DOI: 10.11844/cjcb.2025.07.0023
中国细胞生物学学报 Chinese Journal of Cell Biology 2025, 47(7): 1706–1722 CSTR: 32200.14.cjcb.2025.07.0023

细胞外基质硬度在细胞行为调控与疾病进展中的作用

陈锡莹 伊莉 李姝璨 胡懿文 谢珊珊*
(浙江大学医学院附属儿童医院, 国家儿童健康与疾病临床医学研究中心, 杭州 310052)

摘要 细胞外基质(extracellular matrix, ECM)是细胞外部的重要结构成分, 其不仅为组织提供物理支撑, 还通过生化和力学生物学信号调控细胞行为。近年来的研究表明, ECM硬度(stiffness)作为关键的生物物理特性, 能够显著影响细胞的形态、增殖、分化、迁移和代谢等基本生物学过程。细胞通过整合素(integrin)、踝蛋白(talin)和黏着斑蛋白(vinculin)等机械传感器感知ECM硬度, 并通过微丝骨架(actin cytoskeleton)-核骨架(nuclear cytoskeleton)机械转导通路激活YAP(Yes-associated protein)/TAZ(transcriptional coactivator with PDZ-binding motif)等关键信号网络来调控基因表达, 进而影响细胞命运。ECM硬度的变化在生理和病理过程中均发挥重要作用。例如, 在胚胎发育和组织稳态过程中, ECM硬度决定干细胞的分化方向, 并影响细胞群体的机械协调行为; 在癌症、器官纤维化、心血管疾病等病理状态下, 异常的ECM硬化或降解可驱动疾病进展, 促进ECM重塑、细胞可塑性变化及免疫微环境改造。此外, ECM硬度还可影响癌症免疫治疗的疗效, 抑制T细胞浸润, 并影响药物渗透性。因此, 针对ECM硬度的干预策略, 如靶向基质金属蛋白酶的ECM软化治疗, 正成为精准医学和个性化治疗的新兴方向。未来, 结合单细胞组学、空间转录组学及生物力学分析, 解析ECM机械信号在组织微环境中的动态变化, 将有助于构建ECM-细胞相互作用的时空图谱, 并为重大疾病的诊断与干预提供创新策略。

关键词 细胞外基质; 细胞外基质硬度; 机械转导; 细胞行为; 疾病微环境

The Role of Extracellular Matrix Stiffness in Regulating Cellular Behavior and Disease Progression

CHEN Xiying, YI Li, LI Shucan, HU Yiwen, XIE Shanshan*
(*Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou 310052, China*)

Abstract The ECM (extracellular matrix) is a crucial structural component outside the cell, providing not only physical support to tissues but also regulating cellular behavior through biochemical and mechanobiological signals. Recent studies have shown that ECM stiffness, as a key biophysical property, significantly influences fundamental biological processes such as cell morphology, proliferation, differentiation, migration, metabolism. Cells sense ECM stiffness through mechanosensors including integrins, talin, and vinculin, followed by the actin cytoskeleton-nuclear cytoskeleton mechanotransduction pathway, and regulate gene expression by activating key signaling pathways like YAP (Yes-associated protein)/TAZ (transcriptional coactivator with PDZ-binding motif), thereby determining cell fate. Changes in ECM stiffness play essential roles in both physiological and pathological

收稿日期: 2025-03-28 接受日期: 2025-05-13
国家自然科学基金(批准号: 32270723)资助的课题
*通信作者。Tel: 0571-81732387, E-mail: sxie@zju.edu.cn
Received: March 28, 2025 Accepted: May 13, 2025
This work was supported by the National Natural Science Foundation of China (Grant No.32270723)
*Corresponding author. Tel: +86-571-81732387, E-mail: sxie@zju.edu.cn

processes. For example, during embryonic development and tissue homeostasis, ECM stiffness dictates stem cell differentiation and influences the mechanical coordination of cell populations. In pathological conditions such as cancer, organ fibrosis, and cardiovascular diseases, abnormal ECM stiffening or degradation drives disease progression by promoting ECM remodeling, altering cell plasticity, and reprogramming the immune microenvironment. Moreover, ECM stiffness can impact the efficacy of cancer immunotherapy by inhibiting T-cell infiltration and affecting drug permeability. Consequently, ECM-targeted intervention strategies, such as ECM softening therapies that are modulated by matrix metalloproteinases, are emerging as promising approaches in precision and personalized medicine. In the future, integrating single-cell omics, spatial transcriptomics, and biomechanical analysis will help unravel the dynamic changes in ECM mechanical signaling within the tissue microenvironment. This will facilitate the construction of a spatiotemporal atlas of ECM-cell interactions and provide innovative strategies for the diagnosis and treatment of major diseases.

Keywords extracellular matrix; extracellular matrix stiffness; mechanotransduction; cell behavior; disease microenvironment

细胞外基质(extracellular matrix, ECM)是组织微环境的核心组成部分, 其生物化学成分和物理性质决定了细胞行为和组织稳态。ECM不仅作为细胞的结构支架, 还能通过调控细胞信号转导来影响细胞黏附、迁移、增殖、分化和凋亡等生物学过程。ECM的动态重塑对于个体发育、组织稳态、损伤修复以及疾病发生至关重要[1-2]。近年来研究发现, ECM不仅通过生化信号影响细胞功能, 其物理特性, 尤其是ECM硬度, 也在细胞行为调控和疾病进展中发挥了至关重要的作用。而ECM硬度指ECM抵抗变形的能力, 主要由其组成成分(如胶原、弹性蛋白、蛋白聚糖等)和组织结构决定[3]。ECM的硬度感知涉及整合素(integrin)-黏着斑(focal adhesion, FA)-微丝骨架(actin cytoskeleton)-核骨架(nuclear cytoskeleton)信号轴的机械转导过程, 最终影响基因表达和细胞命运决定, 对组织细胞的生理或病理过程产生影响。

细胞通过机械感受器(如整合素、talin、vinculin等)感知ECM硬度, 并通过机械转导网络影响细胞骨架张力、核骨架构象及染色质重塑。ECM的力学特性影响细胞的机械应答, 如趋硬性(durotaxis)、细胞骨架重塑及核形态变化, 这些过程涉及肌动蛋白–整合素–机械感应蛋白轴的信号传递。不同的ECM硬度可以调控细胞铺展[4-5]、细胞骨架形成[4-6]、细胞增殖[7-8]、细胞迁移[9-12]和干细胞分化[13-14]等细胞行为。例如, 间充质干细胞(mesenchymal stem cells, MSCs)在硬ECM上更倾向于向成骨细胞分化, 而在软ECM上则更易分化为脂肪细胞。此外, YAP/TAZ信号通路作为细胞机械感应的重要下游效应因子, 对细胞增殖、分化及癌症发生具有重要影响。

