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机械力调节细胞功能影响创面愈合的研究进展

谢苏杰¹, 李子健¹, 胡守一², 张佳怡², 仵敏娟^{3*}

(1 海军军医大学基础医学院一大队, 上海 200433; 2 海军军医大学基础医学院三大队, 上海 200433; 3 海军军医大学基础医学院组织胚胎学教研室, 上海 200433)

摘要: 创面愈合是指机体遭受外力作用, 皮肤组织出现离断或缺损后愈合恢复的连续过程, 包括各种组织再生、肉芽组织增生和瘢痕形成。创面愈合涉及多个细胞群、细胞外基质和各种信号分子, 可以分为3个阶段: 止血与炎症期、增殖期和重塑期。机械力作为细胞结构和功能的调节因素, 参与调节创面愈合中多个细胞群的增殖、迁移和分化等生理过程, 影响创面愈合的进程。现从细胞角度讨论机械力对创面愈合的影响。

关键词: 机械力; 创面愈合; 细胞角度

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Research progress on mechanical forces regulating cell function in wound healing

XIE Su-Jie¹, LI Zi-Jian¹, HU Shou-Yi², ZHANG Jia-Yi², WU Min-Juan^{3*}

(1 Brigade One Team, Basic Medical College, Naval Medical University, Shanghai 200433, China; 2 Brigade Three Team, Basic Medical College, Naval Medical University, Shanghai 200433, China; 3 Department of Histology and Embryology, Basic Medical College, Naval Medical University, Shanghai 200433, China)

Abstract: Wound healing is the continuous process of healing and restoring skin tissue after the body has been subjected to external forces, which includes various forms of tissue regeneration, granulation tissue hyperplasia and scar formation. Wound healing involves multiple cell populations, extracellular matrix and various signaling molecules. This process can be divided into 3 phases: hemostasis and inflammation, proliferation and remodeling. As regulators of cell structure and function, mechanical forces participate in regulating physiological processes such as proliferation, migration and differentiation of multiple cell groups in wound healing, affecting the process of wound healing. This review summarizes the effect of mechanical forces on wound healing from the cellular perspective.

Key words: mechanical forces; wound healing; cellular perspective

正常生理过程将细胞暴露于各种机械力中, 包括细胞外基质 (extracellular matrix, ECM) 的黏弹性、相邻细胞之间的拉力和组织层面的剪切力、压力和拉力, 如: 组织重排或全身功能 (血流、身体运动) 引起的压缩和拉伸^[1]。这些外力可通过细胞连接传导到肌动蛋白细胞骨架, 并可通过核骨架和细胞骨架复合物与核膜偶联, 将机械力传递到染色质, 影响基因转录、表观遗传学和 DNA 的损伤修复等^[1]。细胞自身也可通过肌动蛋白应力纤维内源性产生机

械力, 称为牵引力 (traction force, TF)^[2], 例如: 细胞迁移中推动细胞的牵引力主要由肌球蛋白产生^[3]以及肌成纤维细胞产生收缩力促进伤口愈合^[4]。本文主要讨论外源性机械力。

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*通信作者: E-mail: minjuanwu@163.com

相邻细胞、ECM 以及细胞内的细胞骨架均可转导机械力, 并反馈于细胞的增殖、黏附、迁移和分化等生理过程中^[5]。创面愈合涉及多个细胞群, 历经止血与炎症、增殖和重塑三期^[6]。止血与炎症期时, 血管收缩, 血小板迅速凝集为纤维蛋白凝块进行止血并为炎症细胞充当支架, 巨噬细胞与中性粒细胞一起识别并清除病原体 and 坏死组织; 增殖期时, 成纤维细胞产生肉芽组织填充伤口, 角质形成细胞覆盖创面, 血管内皮细胞形成毛细血管提供营养; 创面再上皮化完成后, 转入重塑期, 沉积的 ECM 由成纤维细胞重塑, 创面愈合并接近皮肤的正常抗拉强度, 异常的机械刺激导致病理性瘢痕的形成^[7]。本文主要综述机械力调节创面愈合各期细胞功能的最新研究进展。

