘤发展过程中扮演着核心角色[1]。口腔鳞状细胞癌（oral squamous cell carcinoma，OSCC）中，可以发现肿瘤组织的硬度显著高于正常口腔黏膜组织[2]，而肿瘤细胞却相对正常细胞更软，这种力学性质的改变与肿瘤的分化程度、浸润深度和预后呈现显著相关性[3-4]，并且主要归因于肿瘤细胞固有力学性质的转变和细胞外基质（extracellular matrix，ECM）的重构。细胞硬度作为细胞力学性质的关键指标，不仅对肿瘤细胞的生物学功能产生重要影响，还通过调控细胞外基质的物理性质，进而影响肿瘤的发展进程[5]。肿瘤细胞通过细胞骨架的重组以及细胞膜胆固醇含量的调节来降低硬度，以获得更好的迁移能力，并降低免疫细胞对自身的杀伤作用。同时，肿瘤ECM通过重塑与纤维交联增加硬度，进一步通过力学信号反馈调控肿瘤细胞行为，形成促癌的机械微环境。

伴随研究技术的演进，生物力学检测方法不断得到发展与优化。从细胞到组织水平的力学性质评估技术为深入探究肿瘤生物力学属性提供了强有力的工具[6]。力学机制在肿瘤演进过程中发挥着核心作用，其影响范围广泛，涉及细胞增殖、血管生成以及药物反应性的调控等多个维度。基于对肿瘤生物力学性质的深入理解，研究者提出了若干以力学机制为靶点的治疗策略。这些策略涉及细胞骨架系统的调控、基质硬度的调整以及力学信号传导等多个层面的干预手段，为新型抗肿瘤治疗方法的开发提出了新颖的策略与路径。本文将从细胞和细胞外基质的力学结构、细胞和细胞外基质力学特性的检测技术、细胞和细胞外基质力学在肿瘤进展中的作用以及目前新兴的机械肿瘤治疗策略等作一综述。

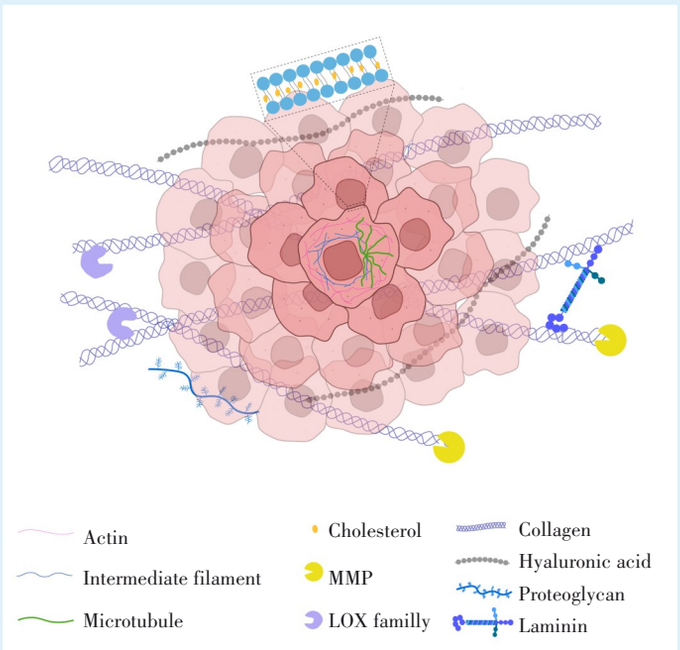
1　细胞力学和细胞外基质的力学结构

1.1　细胞力学结构

细胞的力学性能主要由细胞骨架与细胞膜协同调控（图1）。细胞骨架主要由肌动蛋白、中间丝和微管三种聚合物构成，通过动态重组（如肌动蛋白的聚合/解聚）维持细胞形态、调控物质运输，并决定细胞硬度等机械特性[7]。细胞膜中的胆固醇也是细胞硬度的主要决定因素，高膜胆固醇水平与细胞硬度降低相关[8]。

1.2　细胞外基质力学结构

细胞外基质是一种由多种大分子复合而成的复杂且动态的网络结构（图1），其力学特征对细胞生理活动具有重要调控作用[9]。ECM主要由间质基质与基底膜两大部分构成[10]。基底膜的核心成分为层粘连蛋白和胶原蛋白Ⅳ[11]。间质基质则包含胶原蛋白、弹性蛋白、蛋白聚糖、透明质酸（hylauronic acid，HA）、骨膜蛋白以及纤连蛋白等组分，其成分比例因组织而异[12]。