ECM的机械微环境在胚胎发育、器官形成及组织稳态维持过程中起关键作用。不同组织具有特定的ECM硬度, 能使细胞表现出最佳的生理功能。特定ECM蛋白的局部沉积使微环境硬度发生改变, 不仅可以提供结构支撑, 指导组织向某个方向分化, 还可以诱导信号通路改变、细胞形状改变和群体细胞迁移[1]。例如, 肺组织的ECM硬度影响肺泡形成, 心肌组织的ECM硬度决定心肌细胞的收缩能力, 而神经组织的低硬度环境促进神经元的成熟和轴突生长。然而, 在多种病理状态如癌症、纤维化和心血管疾病下, ECM硬度发生显著变化。同时, ECM硬度还可以通过影响肿瘤细胞的细胞行为调控肿瘤进程, 比如, ECM硬度通过促进肿瘤细胞的上皮–间充质转化(epithelial-mesenchymal transition, EMT)过程[15], 加速癌症进展。除此之外, ECM硬度还可以通过促进成纤维细胞向肌成纤维细胞转变, 加速ECM(胶原等)的沉积, 使局部病理微环境进一步硬化, 又循环加重纤维化或癌症进展[16]。

本综述将系统探讨ECM硬度如何通过机械转导影响细胞行为, 重点解析其在细胞增殖、分化、迁移、凋亡及疾病进展中的作用, 并讨论靶向ECM硬度的潜在治疗策略, 以期为未来研究和临床应用提供新思路。

1 细胞外基质硬度

ECM是所有组织器官的基础成分, 在生物体的整个生命周期中发挥核心作用。ECM由数百种成分

组成, 各种组成成分能够相互交联结合, 形成多样化的几何构型、空间形态和拓扑结构等, 构成一个巨大且复杂的3D网络状结构。同时, 这些组成成分的各种交联与排列为ECM的动态重塑提供了几乎无限的排列组合方式, 以响应机体或细胞的变化[17]。

近年来, 越来越多的研究表明, ECM不仅通过生化信号调控诸多的细胞行为和影响发育、疾病等重要的生理进程, 还通过物理信号对细胞功能产生重要调节作用。ECM的关键物理特性包括基质硬度(matrix stiffness)、基质拓扑结构(matrix topology)、基质黏弹性(matrix viscoelasticity)、基质延展性(matrix extensibility)和基质顺应性(matrix compliance)等[18-25]。这些物理因素具有高度的组织特异性, 不同组织为了维持其独特的生理功能, 会展现出特定的机械特性[24,26-28]。硬度作为关键的ECM物理特性, 已被发现在不同的组织中具有不同的硬度特征, 尤为重要的是在病理条件下也常常伴随组织硬度的变化(表1)。因此, 越来越多的研究开始聚焦于ECM硬度在生理病理中的重要作用, ECM硬度目前已被发现参与调控细胞黏附、增殖、凋亡、迁移、代谢和分化等多种生物学过程, 影响细胞的生理功能及病理状态。

而ECM硬度变化的内在原因是构成ECM的成分或结构发生了变化。根据定位和组成, ECM主要可分为两大类: 间质基质(interstitial matrix)和高度特化的器官(组织)特异性基质, 如基底膜(basement membrane)。间质基质包围细胞, 主要由I型胶原(collagen I)、纤连蛋白(fibronectin)和弹性蛋白(elastin)等组成, 提供细胞间的支架结构。基底膜在结构上比间质基质更紧密, 主要由IV型胶原(collagen IV)、层粘连蛋白(laminin)、蛋白聚糖(proteoglycans)和其他蛋白等组成, 为上皮细胞、血管内皮细胞及其他结构提供支持[1,62]。目前认为, 在功能上间质基质决定了组织器官的硬度特性, 并支持间充质细胞的功能, 比如纤维化疾病中间质基质过度积累; 而基底膜有助于支撑和稳定组织结构, 使细胞极化并形成机械和物理屏障(肾小球滤过、血脑屏障等)[63-65]。

胶原是ECM中最丰富的成分, 可分为纤维状(包括I~III、V和XI型胶原)和非纤维状[66]。目前对于胶原力学特性的测量主要集中在来源于肌腱的胶原纤维(collagen fibril), 并由于测量环境和分析模型的不同, 压痕模量具有一定差异, 但总体在GPa级别以上[21,67]。肌腱中主要的胶原成分为I型胶原, 而在肌腱损伤愈合的过程中III型胶原和纤连蛋白表达水平升高[68]。胶原的结构和特殊的结构域能够发生碳化(mineralized)从而形成坚硬的ECM(骨骼中的ECM)[60,69]。而在肺组织和皮肤组织中, III型胶原的含量相对较高[67]。在肺纤维化中, 胶原交联失调导致组织硬化[70]。以上研究提示, 胶原纤维的成分和结构改变了ECM基质硬度, 这种间质基质的力学特性在维持生理环境或影响病理进程中具有关键作用。弹性蛋白也是间质基质的组成部分, 为组织提供力学信号, 具有高杨氏模量[21,71-72]。弹性蛋白和胶原一样也可以形成纤维网络, 而在胶原仿生支架中, 加入弹性蛋白, 能够降低胶原支架的硬度[73]。由此可见, 这些主要的ECM蛋白具有不同的杨氏模量, 并以不同的方式交联排列, 影响ECM的硬度。因此, ECM硬度主要由其组成成分(如胶原、弹性蛋白、蛋白聚糖等)和组织结构决定, 是ECM抵抗变形的能力[74]。

2 细胞感知细胞外基质硬度的分子机制

细胞通过自身的机械转导系统来感知并响应细胞外微环境中的硬度变化, 并传递到细胞内, 引起细胞内的生物级联反应。这一过程通常涉及几个关键步骤, 包括细胞的物理变形、机械传感器对机械信号的感知、机械信号与化学信号的转化以及下游信号通路的传递过程[25]。目前研究认为, ECM-细胞表面受体(如整合素等)-机械感应蛋白(如talin和vinculin等)-微丝骨架是主要的机械转导轴, 在细胞对机械信号的感知及生物学效应中发挥关键作用[75]。

机械信号的传递过程一般是在力的作用下通过改变蛋白的折叠结构, 暴露其隐藏的结合位点, 从而改变蛋白结合的亲和性, 来启动机械信号的感应过程, 而细胞黏附受体的密度、受体间的距离以及ECM配体的结构在机械信号传递的过程中具有非常重要的作用[76-78]。具体可表现为, 来自于ECM的力学作用(硬度)可以打开整合素弯曲的头部结构, 并将腿部的α和β亚基结构分开, 激活并增强其对ECM配体的亲和力, 允许talin蛋白与β亚基结合。而talin[74]和vinculin[79]等机械感应蛋白能在力作用下发生构象变化, 从而暴露其隐藏的结合位点, 介导下游信号的传递。但是只有当力达到一定的机械阈值时, talin才能发生去折叠并打开C-端结构域, 使其能够与微丝骨架结合[80-81], 同时促进vinculin以及其他蛋白的局部聚集, 进一步增强黏着斑的成熟; 而一旦低