1 止血与炎症期

1.1 机械力对血小板的影响

生理条件下, 健康的内皮细胞保护血小板不被激活, 防止血栓形成。当伤口出现时, 血管平滑肌反射性痉挛引起血管收缩减少出血^[7]。血管收缩引起的剪切梯度由 3 部分组成: 狭窄近端的剪切加速区、狭窄顶端的剪切峰值区和狭窄远端的剪切减速区。高剪切力可增强血小板活化, 但血管收缩狭窄区后方的低剪切区域为血小板过度聚集和血栓进展提供了足够的时间和有利的流动条件^[8]。血管损伤导致 ECM 成分释放, 血小板暴露在血管性血友病因子 (von Willebrand factor, vWF) 和多种胶原蛋白环境中, 其表面的糖蛋白 (glycoprotein, GP) 受体与两者结合, 导致血小板活化^[9]。血小板活化后快速聚集形成血小板栓子, 血小板栓子充当保护伤口的临时屏障, 并释放多种细胞因子, 募集炎症细胞, 促进成纤维细胞的增殖^[10]。

其中机械力影响血小板的黏附、激活、聚集多个过程。血流剪切应力增加导致 vWF 的 A1 结合位点暴露, 与血小板 GPIIb α 受体结合, 将流动的血小板固定在 vWF 上。并且, vWF 的 A3 位点负责固定胶原蛋白 I 和 III, 在高剪切应力作用下, 开放的 A1 结构域可充当 A3 结构域的替代物, 将血小板聚集到胶原蛋白中^[11], 为下一步 GPIIb/IIIa [又称: 整合素 $\alpha_{IIb}\beta_3$ (integrin $\alpha_{IIb}\beta_3$)] 与纤维蛋白原的结合打下基础。剪切应力的改变引发胞内瞬时 Ca^{2+} 浓度升高^[12], 从而导致 GPIIb/IIIa 构象变化, 血小板转变为高亲和力状态, 启动由内而外的整合素信号激活

途径^[9]。每个纤维蛋白原分子可以与两个 GPIIb/IIIa 分子结合, 这种结合短时间内是可逆的, 随着 Ca^{2+} 浓度下降, 纤维蛋白原和 GPIIb/IIIa 的结构都发生了改变, 使得结合不可逆, 最终形成稳定的血小板栓子^[13]。P-选择素 (P-selectin) 易位是血小板活化过程中发生的关键事件, 当血小板激活后, P-选择素在血小板表面高度上调^[14]。Fang 等^[15]研究发现, 剪切应力的累积可通过 PI3K/Akt 通路诱导血小板 P-选择素易位, 有助于血小板聚集和随后的中性粒细胞募集^[16]。

1.2 机械力对炎症细胞的影响

创面形成后, 细菌或破损组织激活朗格汉斯细胞和基质细胞以产生炎症细胞因子和透明质酸以促进水肿并将炎症细胞吸引到感染部位, 由此产生的水肿和炎症会导致组织力学发生变化^[17]引起基质硬度的增加^[18]。血液中循环的中性粒细胞在足够的剪切应力下渗出血管, 成功渗出后, 继续承受压力导致胞质变形, 从而进入伤口周围^[19]。中性粒细胞释放活性氧、溶酶体酶等杀伤病原体^[20], 并且使用中粒细胞胞外诱捕网 (neutrophil extracellular traps, NETs) 捕获病原体进行清除^[21]。骨髓源性单核-巨噬细胞在挤压通过毛细血管时会被拉伸, 而组织驻留的巨噬细胞通常会暴露在皮肤破损后形成的张力下, 也会拉长它们的形状^[22]。巨噬细胞在炎症早期释放促炎介质对抗病原体, 后期吞噬凋亡的中性粒细胞。肥大细胞脱颗粒防止皮肤感染并与巨噬细胞一起释放细胞因子促进增殖期细胞生长^[23]。