The composition of cell mechanical structure: actin, intermediate filament, microtubule, and cell membrane cholesterol. The composition of extracellular matrix mechanical structure: matrix metalloproteinase (MMP), lysyl oxidase (LOX) family, collagen, hyaluronic acid, proteoglycan, and laminin

Figure 1　Structural diagram of cell mechanics and extracellular matrix mechanics

图1　细胞力学和细胞外基质力学的结构示意图

2　细胞力学和细胞外基质力学特性的检测

生物力学检测技术的发展为深入研究肿瘤细胞及其微环境的力学特性提供了重要工具。根据检测对象和尺度的不同，这些技术可分为单细胞水平和组织水平两大类。

2.1　单细胞水平力学特性检测技术

2.1.1　原子力显微镜技术　原子力显微镜（atomic force microscopy，AFM）是基于探针-样品相互作用的高分辨率检测技术，通过检测微悬臂梁探针与样品间作用力引起的偏转，结合激光反射系统实现纳米级空间分辨率和皮牛级力灵敏度，可精确测量杨氏模量等力学参数[13]（图2a）。该技术虽为单细胞力学研究提供了理想工具，但其测量速度较慢、需固定样品的特点可能限制某些实验应用[14]。

2.1.2　微流控变形技术　微流控变形技术（microfluidic deformation method，MDM）基于流体力学原理，利用特定大小（15~30 μm）的微通道模拟微血管环境，通过分析细胞在流体剪切力和压力作用下的变形来评估其力学特性（图2b），特别适合循环肿瘤细胞等流动条件下的力学研究[15]，但其测量结果反映整体细胞的平均力学特性，难以获得局部区域的信息，且流体剪切力的精确控制和校准存在难度[16]。

2.1.3　实时形变细胞仪　实时形变细胞仪（real-time deformability cytometry，RT-DC）通过微流控通道中的纯剪切流场使细胞变形，利用高速摄像（>1 000 fps）实时捕获细胞轮廓并分析形变参数（图2c）。该技术无需细胞-通道接触，可在保持细胞完整性的同时实现高通量检测（每秒数百个细胞），为细胞力学研究提供了高效解决方案[17]。

2.2　组织水平力学特性检测技术

2.2.1　流变学测量　流变学测量（rheological measurement，RM）通过分析样品在剪切应力或应变下的形变或应力响应，通过计算量化肿瘤组织的静态弹性模量和动态黏弹性特征（图2d）[18]。但流变学测量难以解析异质组织中不同细胞类型的力学贡献，无法实现单细胞水平的动态力学监测，且测量环境与生理条件存在差异，可能改变细胞固有力学状态[19]。

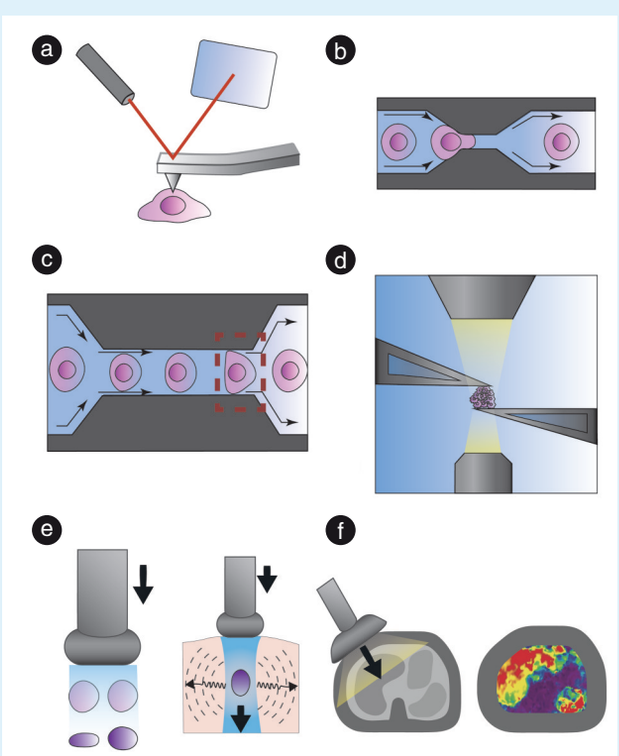
2.2.2　弹性成像技术　超声弹性成像技术主要包括两种方法：压力弹性成像（strain elastography，

SE)通过组织受压形变差异反映相对硬度[20];剪切波弹性成像(shear wave elastography, SWE)则通过测量声辐射力诱导的剪切波传播速度定量计算弹性模量[21](图2e)。该技术具有实时无创、可重复性好的优势,在浅表器官(如甲状腺、乳腺、浅表淋巴结等)检查中能获得较高分辨率[22-23]。但仍存在深部器官成像质量受限、操作者依赖性以及含气组织检测困难等技术局限[24]。