表1 生理或病理情况下的组织硬度

Table 1 Elastic moduli of tissues under physiological or pathological states

组织 Tissue	生理 Physiological state	病理 Pathological state	文献 References
Brain	1.89±0.59 kPa (white matter) 1.39±0.29 kPa (grey matter)	/	[29]
	~0.4 kPa	~0.1 kPa	[30]
Adipose	~1 kPa	/	[31-32]
Liver	0.3-0.6 kPa	1.6-20 kPa	[33-35]
	3.6-4.1 kPa	3.7-20 kPa (fibrosis) 4.8-50 kPa (cirrhosis)	[36]
	4.5-5.5 kPa	5.0-10.8 kPa (chronic heart failure) 8.3-18.8 kPa (acute decompensated heart failure)	[37]
Lung	~10 kPa	~25-35 kPa	[33,38]
	1.4±0.4 kPa	/	[39]
	1.96±0.13 kPa	16.52±2.25 kPa	[40]
	3.7±1.3 kPa	18.9±11.1 kPa	[41]
Heart	12±4 kPa (embryonic) 39±7 kPa (neonatal)	~120 kPa	[42-44]
	2.2±0.7 kPa	4.6±1.2 kPa	[45]
Kidney	/	7.76±5.16 kPa (without fibrosis) 12.83±9.80 kPa (with fibrosis)	[46]
	15.55-29.70 kPa	32.22-44.54 kPa	[47]
Breast	0.4-2 kPa	4-12 kPa	[33]
	~400 Pa	>5 kPa	[48]
Pancreas	1.06±0.25 kPa	2.15±0.41 kPa (pancreatitis) 5.46±3.18 kPa (tumors)	[49]
	/	1.24±0.13 kPa (fibrosis stage, F0) 1.42±0.12 kPa (fibrosis stage, F1) 1.65±0.08 kPa (fibrosis stage, F2) 1.94±0.28 kPa (fibrosis stage, F3)	[50]
Colon	0.8±0.4 kPa	2.4±1.83 kPa	[51]
Bone	1.3-7.8 GPa (cancellous bone) 12-20 GPa (cortical bone)	/	[31,52]
	1.28-1.97 GPa (young-old)	/	[53]
	2-14 GPa	>689 MPa	[33]
Thyroid	15.9±7.6 kPa	36±30 kPa (benign nodules) 150±95 kPa (malignant nodules)	[54]
Cornea	696±113 kPa	/	[55]
	281±214 kPa (anterior stroma) 89.5±46.1 kPa (posterior stroma)	/	[56]
	1.9-4.2 kPa (anterior stroma) 1.6-2.9 kPa (posterior stroma)	/	[57]
	7.5±4.2 kPa (anterior basement membrane) 109.8±13.2 kPa (bowman's layer) 33.1±6.1 kPa (anterior stroma) 50±17.8 kPa (descemet's membrane)	/	[58]
Trabecular meshwork	4 kPa	80.8 kPa	[59]
Lens	/	353.36±321.57 kPa (nondiabetic) 221.92±161.18 kPa (diabetic)	[60-61]

于这个机械阈值, 整合素就会在talin展开之前脱离并释放力[82-83]。

在软的ECM硬度环境中, 整合素和ECM初始激活并结合, 形成瞬时焦点黏附(transient focal points), 并与F-actin(filamentous actin)呈松散的结合状态。而在硬的ECM硬度上, 大量整合素被招募并聚集, 与ECM形成稳定的结构[80,84], 来自于硬的ECM的力学作用打开了诸如talin、vinculin等机械蛋白的

折叠结构，使得talin、vinculin、黏着斑激酶(focal adhesion kinase, FAK)能够与成簇的整合素结合，形成复合物，该复合物进一步连接具有高度收缩力的微丝骨架(应力纤维)。该过程帮助新生黏附(nascent adhesions)向成熟的黏着斑转变[3,83,85-86]。

细胞感知ECM硬度的另一个关键机制是黏着斑离合器(focal adhesion clutch)模型。在该模型中，微丝骨架通过整合素黏附复合物连接到ECM，并受细胞前缘(leading edge)微丝聚合产生的推力和细胞中央肌球蛋白II(myosin II)收缩力的共同作用，形成微丝(肌动蛋白)的逆行流动(actin retrograde flow)[75]。当微丝骨架与ECM连接时，该肌动蛋白的流动可拉动基质并引发形变。而整合素和连接蛋白(如talin等)以适中的速率移动，通过摩擦力降低肌动蛋白的逆行流动速度，从而促进力的传递[75,87-88]。在硬的ECM环境中，离合器紧密结合，力的传递效率高；而在软的ECM上，较少的离合器被激活，力传递较少，导致细胞骨架张力降低。此外，细胞可以通过调控myosin II的收缩性和细胞骨架张力，动态调整自身的弹性模量，以适应局部微环境的机械特性[33]。

除了整合素–黏着斑–细胞骨架轴外，核膜也是细胞内重要的机械感应装置。机械转导通过近端机械感应装置传递到微丝骨架后，能够进一步通过LINC(the linker of nucleoskeleton and cytoskeleton)复合物(包括nesprins、SUN等)和核骨架连接，实现力的核转导，并最终影响基因表达[89-90]。比如，微丝骨架的张力变化能够使细胞核形变，打开细胞核的核孔结构允许转录调控因子YAP的核易位，激活下游的转录反应，调控诸如增殖和分化的进程[91-92]。这种通过机械信号调控转录因子的方式，远快于传统的生化信号转导机制[93-94]。因此，细胞内在骨架之间机械传递的建立在细胞功能的调节过程中具有十分重要的意义。

此外，细胞还存在其他力学感应通路。PIEZO(包含PIEZO1和PIEZO2)是一个非常重要的机械激活的阳离子通道，对钙离子(Ca^{2+})信号具有偏好性。PIEZO1可以响应多种机械刺激，而PIEZO2的激活似乎对机械刺激的类型具有一定选择性[95-97]。机械刺激改变了膜张力使PIEZO1从弯曲–闭合(curved-closed state)状态向平坦–开放(flattened-open state)状态转变，在此过程中PIEZO1的关键结构域改变引起离子渗透途径从闭合向开放转变，离子信号内流，形成机械转导路径。而PIEZO2也具有与PIEZO1相似的弯曲–闭合构象，但目前尚未证实PIEZO2是否也依赖这种基于膜曲率的门控机制[95]。DDR1(discoidin domain receptor tyrosine kinase 1)是一种新发现的机械传感器，在血管平滑肌细胞(vascular smooth muscle cells, VSMCs)中响应ECM硬度变化，发生寡聚化、内吞和磷酸化。这一激活过程可诱导DDR1的液–液相分离(liquid-liquid phase separation)，导致Hippo信号通路的丝氨酸–苏氨酸蛋白激酶LATS1(large tumor suppressor kinase 1)聚集并失活，从而释放YAP1并促进其核定位，最终调控细胞增殖和存活[98]。