机械力对多种炎症细胞产生影响。ECM 硬度可以改变中性粒细胞、肥大细胞和巨噬细胞的迁移速度, 中等硬度的 ECM 可以使炎症细胞获得最佳迁移速度^[24-26]。并且, 内皮细胞的机械硬度也可激活中性粒细胞 Ca^{2+} 内流, 引发后续的炎症反应^[27]。血流剪切力也可增加 P-选择素诱导的钙信号转导的速率和强度, 通过增加 P-选择素/PSGL-1 复合物上的张力激活中性粒细胞的力依赖性钙信号转导^[28]。Shimbori 等^[29]的实验表明, 机械拉伸可以激活大鼠肺中的肥大细胞脱颗粒和转化生长因子 $\beta 1$ (transforming growth factor- $\beta 1$, TGF- $\beta 1$) 信号通路, TGF- $\beta 1$ 促进成纤维细胞的增殖和 ECM 的产生。此外, 机械力还可以影响巨噬细胞的分化和吞噬。巨噬细胞在创面愈合中主要有 M1、M2 两种表型, M1 型 (促炎表型) 巨噬细胞在炎症早期出现, 负责释放炎症介质和杀灭微生物; M2 型 (抗炎表型) 巨

噬细胞负责产生抗炎介质、启动成纤维细胞的增殖,促使创面由炎症期转为增殖期^[30]。Sridharan等^[31]发现,较高的基质硬度(323 kPa)使巨噬细胞趋向分化为促炎表型,而相对柔软的基质硬度(11 kPa/88 kPa)使细胞趋向于抗炎表型。高硬度的基质通过激活机械门控离子通道Piezo1,触发Ca²⁺流入,从而增强骨髓来源的巨噬细胞中的NF- κ B活化和F-肌动蛋白(F-actin)形成,趋向分化为促炎表型^[17]。行走于ECM的间质流(interstitial flow, IF)也可以通过ECM产生动态应力影响巨噬细胞的分化。IF通过整合素/Src介导的STAT3/6机械转导途径将巨噬细胞极化为M2表型^[32]。在炎症期,机械力可通过基质硬度、剪切应力和机械离子通道等改变影响各类炎症细胞的迁移、分化和各类细胞因子的表达,引发炎症期到增殖期的转变。

2 增殖期

2.1 机械力对成纤维细胞的影响

成纤维细胞在创面愈合中主要负责形成肉芽组织填充伤口、沉积和重塑ECM并参与免疫调节。成纤维细胞位于真皮层中,具有异质性,分为多个亚群:网状成纤维细胞、肌成纤维细胞、乳头状成纤维细胞、毛囊真皮乳头成纤维细胞、血管相关成纤维细胞(周细胞)和前脂肪细胞^[33]。当出现伤口时,成纤维细胞受到刺激,激活网状成纤维细胞后分化为肌成纤维细胞促进ECM沉积加快伤口愈合^[34]。其他的几个细胞亚型也在创面愈合中发挥重要作用:乳头状成纤维细胞主要参与免疫调节,促进再上皮化^[35];毛囊真皮乳头成纤维细胞可诱导毛囊再生并帮助创面愈合^[36];血管相关成纤维细胞可发挥类似肌细胞的功能为血管内皮细胞提供张力^[7];前脂肪细胞可分化为脂肪细胞有助于伤口恢复^[37]。

机械力在成纤维细胞的增殖、迁移、分化中发挥重要作用。当皮肤出现破损时,成纤维细胞、角质形成细胞和巨噬细胞等组织驻留细胞会承受由皮肤对破裂的抵抗力产生的张力^[17]。这种张力可直接激活网状成纤维细胞^[38][其他信号也可激活网状成纤维细胞,如:病原体暴露,血小板、巨噬细胞释放TGF- β 和血小板衍生生长因子(platelet-derived growth factor, PDGF)等信号因子^[39]]。在伤口愈合过程中,肌成纤维细胞的收缩增加了ECM的硬度和机械张力。机械应力下降或ECM硬度降低可诱