2.2.3　磁共振弹性成像　磁共振弹性成像(magnetic resonance elastography, MRE)通过体外振动器在组织中产生剪切波(频率通常为60 Hz),并利用同步的运动敏感梯度场对其在组织中的传播进行编码,通过相位重建算法提取出剪切波的波长信息,计算组织的弹性模量(图2f),其优势在于它可以获得深部组织的三维弹性分布图像[25]。

2.3　细胞力学与细胞外基质力学检测技术应用与前景

在细胞力学与细胞外基质力学检测中,几种关键技术展现出突出优势。AFM技术因其在组织微环境和单细胞测量方面的精确性,结合临床活检样本分析能力,在肿瘤诊断分型中优势显著。而MRE技术以无创三维检测能力,在肿瘤早期发现和疗效监测中展现价值。微流控芯片技术因其高通量筛查能力和自动化潜力,在个体化治疗和药物敏感性测试领域具有应用前景。多模态力学检测技术,如AFM与全息断层扫描显微镜联合应用,更能实现细胞结构与力学的同步三维解析[26]。这些技术的临床转化将受益于标准化流程的建立、便携式设备的发展和人工智能辅助分析,推动肿瘤精准诊疗发展。



a: atomic force microscopy (AFM) measures surface forces via probe deflection on a cantilever, detected by laser reflection and converted into mechanical parameters such as Young's modulus. b: microfluidic deformation method (MDM): cells deform as they pass through narrow microchannels under fluid-induced stress. The deformation extent reflects their mechanical properties. c: real-time deformability cytometry (RT-DC): cells flow through a shear region in a microfluidic channel. High-speed imaging captures deformation, enabling rapid mechanical analysis. d: rheological measurement (RM): a defined shear stress or strain is applied to the sample. The resulting response reveals its viscoelastic properties. e: strain elastography/ shear wave elastography (SE/SWE): tissue stiffness is assessed by observing deformation under compression (SE) or by measuring shear wave speed (SWE). f: magnetic resonance elastography (MRE): shear waves are introduced into tissue and visualized via phase-contrast magnetic resonance imaging to reconstruct stiffness distribution

Figure 2　Detection techniques for cell mechanics and extracellular matrix mechanics

图2　细胞力学和细胞外基质力学特性的检测技术

3　细胞力学和细胞外基质力学在肿瘤进展中的作用

3.1　肿瘤生长增殖

ECM硬度是调控肿瘤生长增殖的关键机械信号。随着ECM硬度增加,肿瘤细胞通过整合素受体感知机械应力刺激,触发受体聚集并激活下游FAK/Src信号通路。该通路通过磷酸化级联反应激活ERK2/MAPK等促增殖通路,加速DNA合成及细胞周期进展,从而驱动肿瘤增殖[27-28]。此外,ECM硬度重塑肿瘤微环境:较硬的ECM能通过增强肿瘤细胞与肿瘤相关成纤维细胞(cancer-associated fibroblast, CAF)的机械互作[29],促使CAF

分泌转化生长因子-β（transforming growth factor beta，TGF-β）、血管内皮生长因子（vascular endothelial growth factor，VEGF）等。这些因子通过旁分泌作用直接刺激肿瘤细胞增殖[30]。同时，ECM硬度变化显著影响肿瘤血管生成，改善局部氧供与营养交换效率，为肿瘤持续增殖提供了物质支持和条件保障[31]。

3.2　肿瘤侵袭转移

肿瘤侵袭转移是癌症相关死亡的主要原因。在对多种卵巢癌细胞系的研究中发现，侵袭迁移能力最强的细胞系硬度仅为最弱者的五分之一，细胞硬度与侵袭性呈现显著负相关性[32]。且软肿瘤细胞（< 400 Pa）具有高度的致瘤性和干性，而硬肿瘤细胞（> 700 Pa）则不具备这些特性，在免疫功能正常的小鼠中，仅需接种100个软肿瘤细胞即可形成肿瘤，而硬肿瘤细胞则无法形成肿瘤[33]，提示细胞硬度可作为评估肿瘤侵袭转移潜力的生物力学标志。

原发肿瘤的侵袭转移是一个复杂的过程，包括基底膜的局部侵袭和细胞迁移、穿透既有及新生血管和淋巴管、循环中细胞的存活与滞留、远处器官部位停滞和外渗、转移部位定植[34]。密集的肌动蛋白网络通过构成片状伪足和与细胞体长轴平行的应力纤维等，支持肿瘤细胞迁移[35]。研究发现，TGF-β可诱导非小细胞肺癌细胞骨架发生重塑，表现为肌动蛋白应力纤维增多、波形蛋白中间丝过表达等，可增强与周围细胞及基质黏附与伪足形成能力，有助于细胞在组织中迁移，促进侵袭[36]。Plectin是一种主要的细胞骨架交联蛋白，在肝癌中其表达上调，导致细胞骨架过度交联，促进癌细胞转移[37]。