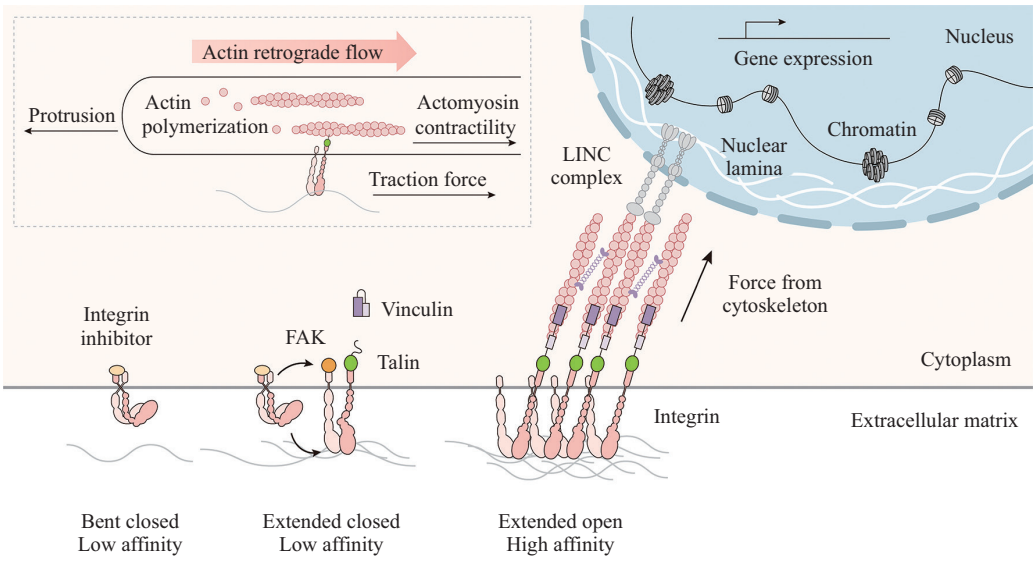
综合以上机制，细胞在感受并响应外界力学信号时，可以通过去折叠整合素、talin、vinculin等机械敏感蛋白的结构，形成成熟的黏着斑复合物并进一步和微丝骨架相连，微丝骨架又可以通过LINC复合物和核骨架相连调控下游基因的表达(图1)，也可通过改变门控离子通道的结构，引起离子流，进行机械转导。细胞通过这种力学响应，调节跨膜受体、重组细胞骨架结构、调控肌球蛋白收缩以及细胞骨架张力，动态改变自身的弹性模量，进而重塑局部微环境实现机械平衡[33]。

3 细胞外基质硬度对细胞基本生物学行为的调控

研究表明，ECM硬度在细胞行为的调控中发挥至关重要的作用，影响细胞的形态和骨架重塑、细胞增殖、细胞分化、细胞迁移和细胞凋亡等过程(图2)。不同组织的ECM硬度存在显著差异，而细胞通过机械转导机制感知ECM硬度，并通过整合素、黏着斑以及Rho(Ras homolog family member)-ROCK(Rho associated coiled-coil containing protein kinase)信号轴调控自身生物学特性。深入研究ECM硬度对细胞基本行为的影响，有助于理解生物物理信号在细胞命运决定中的作用，并为组织工程、再生医学及肿瘤治疗提供新的研究思路。

3.1 细胞形态和骨架重塑

ECM硬度的改变可以引起细胞的形态变化和内部细胞骨架结构的重排，包括微丝骨架和核骨架等。相较于软基质，在硬基质上培养的细胞具有更好的铺展和微丝骨架的形成[4-5]。微丝细胞骨架本身是一个高度动态的多态结构，作为关键的机械感应骨架，能够在生物力学刺激下迅速重组。结合计算



ECM的力学作用可以帮助蛋白去折叠, 增强配体和受体结合的亲和力, 引起机械转导过程。细胞通过整合素感应ECM的硬度变化, 在ECM的硬度的作用下能够打开整合素弯曲的头部结构, 并将腿部的α和β亚基结构分开, 细胞内–外信号能够帮助移除整合素抑制蛋白, 允许talin蛋白结合在整合素的β亚基上。力达到一定的力学阈值可以打开talin和vinculin的折叠结构, 并通过talin打开的C-端结构域和微丝骨架进行结合, vinculin进一步增强了这种结合作用。而微丝骨架可以通过LINC复合物和核纤层进行连接, 引起核纤层的改变, 导致染色质结构和分布改变, 影响下游基因的转录。而微丝骨架上myosin II产生的收缩力通过微丝骨架和整合素黏附复合物作用在ECM上, 拉动ECM并使其变形。这种来自细胞中央myosin II的收缩力与细胞前缘微丝骨架聚合产生的推力共同作用, 驱动微丝骨架的逆行流动。

The mechanical role of the ECM can assist in protein unfolding, enhance the binding affinity between ligands and receptors, and trigger mechanotransduction processes. ECM stiffness allows integrins to extend and separate the α and β subunit legs. Inside-out signals help remove integrin inhibitor, allowing talin to bind to the integrin β subunit. The structures of talin and vinculin can be unfolded only when ECM stiffness exceeds a certain threshold. Further, the exposed C-terminal domain of talin binds to the actin cytoskeleton, with vinculin further reinforcing this binding. Actin cytoskeleton connects to the nuclear lamina through LINC complex, inducing alterations in the nuclear lamina that lead to chromatin structure and distribution changes, ultimately affecting gene transcription. Meanwhile, tension generated by myosin II is exerted on the ECM through actin cytoskeleton and integrin adhesion complexes, pulling and deforming the ECM. Contractility generated by myosin II from the cell center cooperates with protrusion forces produced by actin polymerization at the leading edge, driving the actin retrograde flow.

图1 细胞的机械响应过程(根据参考文献[80,88]修改)

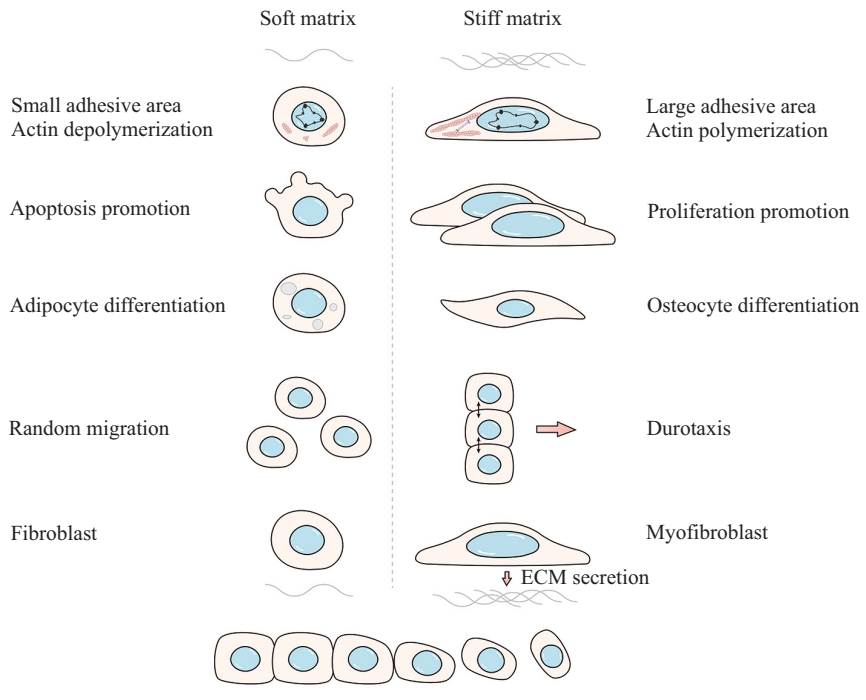
Fig.1 Cellular mechanotransduction (modified from references [80,88])