导细胞凋亡并降低 α -平滑肌肌动蛋白(α -smooth muscle actin, α -SMA)的表达和肌成纤维细胞的收缩能力^[4]。有趣的是,Wahlsten等^[40]建立了一种新型动态生物反应器系统对人体皮肤等效物施加循环双轴张力,结果表明循环加力导致的真皮基质变硬会刺激成纤维细胞快速增殖,但不影响成纤维细胞分化为肌成纤维细胞。Yes-相关蛋白(yes-associated protein, YAP)在机械信号与细胞增殖之间起到重要作用。基质硬度改变后,与静态培养相比,成纤维细胞核中YAP显著上升^[40],YAP通过由转录增强结构域(transcriptional enhanced associate domain, TEAD)家族介导的转录程序促进细胞增殖^[41]。成纤维细胞可以通过肌动蛋白细胞骨架和相关复合物产生迁移所需的不对称力^[42]。周期性轴向拉伸通过机械转导上调整合素信号分子(如:整合素 β_1 、整合素 α_{10}),影响细胞骨架成分,促进成纤维细胞迁移,覆盖缺损伤口^[43]。网状成纤维细胞获得机械应力成为原始肌成纤维细胞。之后在纤连蛋白ED-A剪接变体作用下,原始肌成纤维细胞激活 α -SMA阳性的肌成纤维细胞,促进ECM沉积,加快伤口愈合^[44]。过度的机械力抑制了肌成纤维细胞的凋亡,导致肥厚性瘢痕的形成,具体将在重塑期叙述^[45]。

2.2 机械力对角质形成细胞的影响

角质形成细胞位于皮肤表皮。皮肤受损后,角质形成细胞被机械张力、电梯度、炎症细胞释放的细胞因子和生长因子等激活^[6],迁移到皮肤破损处进行增殖,覆盖创面完成再上皮化过程。若皮肤损伤较深,则填充肉芽组织后闭合创面。

破损的皮肤引发细胞机械环境的紊乱,角质形成细胞迁移、增殖和细胞间相互作用等生理活动受到影响。角质形成细胞受到机械张力后,释放原本位置的部分桥粒与半桥粒连接,形成临时基底膜,为细胞集体迁移提供必要的机械支持。在细胞迁移中,推动细胞的牵引力主要由肌球蛋白II马达(myosin II motors)产生,而极性肌动蛋白丝的聚合在细胞膜上产生推力,从而使细胞的前缘能够突出^[3]。肌动球蛋白对细胞-ECM黏附和细胞间连接施加作用力,使细胞能够通过基质迁移并分别拉动左右细胞^[46]。随着ECM硬度的增加,整合素 β_1 可随之增加^[47]。其中整合素 $\alpha_5\beta_1$ 和整合素 $\alpha_v\beta_1$ 等纤连蛋白受体可以协调细胞-基质牵引力和细胞-细胞应力^[48]。Di Russo等^[49]发现,整合素 $\alpha_5\beta_1$ 的密度(纳米级间距最佳)可以调节角质形成细胞单层

内应力。当细胞-基质黏附性达到中等比率时, 角质形成细胞的迁移速率最大^[50]。在角质形成细胞增殖方面, Peyret 等^[51]模拟组织压缩与伸展的交替情况, 对 HaCaT 细胞给予集体振荡的机械应力, 发现组织变形可改变细胞内 YAP 的机械转导。YAP 入核增加后激发下游效应分子 TEAD, 可进一步调控转录因子 E2F1 促进角质形成细胞的增殖^[52]。机械力可以促进角质形成细胞与其他细胞的相互作用从而促进创面的愈合。Chung 等^[47]研究发现, ECM 硬度增加会导致角质形成细胞中局部黏着斑激酶 (focal adhesion kinase, FAK) 表达增加并通过 PI3K/Akt 通路参与白介素-6 (interleukin-6, IL-6) 产生, 调节成纤维细胞中角质形成细胞生长因子的表达。在动态伤口愈合中, 角质形成细胞在机械张力和趋化因子的作用下穿过表皮横向迁移, 机械拉伸成纤维细胞可增加表皮生长因子 (epidermal growth factor, EGF) 的分泌促进角质形成细胞的不对称迁移^[53]。

2.3 机械力对血管形成相关细胞的影响

新血管的形成在创面愈合中起到至关重要的作用, 为破损组织输送必要的营养和氧供, 支持伤口修复过程中诸多细胞的增殖迁移和分化^[54]。这一过程可以归纳为 5 个步骤: 血管基底膜脱落、内皮细胞分化迁移和增殖、新生血管芽形成、血管芽相互融合形成管腔和基底膜沉积血流恢复^[55]。其中发挥主要作用的是血管内皮细胞和周细胞, 机械力对这两种细胞有重要影响。