ECM硬度在肿瘤侵袭转移中扮演关键角色。高硬度ECM通过激活机械敏感离子通道，引起细胞内钙离子浓度变化。这一变化能够驱动肌动蛋白丝重组，使肿瘤细胞前端形成片状或丝状伪足，增强迁移能力[38]。同时，高硬度ECM促使肿瘤细胞释放基质金属蛋白酶（matrix metalloproteinase，MMP）等降解酶，分解ECM成分，破坏基底膜，促进肿瘤细胞侵袭[39]。此外，高硬度ECM还能通过肿瘤细胞与其他细胞间的相互作用，促进预转移微环境形成。肿瘤细胞分泌细胞因子以激活CAF，促使CAF释放更多ECM成分和细胞因子，加剧肿瘤微环境的硬度和生化改变，吸引血管内皮细胞和免疫抑制细胞聚集，为肿瘤细胞的转移提供有利的微环境条件[40]。例如，CAF释放的TGF-β通过促进肿瘤细胞的上皮-间质转化进程，增强肿瘤细胞侵袭性[41]。

3.3　血管生成、淋巴管生成

血管生成是从已有血管形成新血管的过程，为肿瘤生长和血行转移提供营养和氧气[42]。肿瘤细胞硬度与血管生成之间存在着密切关系。在肿瘤血管生成中，肿瘤细胞硬度通过调控血管生成因子的分泌，激活相关信号通路，诱导肌动蛋白聚合形成伪足，驱动内皮细胞迁移以启动血管生成，肌动蛋白结合蛋白（如肌球蛋白）通过调节细胞收缩和形态重塑进一步促进血管成熟与稳定[43]。微管系统同样发挥重要作用，微管相关蛋白生存素可稳定微管，促进内皮细胞的增殖和迁移，进而促进血管生成，而微管解聚蛋白则具有相反的作用[44]。此外，适度提升ECM硬度可激活内皮细胞表面整合素信号通路，尤其是β3整合素，进而诱导血管内皮生长因子受体（vascular endothelial growth factor receptor2，VEGFR2）活化，促进内皮细胞迁移、增殖以及管腔构建[45]。

在肿瘤淋巴管生成中，ECM硬度作用十分关键。一方面，其变化能直接影响VEGFR3的表达和功能，促进淋巴管内皮细胞增殖、迁移及淋巴管生成[46]。另一方面，在适宜ECM硬度的环境中，肿瘤细胞可分泌特定细胞因子或生长因子，促进淋巴管生成，为肿瘤细胞的淋巴循环转移及远端播散提供有利条件[47]。

3.4　耐药性

肿瘤耐药性是现今肿瘤临床治疗面临的难点，对患者的生存和预后产生了不利的影响。肿瘤细胞硬度与耐药性之间存在着复杂的关系。研究表明，卵巢癌中顺铂耐药的卵巢癌细胞比顺铂敏感细胞更硬，且耐药细胞的肌动蛋白细胞骨架更发达，含有长的肌动蛋白应力纤维[48]。然而，也有研究发现细胞硬度与耐药性呈负相关，在结直肠癌中连接蛋白43的表达下调通过降低细胞硬度增加了细胞的干性，从而促进了耐药性[49]。

细胞骨架与细胞耐药性相关。胶质母细胞瘤中，对微管靶向药物耐药的细胞表现出α-微管蛋白和β-微管蛋白表达降低，同时干细胞特性增强[50]。乳腺癌中，波形蛋白过表达通过改变细胞力学特性对化疗药物产生耐药性[51]。Rho GTPase介导的肌动蛋白重塑影响卵巢癌细胞硬度和顺铂耐药性，Rho激活可增加细胞硬度并降低顺铂敏感

性，Rho抑制则相反[48]。

在肿瘤微环境中ECM硬度变化显著影响肿瘤细胞的生理状态与代谢途径，且与肿瘤耐药性密切相关。ECM硬度提升可过度激活肿瘤细胞内整合素信号通路，经FAK等下游分子调控细胞存活和抗凋亡蛋白表达。这些蛋白的异常表达使肿瘤细胞对化疗药物更具抵抗力，降低药物诱导的细胞凋亡效率，促进耐药性形成[52-53]。此外，高硬度ECM阻碍治疗药物在肿瘤内的有效递送，增加肿瘤耐药性[54]。ECM硬度改变还可增强肿瘤细胞药物外排能力，通过上调细胞膜上多药耐药相关蛋白1（multidrug resistance protein 1，MRP1）表达，提升肿瘤细胞将化疗药物泵出细胞外的能力，降低治疗效果，促进耐药性形成[55]。