分析发现, 应力纤维的方向强烈影响细胞的边缘形状, 在细胞骨架均匀排列的情况下, 细胞边缘可以很好地近似于椭圆弧[5]。软骨细胞在硬的基质上培养时, 细胞铺展面积更大, 出现大量的突触, 并影响F-actin的数量和长度。这种在软骨细胞中由硬度介导的微丝骨架重组可能是通过laminin-FAK的信号转导实现的[6]。而微丝骨架的重塑不仅影响细胞的形态和黏附能力, 还能够通过影响下游染色质的开放性调控基因表达[99-100]。此外,微丝骨架的重排导致微丝骨架张力的变化又能进一步引起细胞核形变即核骨架的改变。研究表明, 微丝骨架张力能够引起细胞核极化, 导致核骨架重排, 染色质结构改变开始向内迁移。这一过程往往伴随着基因转录活性的激活[26,101-102]。以上研究提示, ECM硬度的改变和随后驱动的细胞力学结构的变化, 包括微丝骨架张力的变化和核骨架的改变, 可以通过影响染色质的结构来干扰基因的表达, 启动下游的表型变化。

此外, ECM硬度还会影响细胞体积, 在27 kPa至2.2 MPa硬度范围内, 活细胞的体积随着硬度增加而减小但是固定细胞的体积随着硬度增加而增加[103], 且ECM硬度引起的细胞体积的差异还取决于细胞类型, 比如3T3细胞和MSC细胞在12.6 kPa下培养细胞的体积大于3 kPa的细胞体积, 但NuFF细胞的体积大小在这两种基质硬度下, 表现为相反的趋势[104]。而ECM硬度影响细胞体积的因素可能与细胞的黏附和收缩力有关, 并和YAP/TAZ的核定位具有相关性[104]。

3.2 细胞增殖

ECM硬度是调控细胞增殖的重要物理信号。研究发现, 较硬的基质可加快细胞周期进程, 促进细胞增殖[8]。这一过程依赖于FAK-Rac(Rho family, small GTP binding protein rac)-cyclin D信号通路的



ECM的硬度改变可以影响细胞黏附并通过微丝骨架和核骨架影响下游基因的表达。软基质可以促进细胞凋亡, 而硬基质能够促进细胞增殖。间充质干细胞在不同的硬度条件下可以分化成不同类型的细胞, 在软基质上能够表达脂肪细胞和神经细胞的相关标志物, 而在硬基质上可以表达肌细胞和成骨细胞的相关标志物。细胞能够感受外界的硬度变化并向更硬的一侧发生迁移, 而这种趋硬性行为在细胞集体迁移中更明显。疾病的进展往往会伴随病灶组织的硬度增加, 这种疾病微环境中硬度的改变会使成纤维细胞向肌成纤维细胞转变, 肌成纤维细胞分泌大量的ECM又增加了病灶组织的硬度, 进一步促进了疾病进展, 最终形成恶性循环。此外, 病灶组织硬度增加还可以通过促进癌细胞的EMT过程进而促进癌症进展。

ECM stiffness can influence cell adhesion and regulate gene expression through actin cytoskeleton and nuclear cytoskeleton. Soft matrix promotes cell apoptosis, whereas stiff matrix enhances cell proliferation. Matrix stiffness directs stem cell lineage specification, mesenchymal stem cells express adipocyte and neuronal markers in soft matrix, while they upregulate myocyte and osteoblast markers in stiff matrix. Cells sense external stiffness gradients and migrate toward stiffer regions, which is termed “durotaxis”, and is more pronounced during collective cell migration. Disease progression is often accompanied by increased tissue stiffness in lesion areas. This altered mechanical microenvironment drives fibroblast-to-myofibroblast differentiation, and subsequent excessive ECM secretion by myofibroblasts further elevates tissue stiffness, accelerating disease progression. Additionally, stiff lesion promotes cancer progression by inducing EMT.

图2 细胞外基质硬度对细胞行为的调控(根据参考文献[80]修改)

Fig.2 Regulation of cellular behavior via extracellular matrix stiffness (modified from references [80])

激活[7]。FAK在硬ECM上被磷酸化, 进一步激活Rac-GTP信号, 促进cyclin D的表达, 加速G_1/S期转换, 从而促进细胞周期进程。此外, 细胞还可以通过Rho-ROCK信号通路响应基质硬度的改变, 进而影响细胞增殖。ECM硬度变化可调控细胞骨架(肌动球蛋白)张力, 硬基质上肌动球蛋白产生的张力变大, 促进细胞增殖; 减弱这种张力或者抑制其上游的Rho-ROCK信号通路, 则可抑制细胞增值加快[105]。ECM硬度还能通过调控细胞内Ca^{2+}信号, 从而影响细胞增殖。在硬ECM上, 整合素激活可促进Ca^{2+}通道开放, 提高细胞内Ca^{2+}浓度, 并通过ERK(extracellular regulated protein kinases)信号通路促进细胞增殖和血管重塑[106]。ECM硬度对免疫细胞增殖也具有重要影响。例如, 在嵌合抗原受体T细胞治疗(chimeric antigen receptor T-cell therapy, CAR-T)中, 水凝胶的硬度和孔隙率可直接影响CAR-T细胞的增殖及CAR表达水平。优化ECM硬度可增强CAR-T细胞的扩增能力, 提高其抗肿瘤活性, 为CAR-T免疫治疗的优化提供新思路[107]。

3.3 细胞分化

干细胞的分化过程受其局部微环境(即“干细胞生态位”)的严格调控, 而ECM硬度作为关键的生物物理信号, 能够影响干细胞的命运。研究表明, ECM的机械信号可通过整合素介导的信号通路、细胞骨架的张力调控以及机械感受蛋白(如YAP/TAZ)的激活来调控干细胞谱系分化[14,91,108]。

不同组织具有特定的ECM硬度, 而干细胞在不

同硬度环境下的分化倾向与其目标组织的硬度相匹配。例如, MSCs在较软的ECM上更易分化为脂肪细胞或神经元, 而在较硬的ECM上则更倾向于分化成肌细胞或成骨细胞[13,109]。硬ECM以integrin α5、Akt(AKT serine/threonine kinase)和GSK3β(glycogen synthase kinase 3 beta)依赖的方式介导MSCs在硬基质上向成骨细胞分化事件[14]。NA等[108]利用原位Hi-C(high-throughput chromosome conformation capture)技术绘制不同硬度环境下的MSCs基因组三维结构图谱, 发现硬基质促进MSCs的A/B区室(active compartment A和inactive compartment B)及拓扑关联结构域(topologically associating domains, TADs)的重塑, 从而激活成骨相关基因(如*SP1*、*ETS1*)并抑制脂肪分化相关基因表达, 最终驱动MSCs向成骨方向分化。这提示ECM硬度可以通过细胞信号通路以及染色质高级结构的重塑影响干细胞分化。

YAP和TAZ是重要的机械响应蛋白, 在干细胞分化过程中发挥关键作用[110-111]。研究表明, YAP/TAZ的活性受ECM硬度调控, 在硬ECM上, Rho-ROCK信号通路介导细胞骨架的收缩力增强, 促使YAP/TAZ进入细胞核, 从而促进成骨分化并抑制脂肪分化[91]。YAP/TAZ在其他干细胞类型中的作用也受到ECM硬度的调节。例如, 在肠类器官形成过程中, 较硬的ECM可提高肠干细胞(intestinal stem cells, ISCs)在克隆形成过程中的存活率, 这一过程依赖于YAP的核易位, 而在较软的ECM上则促进ISCs向终末分化[112]。此外, 在运动或损伤后, 骨骼肌的微环境发生硬度变化, 促进YAP/TAZ活化, 使肌肉干细胞(satellite cells, SCs)增殖和迁移, 从而支持肌肉再生[113-115]。