血管形成是由血管内皮细胞驱动的, 血管内皮细胞位于动态环境中, 对广泛的外力作出反应, 包括由流动血液的摩擦产生的剪切应力、由流体导致血管壁变形引起的应变以及静水压力^[56]。剪切应力和机械刚度会影响血管生成, 可用于调节发芽^[57]。血管内皮细胞分化为尖端细胞 (tip cell) 和茎细胞 (stalk cell)^[58]。尖端细胞响应趋化因子号召, 向破损部位迁移, 茎细胞不断增殖形成管腔。内皮细胞是否成为尖端细胞或茎细胞的决定主要由 Notch 途径及其效应物 delta 样配体 4 (delta-like 4, Dll4) 和 Jagged1 调节^[59]。Matsuo 等^[60]研究表明, 血管内皮细胞可借助 YAP 感知 ECM 硬度, 激活 Dll4-Notch 信号通路, 进而影响血管内皮细胞的分化。Bordeleau 等^[61]证明机械力影响血管基底膜脱落, ECM 硬度增加可上调基质金属蛋白酶 (matrix metalloproteinase, MMP) 活性, 降解基底膜便于血管内皮细胞迁移。并且,

血管内皮细胞上的 VEGFR-2 激活, 作为机械传感分子促进新血管的形成^[62]。剪切应力诱导 VEGFR-2 核转位并形成 VEGFR2-VE-钙黏着蛋白 (cadherin)- β -连环蛋白 (catenin) 复合物作为机械转导传感器, 促进血管内皮细胞增殖和迁移^[63]。血流对新形成的血管内部细胞施加机械刺激, 机械刺激既可以作为切向血管的剪切应力, 也可以作为横向于血管内皮细胞上血流方向的机械应变^[64]。由生理血流引发的连续剪切应力会降低 VEGF 的表达, 抑制血管内皮迁移活性和尖端细胞诱导的基质重塑, 血管伸长停止, 血管稳定^[65]。周细胞主要负责维持新生血管的稳定性。当血管内皮细胞形成的血管芽互相融合形成血管腔后, 周细胞与募集纤连蛋白和 nidogen-1 (一种连接基底膜组分的基质桥接蛋白) 重建血管周围 ECM^[66]。周细胞可以感知剪切应力, 释放具有保护功能的基质金属蛋白酶的抑制剂 3 (tissue inhibitor of metalloproteinase, TIMP3), 防止基质降解并保持血管稳定性^[67]。总的来说, 在创面愈合中, 机械力影响血管内皮细胞的增殖、迁移与分化, 并且可以通过周细胞维持血管的稳定性。

3 重塑期

伤口的重塑主要包括: 未灌流血管的退化和 ECM 的重塑。伤口愈合增殖期的毛细血管密度比未受伤皮肤高 2~3 倍^[54]。当伤口表面再上皮化完成后, 促血管生成因子逐渐减少, 抗血管生成因子 (如: PEDF 和 sprouty-2) 分泌增加, 使得未灌流血管的内皮细胞凋亡^[68]。在正常人体皮肤 ECM 中 I 型胶原蛋白:III 型胶原纤维的比例是 8:1, 而在肉芽组织中该比例是 1:3^[69]。成纤维细胞将伤口 ECM 中多余的 III 型胶原纤维转化为 I 型胶原蛋白并排列整齐, 增强伤口的拉伸强度^[6]。创面愈合后期, 皮肤破损处出现瘢痕组织进行填充, 过度的纤维化导致肥厚性瘢痕和瘢痕疙瘩的出现^[70]。多种细胞参与瘢痕的形成过程, 其中机械力主要作用于成纤维细胞影响瘢痕的形成。

成纤维细胞在瘢痕形成过程中发挥重要作用。成纤维细胞稳态功能包括感知和响应 ECM 的变化, 以维持组织的机械稳态。为此, 成纤维细胞配备了特定的正反馈和负反馈机制, 用于评估机械稳态。皮肤损伤会破坏成纤维细胞稳态反馈机制, 导致它们被激活为形成瘢痕的肌成纤维细胞, 以便快速闭合伤口^[71]。网状成纤维细胞在伤口出现后响应各类