3.5　免疫逃逸

肿瘤免疫逃逸的机制复杂多样，给临床治疗带来了诸多困难。肿瘤细胞硬度的改变可通过多种机制影响其逃逸机体免疫系统的识别和攻击。乳腺癌细胞通过免疫突触处F-肌动蛋白的快速积聚，形成“肌动蛋白反应”，阻碍细胞毒性蛋白质从自然杀伤（natural killer，NK）细胞向靶细胞的转移，并通过肌动蛋白重组形成物理屏障，阻碍免疫细胞与肿瘤细胞的接触，降低免疫细胞对肿瘤细胞的杀伤效果[56]。尿路上皮癌和肺癌波形蛋白表达上调以增强抵抗NK细胞攻击能力[57]。此外还发现，经过NK细胞杀伤后存活的胃癌干细胞，胆固醇水平明显升高，细胞硬度降低，因其能够减少NK细胞分泌的穿孔素在其细胞膜上形成孔隙，从而避免被NK细胞杀伤[58]。

在肿瘤微环境中，ECM硬度显著影响免疫细胞的渗透与活性。被基质包围的T细胞在较软的ECM中迁移能力更高[59]。ECM硬度还会影响免疫细胞的代谢与活化状态。高硬度环境促使巨噬细胞向免疫抑制的M2型极化，使TGF-β和白细胞介素-10（interleukin-10，IL-10）等细胞因子增多，进而抑制T细胞功能，促进肿瘤免疫逃逸[60]。此外，ECM硬度还能调控肿瘤细胞表面免疫检查点分子（如PD-L1）的表达，通过与T细胞表面的PD-1受体结合，抑制T细胞免疫反应，使肿瘤细胞逃避免疫攻击[61]。同时，ECM硬度变化会影响肿瘤细胞释放的外泌体等生物活性物质，这些外泌体可能携带免疫抑制分子或信号，进一步促进免疫逃逸[62]。

3.6　细胞力学和细胞外基质力学的相互作用

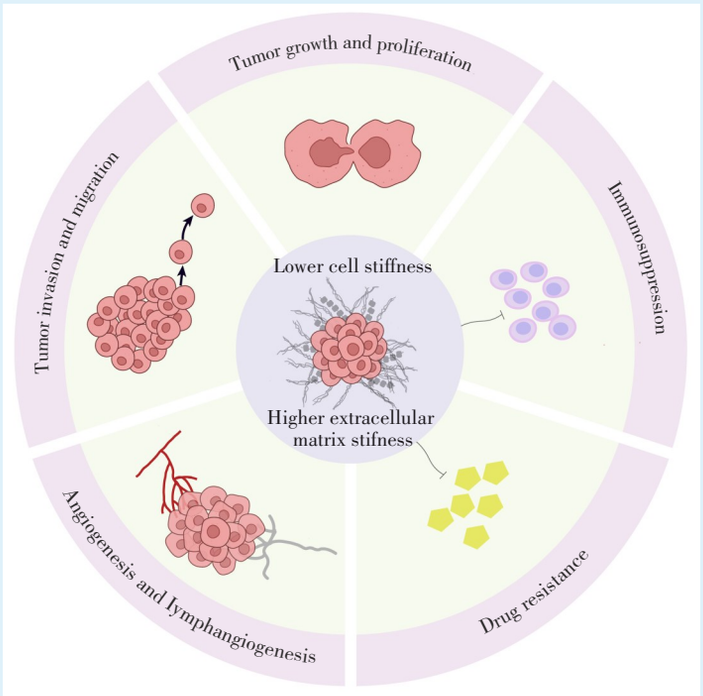
细胞力学与细胞外基质力学之间存在着紧密的双向调控关系，这种相互作用在维持组织稳态和推动病理进程方面扮演着关键角色（图3）。一方面，肿瘤细胞与ECM通过各自的力学特性直接影响彼此的生物学功能。在细胞对ECM的力学调控方面，细胞依靠主动收缩力和机械重塑能力动态地调节ECM的物理特性。例如，间充质癌细胞（如MDA-MB-231）凭借其收缩力能够诱导周围胶原纤维的排列，并导致局部基质的非线性硬化[63]。在ECM对细胞的力学反馈方面，硬质基质通过整合素介导的机械信号触发肌动蛋白应力纤维组装和YES相关蛋白（Yes-associated protein，YAP）核转位，增强糖酵解代谢与线粒体融合，激活成骨基因表达，驱动间充质干细胞向成骨分化；而软质基质通过降低细胞张力阻滞YAP入核，抑制成骨程序并倾向脂肪分化[64]。另一方面，肿瘤细胞和ECM还通过肿瘤微环境中的其他组分如CAF等，间接地调节彼此的生物学功能[65]。