ECM硬度不仅通过细胞骨架和转录因子调控干细胞分化, 还通过能量代谢途径介导该过程。研究发现, 硬基质能够促进糖酵解(glycolysis)、氧化磷酸化(oxidative phosphorylation)及抗氧化防御, 从而促进MSCs向成骨细胞分化。具体机制是硬基质通过上调线粒体融合蛋白1/2(mitofusin 1/mitofusin 2, MFN1/2)的表达并抑制动力蛋白相关蛋白(dynamin-related protein 1, DRP1)的活性, 促使线粒体相互融合, 最终促进向成骨细胞转化。此外, 硬基质通过激活机械敏感蛋白YAP, 同步协调糖酵解强度、谷氨酰胺代谢、线粒体动力学及线粒体生物合成引起成骨分化。糖酵解反过来通过细胞骨架张力介导的细胞核形变来调节YAP的定位和活性。因此, YAP是一个重要的机械传感器, 可以整合ECM机械信号和能量代谢信号来影响干细胞的命运[116]。

综合来看, ECM硬度在干细胞命运决定中具有多层次调控作用, 包括机械转导、染色质结构调控、代谢重编程等。YAP/TAZ信号通路作为机械传感核心元件, 在该过程中发挥关键作用。

3.4 细胞迁移

在发育、伤口愈合、免疫反应和癌症转移过程中都会伴随细胞迁移的现象[3,117-119]。细胞可以感应外界环境中的硬度变化, 并向硬度较高的区域迁移, 这一行为被称为趋硬性(durotaxis)[9,11,120]。目前研究发现, 单个成熟的黏着斑具有两种牵引力模式, 分别为稳定的牵引力和动态波动(拖拽)的牵引力。细胞的durotaxis过程依赖于动态波动的拖拽牵引力, 即单个FA通过对ECM施加周期性拖拽力, 动态采样局部的ECM硬度, 使细胞能够在较大范围的基质硬度梯度中感受力学信号, 并引导自身的迁移方向。这一过程由FAK-磷酸化桩蛋白(paxillin)-vinculin信号通路调控[12]。值得注意的是, 趋硬性所需的动态拖拽牵引力并不是FA成熟、趋化性(chemotaxis)或趋触性(haptotaxis)的必需因素, 但它在细胞向硬基质迁移的过程中起着关键作用。此外, 细胞的趋硬性行为也需要合适的离子通道活性[121]。

不仅单个细胞能够表现出趋硬性, 细胞群体在迁移过程中同样展现出趋硬性行为。例如, 在上皮细胞单层扩展的过程中, 细胞会通过向两侧产生相同大小的收缩牵引力进行扩展, 这些力可以在细胞群体之间进行传递, 从而使细胞群体整体朝向更硬的基质区域扩张[122]。基于分子离合器(molecular clutch)模型的模拟研究发现, 在软基质上, 由于ECM更容易发生变形, 细胞骨架聚合受到抑制, 导致细胞无法产生足够的收缩力, 从而限制其迁移能力; 在硬基质上, 细胞骨架更加稳定, F-actin聚合增强, 使得细胞更易感知外界硬度变化, 并驱动集体趋硬性迁移。

近年来的研究提出了一种相反的迁移模式, 被称为负向趋硬性(negative durotaxis), 即细胞会向较低硬度的区域迁移, 而并非向硬度更高的区域迁移[123]。例如, 在U-251MG胶质瘤细胞中观察到, 这些细胞并未像大多数细胞一样趋向硬基质, 而是表现出朝向软基质的迁移行为, 这一现象与经典的机械感知和肌动球蛋白信号转导不完全一致。通过

Motor-Clutch模型的计算模拟，发现细胞倾向于迁移至最优硬度区域，即在该区域细胞能够产生最大的牵引力，而细胞的这种负向趋硬性现象可通过部分抑制肌动球蛋白收缩被破坏，转变为经典的趋硬性行为。同时，下调分子离合器中的关键组件talin，通过降低细胞的最优硬度阈值，使其从趋硬性转变为负向趋硬性[123-124]。

这些发现表明，细胞趋硬性的方向取决于其细胞骨架的收缩力与分子离合器的调控状态，不同类型的细胞可能表现出不同的机械响应，以适应其特定的生理或病理需求。

3.5 细胞凋亡

细胞凋亡(apoptosis)是生物体维持组织稳态的一种程序性细胞死亡机制，由基因精确调控。凋亡的正常发生对于清除受损或异常细胞、维持组织功能至关重要，而其异常调控常与癌症等病理过程密切相关[3]。研究发现，ECM硬度在调控细胞凋亡过程中起重要作用，不同的ECM硬度可通过机械信号影响细胞存活或凋亡。ECM硬度降低(变软)通常会促进细胞凋亡的发生[8,125]。基质硬度变硬可增加Ras的活性，进一步激活PI3K/Akt和MAPK/ERK信号通路使转录因子FOXO3a(forkhead box protein O3a)磷酸化和促凋亡因子Bim降解，促进肺成纤维细胞的存活，抑制凋亡[126]。

3.6 细胞代谢

ECM硬度对细胞基本生物学行为的调控都需要细胞通过代谢来产生所需的物质以及提供能量[83]。

ECM硬度可以改变线粒体的结构和功能[127-128]，在硬基质中线粒体呈现出碎片化和环状结构，这一过程是SLC9A1(solute carrier family 9 member A1)间接上调线粒体的离子信号以及活性氧(reactive oxygen species, ROS)水平，进而通过HSF1(heat shock factor 1)-YME1L1(mitochondrial escape 1 like 1)触发线粒体的氧化应激恢复机制(oxidative stress resilience, OxSR)和线粒体结构重组[127]。

ECM硬度可以调控细胞内的葡萄糖代谢。相较于硬基质，在软基质上培养的人支气管上皮细胞的微丝骨架解聚，从而释放与微丝共定位的E3泛素连接酶TRIM21(tripartite motif containing protein 21)，TRIM21靶向磷酸果糖激酶(phosphofructokinase, PFK)，PFK通过蛋白酶体途径被降解，最终下调糖酵解速率[129]。

ECM硬度还可以调控细胞内的脂肪生成。软基质减弱肌动球蛋白的收缩力，并影响高尔基体的流变学和引起Lipin-1失活，导致高尔基体中二酰基甘油积累，减少ARF1(ADP ribosylation factor 1)的募集，最终导致SREBP1/2(sterol regulatory element binding proteins 1/2)转录因子的激活，驱动脂质合成和积累[130]。

4 细胞外基质硬度在生理和病理过程中的调控作用

4.1 细胞外基质硬度在生理过程中的作用

目前研究发现维持微环境中的机械稳态平衡对于调控细胞的行为、胚胎发育及分化过程具有重要的生理学意义。ECM的成分和机械特性具有组织特异性，且会随着发育和生理状态的改变而改变。不同组织具有对应的最佳组织硬度范围，以正确进行机械信号的传递，维持生命体的活动[31,33,131-133]。