信号刺激分化为肌成纤维细胞,进行伤口收缩。机械应力刺激通过蛋白激酶 B (protein kinase B, Akt) 抑制肌成纤维细胞凋亡导致肥厚性瘢痕形成^[45]。成纤维细胞可通过整合素-FAK 途径感知机械刺激(如:力、基质硬度、配体分布等)^[72]。接收到机械刺激后,FAK 激活下游多个效应蛋白,比如前面提到的 PI3K/Akt 通路^[73]。Mascharak 等^[74]发现的 *Engrailed-1* 谱系阴性成纤维细胞为相关研究打开了新的思路。*Engrailed-1* 谱系阴性的成纤维细胞可在高硬度的基质环境中通过整合素-FAK 途径使 YAP 分子入核表达,驱动 *Engrailed-1* 的激活,导致肥厚性瘢痕形成。除了传统的整合素-ECM-FAK 机械转导通路,He 等^[75]发现, Piezo1 作为机械门控离子通道可感知伤口的机械拉伸,促进 Ca^{2+} 内流,增强成纤维细胞的增殖迁移,导致肥厚性瘢痕的形成^[75]。并且, Piezo1 可在机械外力的影响下通过其介导的 Ca^{2+} 内流激活 FAK^[76] 或直接激活 FAK^[77],导致肌动蛋白细胞骨架的重组,引发相关下游分子效应。机械力通过多种机械转导相关分子影响成纤维细胞,最终导致瘢痕的形成。

4 总结与展望

创面愈合中的力学因素有多种:拉力和推力会

延长或缩短细胞,导致细胞骨架重组和产生收缩力,从而引起细胞外成分的相互张力^[78];剪切应力,细胞与流动的血液或间质液接触时产生;间质流,存在于所有活组织中的动态应力驱动小的流体流动通过细胞外基质产生机械作用^[79];细胞可通过肌动蛋白-踝蛋白-整合素-纤黏蛋白 (actin-talin-integrin-fibronectin) 力学感应器响应 ECM 基质刚度,转化为生化信号^[80]。机械力对创面愈合不同阶段中的各细胞活动均有影响。在止血与炎症期,机械力的增加改变血小板构象,促进血小板栓子的形成;适度的机械力提高炎症细胞的迁移速率,保证创面形成后病原体和坏死组织的清除(图1)。增殖期时,较高的机械刺激使角质形成细胞和成纤维细胞增殖加快,血管内皮细胞分化,形成肉芽组织并促进新血管的形成完成创面再上皮化(图2)。在重塑期,过度的机械刺激引发成纤维细胞的过度激活,最终导致病理性瘢痕的产生(图3)。目前已有传统组织扩张、皮肤减张器和负压伤口疗法等运用机械原理帮助创面愈合^[81],但针对具体细胞的机械原理治疗仍较少见。随着单细胞技术的日渐发展,或许可以从某一细胞入手,甚至从细胞的亚型入手,制定相应的细胞疗法,为促进创面愈合、防止病理性瘢痕产生提供新的治疗策略。