4　新兴的机械肿瘤治疗策略

4.1　靶向肿瘤细胞力学以调节细胞硬度

肿瘤细胞通过降低自身硬度形成物理免疫逃逸机制，从而抵抗淋巴细胞杀伤[66]。已有诸多研究探讨了通过调控细胞骨架和胆固醇水平以增强肿瘤细胞的硬度，这一策略为肿瘤的治疗开辟了新途径（图4a）。

抗肿瘤治疗可能通过调控细胞骨架的结构和动态来发挥作用。沙利霉素能够促进肝癌干细胞中F-肌动蛋白的合成，进而导致细胞硬度的增加，抑制细胞的迁移和侵袭能力[67]。二硫化四氮唑与铜离子形成的复合物对鼻咽癌细胞展现出显著的选择性细胞毒性作用，可能归因于复合物诱导的肌动蛋白和微管细胞骨架重组导致细胞硬度的显著增加[68]。在前列腺癌的治疗中，顺铂和多西他赛显著影响了癌细胞的物理特性，表现为细胞硬度的增加和细胞侵袭、迁移能力的降低，顺铂处理增加了肌动蛋白密度，多西他赛则通过促进微管蛋白在细胞外围的积累，导致微管结构发生显著变化，揭示了这两种药物在调控细胞骨架动态平衡方面存在不同的作用机制[69]。另外，也可通过破坏细胞骨架结构来进行肿瘤治疗。应用电刺激可诱导F-肌动蛋白解聚引起肿瘤细胞的细胞骨架破坏，杨氏模量降低，还能诱导线粒体功能障碍，阻碍电子传递链和三羧酸循环途径，导致能量供应危机和最终肿瘤细胞死亡[70]。最近的研究发



This figure illustrates the critical role of cell mechanics and extracellular matrix mechanics in tumor progression, highlighting how lower cell stiffness and higher extracellular matrix stiffness collectively regulate key tumor behaviors, including tumor growth and proliferation, tumor invasion and migration, angiogenesis and lymphangiogenesis, drug resistance, and immunosuppression

Figure 3　Roles of cell mechanics and extracellular matrix mechanics in tumor progression

图3　细胞力学与细胞外基质力学在肿瘤发生发展中的作用

现，在SLC7A11高表达肿瘤细胞中，使用葡萄糖转运蛋白抑制剂可以引发二硫键应激，促使F-肌动蛋白细胞骨架中异常二硫键的形成，破坏肿瘤细胞骨架结构并诱导选择性死亡，称为“二硫死亡”[71]。

肿瘤细胞的细胞膜富含胆固醇，已有研究证明能够通过使用甲基-β-环糊精来消耗肿瘤细胞膜中的胆固醇，进而增加肿瘤细胞的硬度，并使肿瘤细胞对体外及体内T细胞介导的细胞毒性作用更加敏感，显著提高过继T细胞转移免疫疗法在实体瘤治疗中的抗肿瘤效果[8]。在OSCC中，通过氧化石墨炔介导的光动力疗法调节胆固醇水平和F-肌动蛋白，提高细胞硬度，激活细胞毒性淋巴细胞的杀伤能力[72]。在胃癌中，胃癌干细胞上调胆固醇生物合成途径，以降低细胞的机械硬度，从而使其对NK细胞释放的穿孔素不敏感，进而逃避NK细胞介导的免疫清除作用。通过基因敲除胆固醇调节元件结合蛋白2(sterol regulatory element-binding protein 2，SREBP2)或应用增强细胞硬化的药物，可以显著增强NK细胞对胃癌细胞的细胞毒性作用，为胃癌的免疫疗法开辟了潜在的治疗途径[58]。中药制剂中也发现可以通过增加乙酰辅酶A乙酰转移酶1(acetyl-coA acetyltransferase 1，ACAT1)表达水平来降低细胞膜中的胆固醇含量和细胞硬度，从而抑制肝细胞癌的侵袭和转移[73]。

4.2　靶向肿瘤细胞外基质力学以调节细胞外基质硬度

在肿瘤恶性进展中，ECM硬度增加及其生化变化至关重要。基质重塑酶、ECM组成成分和整合素等共同调控肿瘤微环境中基质的机械性质，影响癌细胞的基质感知机制，靶向这些因素以治疗肿瘤展现出良好的临床前景(图4b)。