ECM硬度能够调控早期的胚胎发育、器官形成等关键过程。比如，在肺组织中弹性蛋白是ECM中含量最丰富的蛋白，其累积和重塑对于小鼠肺泡的形成至关重要[134]。由ECM金属蛋白酶和赖氨酸氧化酶调控的组织硬度通过低密度脂蛋白受体相关蛋白(low-density lipoprotein receptor related protein 5, LRP5)/Tie2(TEK receptor tyrosine kinase)信号介导肺发育。抑制赖氨酸氧化酶的活性，影响ECM蛋白交联，会使新生小鼠肺组织软化，并分别下调LRP5和Tie2的表达，最终导致小鼠出生后肺部发育受到影响[131]。而上调赖氨酸氧化酶的活性会使ECM硬化，并上调LRP5和Tie2的表达，导致新生小鼠肺泡形态发生失调[131]，这提示了肺的正常发育依赖合适的生物力学环境。

此外，基质硬度和ROCK介导的myosin II的活性与内皮细胞的分枝状伪足的形成有关[135]。其内在分子机制可能是依赖于Rho/ROCK激活的myosin II通过识别和最小化局部细胞表面曲率来最小化细胞分支[136]。

4.2 细胞外基质硬度在病理过程中的作用

ECM硬度在多种疾病进程中起关键作用，如癌症、器官纤维化和心血管疾病等。在这些疾病进程中，组织硬度的变化主要源于ECM的异常重塑，而ECM失调不仅是疾病发展的结果，还可能是疾病发展的原因。例如，在纤维化和癌症中可以观察到异

常的ECM沉积和僵硬[15,137]。相反, 在骨关节炎等疾病中, ECM过度降解会导致软骨组织丧失弹性和功能, 进而加速病变[138]。

4.2.1 细胞外基质硬度与癌症 ECM硬化与许多癌症进展有关, 包括乳腺癌(breast cancer)、肝细胞癌(hepatocellular carcinoma)、肺癌(lung cancer)和胰腺导管癌(pancreatic ductal adenocarcinoma)等[15,139-144]。在肿瘤微环境中, 癌相关成纤维细胞(cancer-associated fibroblasts, CAFs)被激活, 促进ECM蛋白的表达, 导致ECM蛋白的过度沉积和交联[145-146], 引发组织硬化, 并进一步促进肿瘤侵袭和转移(图2)。

Twist1(twist family BHLH transcription factor 1)过量表达的成纤维细胞呈现诸如过度增殖、促进迁移和微丝骨架重排等CAFs激活表型, 并上调palladin和VI型胶原(collagen VI)表达, 且Twist1引起的成纤维细胞活化, 可上调基质硬度[147]。此外, 乳腺癌上皮细胞在硬基质的培养条件下, 帮助Twist1从分子伴侣G3BP2(G3BP stress granule assembly factor 2)上释放出来, 促进Twist1的核易位, 进而激活EMT过程, 驱动肿瘤侵袭与转移, 而G3BP2的低表达与胶原沉积提示乳腺癌患者的不良预后[15]。同时也有文献提示, 在乳腺癌进展过程中, ECM硬度的增加与胶原线性化高度相关。研究发现, 赖氨酸氧化酶介导的胶原交联可增强ECM硬度, 而抑制赖氨酸氧化酶可延长乳腺癌的潜伏期, 并降低肿瘤发生率。该过程通过整合素β1成簇、PI3K信号转导和FAs的形成, 从而驱动侵袭和肿瘤进展[141]。ECM硬度还能影响组织特异性基因的表达, 两种乳腺癌细胞(SCp2和EpH4细胞)在合适的硬度条件下均能够表达β酪蛋白(β-casein), 诱导这两种细胞发生功能分化[132]。此外, ECM硬度可通过YAP/TAZ信号通路, 以促进外泌体分泌的方式调控乳腺癌的细胞的运动和侵袭[143]。

在肺癌中, PANKOVA等[144]的研究发现, RASSF1A(Ras association domain family 1 isoform A)的抑制可促进YAP的核易位, 并激活P4HA2(prolyl 4-hydroxylase alpha-2), 导致胶原沉积增加, 进而促进癌细胞向干细胞样表型转变, 加速癌症进展。WU等[148]发现, 在硬基质上培养细胞分泌的外泌体能够促进肿瘤的进展, 潜在的分子机制可能是通过硬基质激活并磷酸化Akt, 进一步激活并磷酸化Rabin8(Rab8 guanine-nucleotide exchange factor), 将Rab8(Ras-related protein rab-8)转换为活性的GTP装载形式, 帮助Huh7肝癌细胞分泌外泌体, 这种外泌体高表达Jagged1(jagged canonical notch ligand 1), 激活Notch信号通路, 从而促进肝癌进程, 这与肝癌患者的基因表达分析相一致。

4.2.2 细胞外基质硬度与器官纤维化 机体修复受伤组织的能力对维持生理稳态至关重要。然而, 慢性或反复损伤可能导致组织纤维化, 而ECM硬度的异常升高是纤维化发生的重要特征。器官纤维化与许多实体瘤中的结缔组织增生具有相似的分子机制, 即ECM过度沉积和交联增强[17]。

在小鼠肺纤维化造模中, 伴随着肺实质组织的六倍硬化, 在这种病理硬度下, 肺成纤维细胞从静止向增殖和基质合成的状态转变, 并且抑制COX-2(cyclooxygenase-2)表达和PGE_2(prostaglandin E_2)的合成, 而成纤维细胞的激活又加快了纤维化的进程[137]。同样, 在肝纤维化或者心脏纤维化的进展过程中, 成纤维细胞向肌成纤维细胞转变, 产生更多的ECM, 促进纤维化的进展[149-151](图2)。

心肌细胞只有在适配生理条件的基质硬度上培养, 才能够形成最优的收缩力传递和跳动频率[133,152-155]。在硬基质上培养的心肌细胞会丧失跳动能力, 而心脏祖细胞的增殖能力增强以及细胞周期进程加快, 加速了细胞衰老, 同时刺激了ECM和黏附相关蛋白表达上调[152,156]。YAP参与心脏间质细胞的纤维化过程[157-159], 心脏纤维化造模的小鼠和心力衰竭患者的组织纤维化区的成纤维细胞中具有YAP核定位, 并且这种细胞的细胞核形状更细长, 与细胞外的胶原纤维的排列性相关。心脏成纤维细胞的YAP核易位信号的激活受到力学和拓扑学的作用, 为心脏的抗纤维化治疗提供了潜在的理论基础[160]。此外, YAP的核易位还受到AT_1R(angiotensin II type 1 receptor)的调控, 从而促进心脏成纤维细胞的激活[150,161]。

4.2.3 细胞外基质硬度与心血管疾病 ECM硬度在血管功能中起着关键作用, 能够影响动脉粥样硬化(atherosclerosis)、主动脉瘤(aortic aneurysms)、主动脉夹层(aortic dissection)等疾病进展。随着这些疾病的发展, 血管ECM变得更加僵硬, 影响血管的弹性和功能。

主动脉硬化增加是衰老和心血管疾病的重要特征, 其发生主要归因于ECM组成和机械特性的变化。老年猴子的血管平滑肌细胞的组织硬度高于

年轻猴子，其血管平滑肌细胞中的α-平滑肌肌动蛋白(α-smooth muscle actin, α-SMA)和整合素β1含量增高[162]。此外，腓骨蛋白4(Fibulin 4)低表达的小鼠(*Fibulin-4*$^{R/R}$)表现为上行主动脉扩张以及主动脉扭曲和硬化。进一步的转录组分析提示，*Fibulin 4*缺陷小鼠动脉瘤的发病机制与TGF-β信号通路紊乱有关，并伴随着细胞骨架、黏附、凋亡和代谢等生物学过程的改变[163-164]。而在人类中，*Fibulin 4*突变表现为皮肤松弛、血管扭曲、上行主动脉瘤以及骨骼异常等疾病[165]。