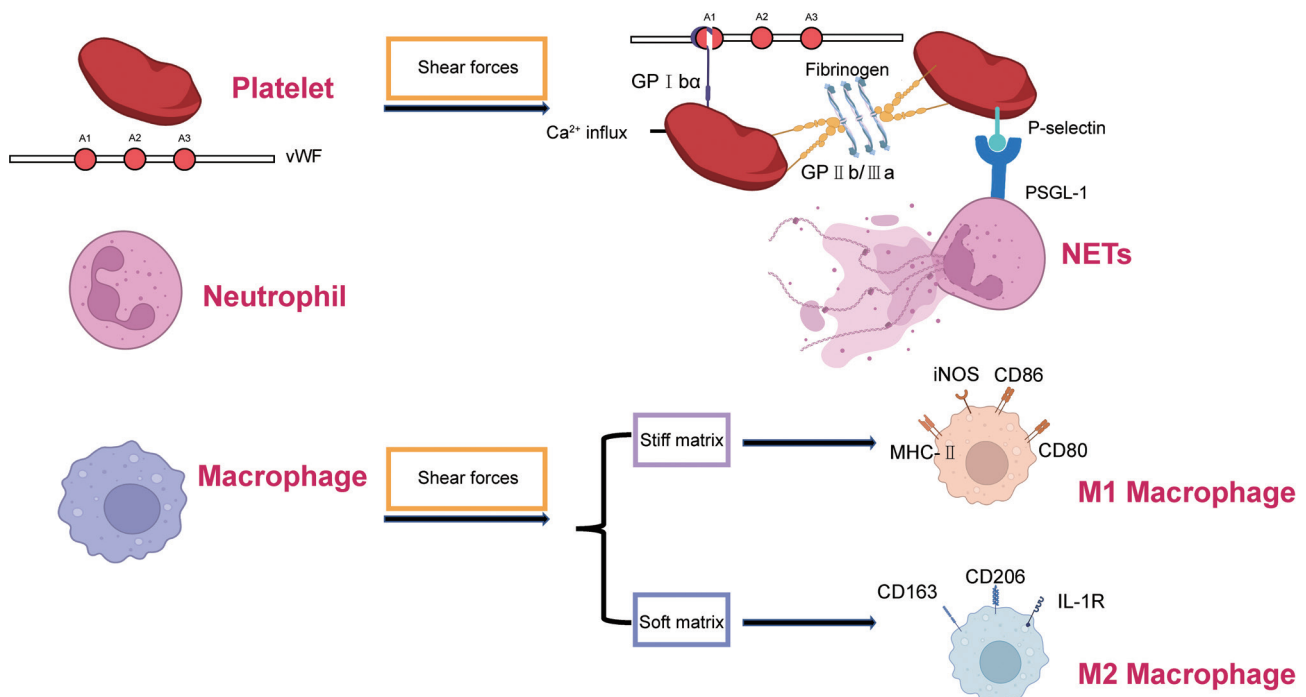


图1 机械力对止血与炎症期主要细胞的影响

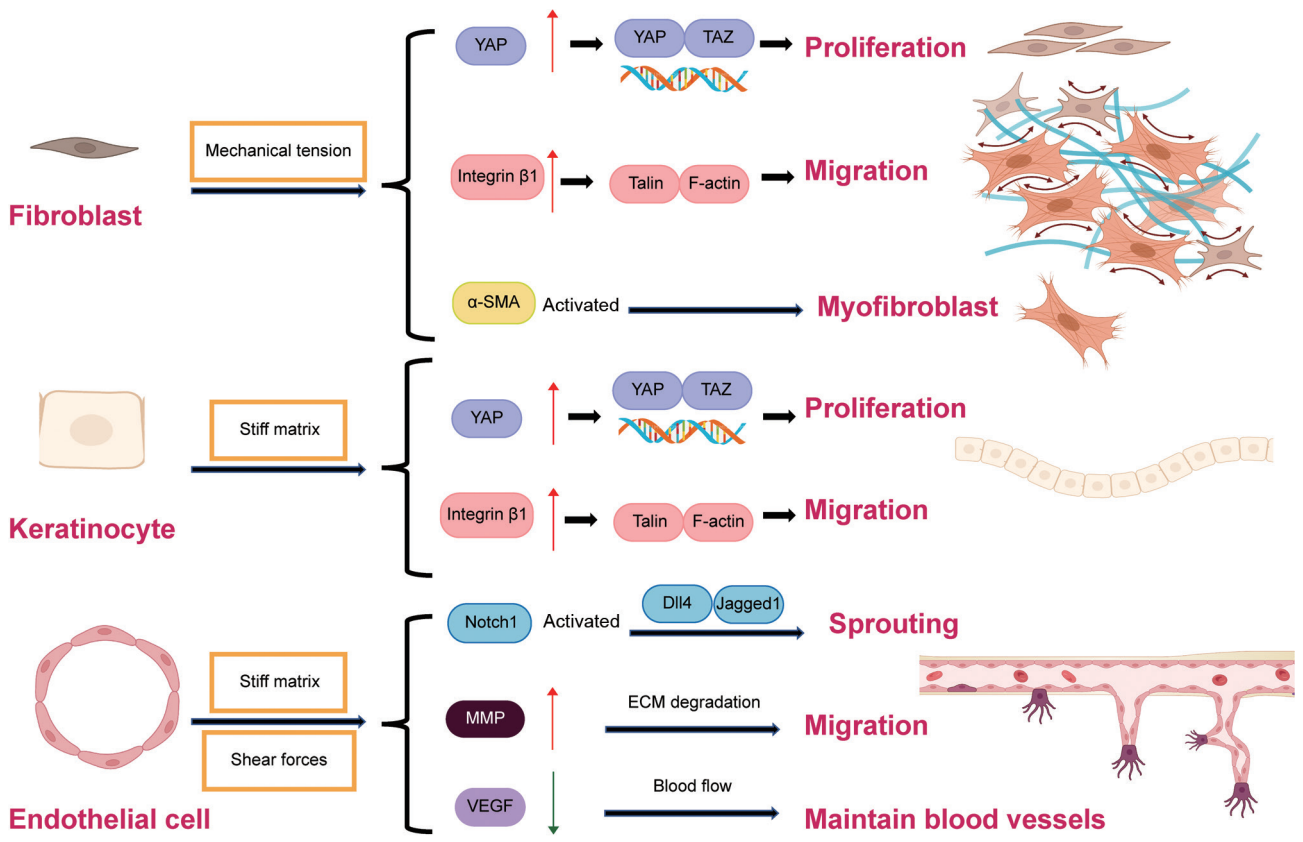


图2 机械力对增殖期主要细胞的影响