基质重塑酶包括基质金属蛋白酶、赖氨酰氧化酶(lysyl oxidase，LOX)和肝素酶等，是ECM重塑的关键因子，通过靶向基质重塑酶以传导机械信号并提升癌症免疫治疗效果的策略展现出显著的治疗潜力。β-氨基丙腈(beta aminopropionitrile，BAPN)能抑制LOX介导的胶原蛋白交联过程，降低ECM硬度，限制肿瘤细胞迁移与侵袭[74]。但长期使用易引发不良反应，因此新型LOX抑制剂的研发备受关注。已有研究发现，基于氨基甲噻吩

结构的LOX抑制剂CCT365623，在乳腺癌动物模型中通过抑制LOX活性，降低ECM硬度，延缓肿瘤生长并减少肺部转移[75]。

ECM成分调节剂也是重要的研究方向之一。4-甲基伞形酮（4-methylumbelliferone，4-MU）通过抑制HA合成降低ECM硬度，改变其生物学功能。在多种肿瘤模型中，4-MU已被证实可抑制肿瘤细胞的增殖、迁移和侵袭能力[76]。还可通过抑制癌干细胞的激活，克服某些肿瘤细胞对化疗药物的耐药性[77]。

受体阻断剂能有效中断肿瘤细胞与ECM之间的异常信号传导，在抗肿瘤策略中扮演关键角色。例如，含有Arg-Gly-Asp（RGD）序列的肽段能特异性识别和结合整合素，干扰其功能，促进肿瘤细胞凋亡，并可作为药物载体将抗肿瘤药物精准输送至肿瘤细胞内，提升药物靶向性和治疗效果[78]。在乳腺癌模型中，DDR1特异性抗体或抑制剂可显著抑制肿瘤生长和转移[79]。

将免疫治疗策略与基质调控机制相整合的联合治疗策略展现出显著的创新潜力。例如，改造后的CAR-T细胞可过表达肝素酶，降解ECM成分，提升其在肿瘤微环境中的浸润效率，有效抑制肿瘤生长[80]。此外，通过光热疗法等物理手段调节肿瘤的基质硬度也展现出一定的治疗潜力。在肝癌中，通过光热消融技术展开针对CAF的靶向治疗能够显著软化肿瘤质地，优化肿瘤微环境，进而增强免疫治疗的效能[81]。

4.3　促进免疫细胞浸润

在肿瘤治疗领域，激活和调控免疫细胞功能是攻克癌症的关键。然而，异常的ECM重塑与细胞硬度改变显著抑制了免疫细胞的抗肿瘤活性，促使研究者探索针对免疫细胞的创新肿瘤治疗策略（图4c）。

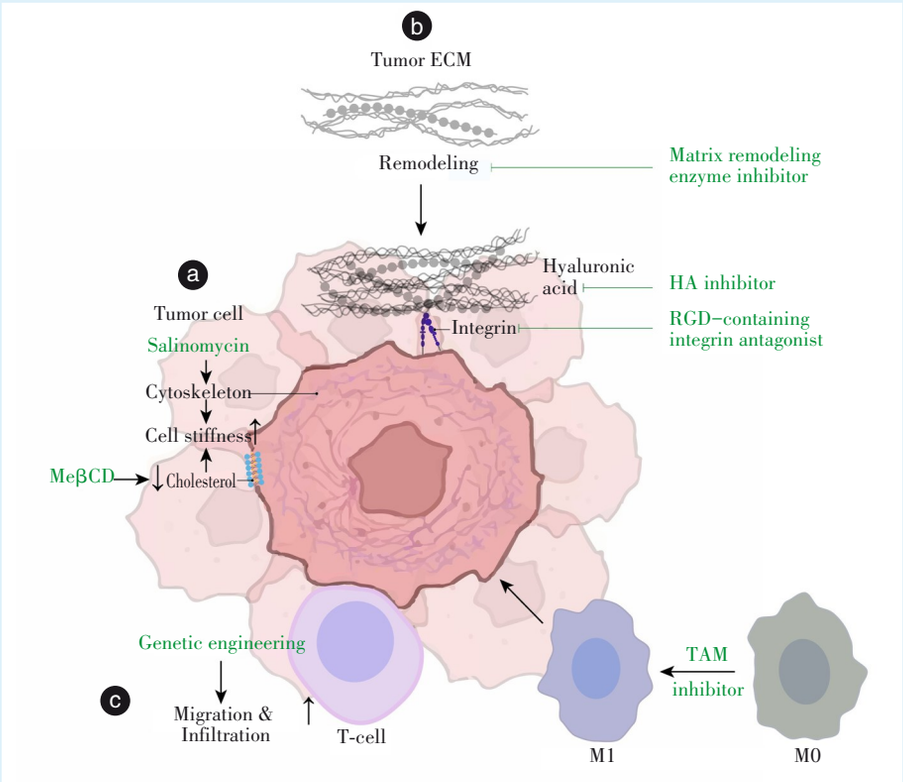
从免疫细胞的角度出发，首要任务是解决其在肿瘤微环境中的迁移与浸润问题。肿瘤ECM为抗肿瘤免疫细胞渗透至肿瘤部位提供了机械障碍。研究发现，通过药理学或遗传手段干预T细胞微管，增强Rho通路介导的皮质收缩能力，可促进$CD4^+$T细胞向变形虫样表型转变，提升其在体外三维培养环境中的渗透能力[82]。此外，基于HA的纳米疫苗可促进$CD4^+$和$CD8^+$T细胞的强力浸润，有效减轻免疫抑制性肿瘤微环境[83]。还有研究提出，肌动蛋白结合蛋白修饰的磁性纳米马达联合旋转磁场的动态调控策略，可重构肌动蛋白细胞骨架重塑肿瘤微环境，促进免疫细胞克服物理屏障并渗透到肿瘤区域，并显著增加$CD8^+$T细胞和M1型巨噬细胞的数量[84]。