血管衰老通过ECM硬度的变化影响血管平滑肌细胞功能。研究发现，Sox9(SRY-box transcription factor 9)的蛋白水平在衰老血管中显著上调。血管衰老通过促进Sox9的表达，协调胶原的表达，降低血管平滑肌细胞的收缩性，导致ECM蛋白成分改变、沉积，并进一步加速细胞的硬化和衰老[166]。

单细胞转录组测序分析表明，在病理性ECM硬度条件下培养的人冠状动脉内皮细胞，表现出更多的间质细胞特征。轨迹追踪实验表明，在高硬度条件下更容易发生内皮向间质转化(endothelial to mesenchymal transitions, EndMT)，同时也存在一种反向的由间质向内皮转化(mesenchymal to endothelial transitions, Mes-to-EndT)的过程。来自人动脉粥样硬化斑块的单细胞测序数据与病理ECM硬度培养条件下的内皮细胞具有高度相似性，这提示由于基质硬度介导的内皮细胞的转变可能参与了动脉粥样硬化的发病机制[167]。

5 总结与展望

ECM不仅是细胞生长的物理支架，还通过其机械特性(如硬度)深刻影响细胞行为和组织功能。ECM硬度调控细胞形态、增殖、迁移、分化和凋亡等生物学过程，并在胚胎发育、器官形成、组织修复及疾病进展(如肿瘤、纤维化和心血管疾病)中发挥关键作用。细胞通过整合素–黏着斑–细胞骨架–核骨架机械信号轴感知ECM硬度，并调控YAP/TAZ、Rho-ROCK、PI3K/Akt等信号通路，影响细胞命运及基因表达。ECM硬度的异常变化可促进癌细胞侵袭、加重器官纤维化，甚至影响免疫细胞浸润，进而影响疾病进程。近年来，针对ECM硬度的调控策略在癌症治疗、再生医学和组织工程中展现出重要的应用潜力。例如，通过降低ECM硬度，可以促进T细胞浸润，提高免疫检查点抑制剂(如PD-1/PD-L1抑制剂)的治疗效果[168]；利用ECM软化或降解技术(如LOX抑制剂、透明质酸酶)可改善药物递送效率[2]；在再生医学领域，优化ECM硬度可引导干细胞定向分化，为器官修复和组织工程提供新思路。因此，深入研究ECM机械信号调控机制，将为疾病诊疗和生物工程提供重要的理论依据。

尽管近年来ECM硬度调控细胞行为及疾病进展的研究取得了重要进展，但仍存在诸多未解之谜和挑战。首先，ECM硬度感知的分子机制仍需进一步解析。目前研究揭示integrin-FAs-YAP/TAZ轴在ECM硬度感知中的重要作用，但ECM如何通过力学信号影响染色质重塑和基因表达仍不清楚。未来研究应结合单细胞测序、超分辨成像及力学生物学技术，解析细胞如何整合机械信号与生化信号，并在不同组织和细胞类型中实现ECM机械响应的特异性。其次，不同组织和病理状态下ECM机械微环境的特异性调控机制尚不明确。不同组织具有特定的ECM硬度，而其在疾病状态下的变化模式亦各不相同。例如，某些癌症(如乳腺癌、肝癌)组织变硬，而神经退行性疾病则表现为ECM软化。未来研究应结合生物材料学、力学生物学和多组学技术，解析ECM硬度在不同组织和疾病状态下的动态变化及其对细胞行为的调控作用。

随着单细胞和空间组学技术的进步，未来可利用单细胞转录组测序(single-cell RNA sequencing, scRNA-seq)、单细胞染色质可及性测序(single-cell assay for transposase-accessible chromatin with high throughput sequencing, scATAC-seq)以及空间转录组测序(spatial transcriptomics)等新兴组学技术，解析ECM机械信号在组织微环境中的动态变化，构建不同疾病状态下ECM-细胞相互作用的时空图谱，为精准医学和个性化治疗提供更深层次的机制解析。例如，ECM硬度变化可能诱导不同细胞群体的基因表达重塑，例如在肿瘤微环境中，硬ECM通过驱动肿瘤相关成纤维细胞CAFs或癌症干细胞样细胞(cancer stem-like cells, CSCs)的基因表达，促进癌细胞的侵袭并增强其耐药性。利用scRNA-seq技术，可揭示ECM硬度对不同细胞亚群的影响，并识别关键的力学生物学调控因子，例如YAP/TAZ依赖的转录调控因子(如TEAD1~4)、整合素信号通路相关分子(integrin β1、FAK)或机械应答相关基因(*PIEZO1*等)。

在临床应用方面，基于ECM硬度调控的精准

治疗策略仍需优化。目前针对ECM硬度的治疗策略主要集中在癌症微环境调控, 如LOX抑制剂、透明质酸酶和ECM降解酶在改善免疫治疗和化疗药物递送方面的应用。例如, 利用LOX靶向肿瘤微环境中的ECM, 干扰胶原的稳定性能够通过降低肿瘤硬度和基质成分促进T细胞的迁移, 从而提高抗PD-1治疗的疗效[168]。纳豆激酶(nattokinase, NKase), 一种可以溶解血栓的保健药物, 通过注射NKase可以降解纤连蛋白(fibronectin)并延缓CAFs介导的纤维化进程, 从而降低肿瘤硬度。而NKase的注射还可以促进CAR-T细胞向肿瘤的浸润, 提高CAR-T治疗实体瘤的整体疗效[169]。溶瘤腺病毒VCN-01可以表达透明质酸酶, 从而降解肿瘤基质, 降低肿瘤硬度, 促进化疗制剂的输送, 使肿瘤的进展得到控制[2,170]。目前结直肠癌常用的治疗方法是通过使用能够阻断血管内皮生长因子(vascular endothelial growth factor, VEGF)信号的药物来抑制肿瘤中血管的形成, 但是这种疗法由于改变了肿瘤微环境中的硬度(透明质酸的沉积), 使后续治疗的药物更难以发挥作用, 而加入透明质酸酶能部分延长抗VEGF治疗和化疗联合的药物作用的时效[171]。然而, 这些策略在临床转化过程中仍面临挑战, 如ECM硬度调控对组织的影响、副作用评估以及个体化治疗方案的优化。因此, 未来需要结合纳米技术、生物工程和高通量筛选技术, 开发更加精准和可控的ECM软化/调控策略, 以提高临床应用的安全性和有效性。

此外, 人工ECM及生物材料在组织工程与再生医学中的应用值得深入研究。近年来, 人工ECM、生物材料支架及3D细胞培养技术在干细胞工程和组织修复领域取得突破。例如, 硬度可调的水凝胶可用于模拟不同组织的微环境, 并诱导干细胞定向分化。未来可进一步结合3D打印、可编程生物材料和细胞力学生物学, 开发更加仿生化的ECM体系, 为组织工程和器官再生提供新的策略。

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