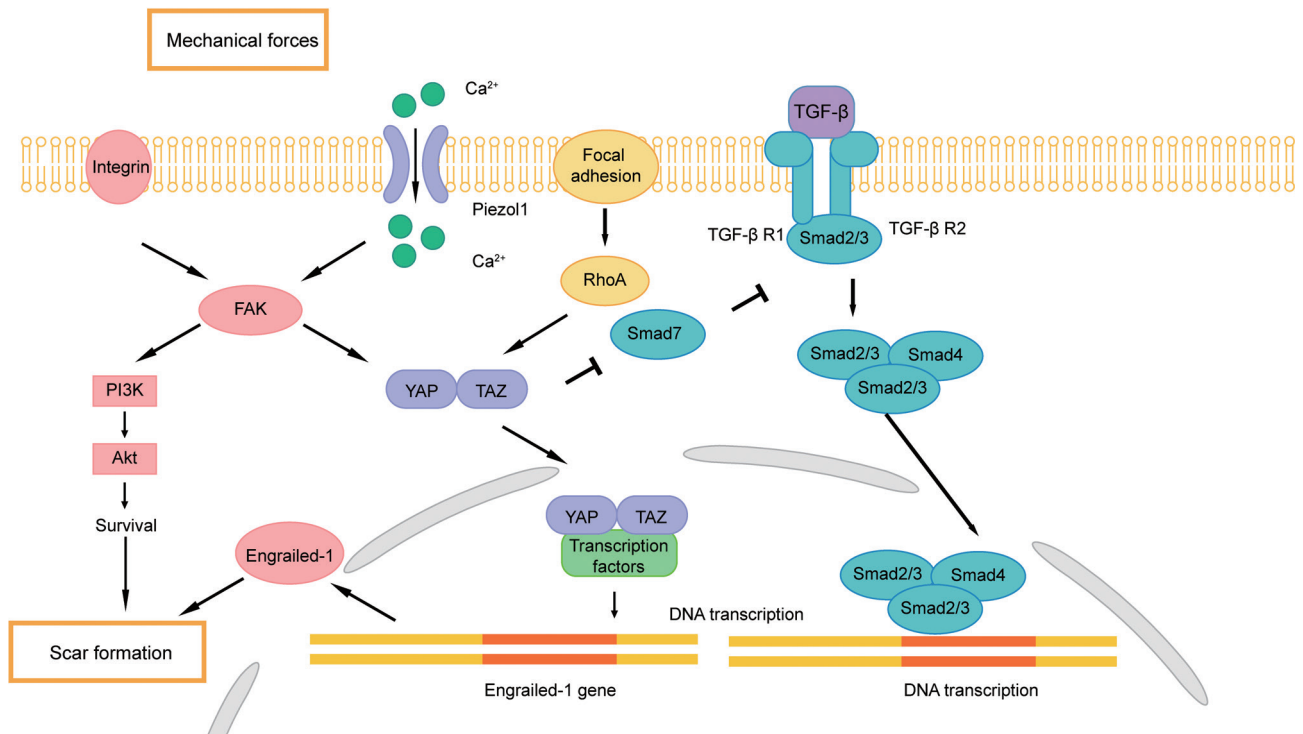


图3 机械力在重塑期对成纤维细胞的影响

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