其次，提升免疫细胞的固有抗肿瘤能力也至关重要。肿瘤微环境中的生物力学信号能够抑制免疫细胞的激活与抗肿瘤活性。例如，肿瘤相关巨噬细胞（tumor associated macrophage，TAM）分泌的基质金属蛋白酶能够降解ECM成分，进而促进肿瘤细胞的迁移和免疫逃逸机制。在乳腺癌中，MMP-11高表达的TAM与肿瘤的转移潜能和不良临床结局显著相关[85]。因此，研究提出设计针对TAM的特异性抑制剂或采用纳米载体技术将药物定向递送至TAM，旨在减少MMP分泌，维持ECM结构稳定性，并促进TAM向抗肿瘤的M1型极化转变，增强免疫细胞对肿瘤的杀伤效能。特定的纳米颗粒能够负载免疫调节性药物，精确定位至TAM，通过调节细胞的表型与功能，增强免疫治疗效能[86]。

5　小结与展望

近年来，随着生物力学检测技术的快速发展，原子力显微镜、微流控技术和实时形变细胞仪等先进手段不断涌现，使得对肿瘤细胞及其微环境力学性质的研究取得丰硕成果。细胞力学和细胞外基质力学，作为肿瘤微环境的关键生物物理属性，其变化不仅对肿瘤的增殖、侵袭和转移产生直接影响，还通过相互间的交互作用与调控机制，间接影响肿瘤的发展进程。然而，关于细胞力学和细胞外基质力学在肿瘤中的具体调控机制、作用途径以及靶向治疗策略的深入研究仍显不足。首先，尽管已知细胞骨架、黏着斑等参与细胞力学调控，细胞外基质的成分及交联程度直接影响其硬度，但现有研究对于这些结构与成分在肿瘤不同发展阶段的动态变化规律和精确调控机制的认知仍显不足。其次，细胞力学与细胞外基质力学影响肿瘤发生发展的详细分子机制尚未得到完全阐明。目前，针对调控肿瘤细胞及细胞外基质力学性质的靶向治疗策略尚处于初级探索阶段，亟需开发具有高特异性、显著疗效且副作用轻微的靶向药物与治疗方案。

随着对肿瘤生物学力学认知的持续深入，力学调控在肿瘤治疗领域揭示了显著的应用潜力。未来，有望开发出更为精准、高效的力学检测技术，为全面探究肿瘤细胞及其细胞外基质的力学



a: targeting cell mechanics via agents such as salinomycin (cytoskeleton remodeling) and methyl-β-cyclodextrin (MeβCD; cholesterol depletion) stiffens cells in anti-tumor therapy. b: targeting extracellular matrix (ECM) mechanics through the use of matrix remodeling enzyme inhibitors, hyaluronic acid (HA) inhibitors, and arginine-glycine-aspartate polypeptide (RGD)-containing integrin antagonists reduces ECM stiffness in anti-tumor therapy. c: genetic engineering strategies enhance tumor immunotherapy efficacy by promoting T-cell infiltration and reprogramming M0 tumor-associated macrophages (TAMs) toward the anti-tumor M1 phenotype

Figure 4　Diagram of cell mechanics and extracellular matrix mechanics in modulating tumor therapy

图4　细胞力学与细胞外基质力学影响肿瘤细胞治疗机制图

特性提供强有力的数据支持，从而为增强抗肿瘤免疫反应提供新的靶点和策略，为肿瘤治疗开拓创新路径。

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