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细胞体积对细胞生理功能的调控作用

杨月华, 姜洪源*

中国科学技术大学近代力学系, 中国科学院材料力学行为和设计重点实验室, 合肥 230027
* 联系人, E-mail: jianghy@ustc.edu.cn

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摘要 细胞作为一个动态的开放系统, 可以与周围环境不断进行物质和能量交换, 因而细胞体积可以发生很大的变化. 研究发现, 细胞体积的变化能够调控细胞的力学性质、代谢活动、细胞活性、细胞繁殖和基因表达等生理活动. 但是细胞体积和压力调控的力学机制, 以及细胞体积的变化对各种生理过程产生影响的物理机制仍有待研究. 本文将介绍相关的研究进展, 特别是关于动物细胞体积和压力调控机制的基本力学生物学模型, 并讨论细胞体积变化对癌细胞迁移以及细胞黏附和脱黏的影响机制.

关键词 离子通道, 水和离子的输运, 体积调节, 癌细胞迁移, 细胞黏附, 力学生物学

1 细胞体积调节的物理机制

1.1 实验现象

动物细胞维持自身体积的稳定对细胞的很多生理功能有十分重要的意义. 细胞体积的变化会影响细胞的力学性质[1,2]、细胞迁移[3,4]、细胞活性[5,6]、细胞增殖[7]和细胞分化[8]等. 不同于植物细胞与细菌, 动物细胞缺少坚硬的细胞壁来抵抗外界的力学刺激和限制体积的变化, 因此动物细胞需要一个调控自身体积的力学机制来适应不同的生理环境[9]. 如图1所示, 在低渗冲击下, 细胞体积首先会快速膨胀, 接着由于水和离子的输运, 细胞体积又会慢慢减小, 这个过程称为调节性体积减小(regulatory volume decrease). 而在高渗刺激下, 细胞体积首先会快速减小, 接着由于水和离子的输运, 细胞体积又慢慢增大, 这一过程称为调节性体积增大(regulatory volume increase). 这些体积恢复的过程, 最后使得细胞体积能够在不同的生理条件下保持稳定. 这种调节行为能够有助于稳定细胞形貌, 例如圆柱形的轴突细胞在低渗环境中的体积膨胀会引起形貌的转变, 由圆柱形变化成蠕动形(peristaltic shape). 通过自身的体积调节, 轴突细胞可以消除这种形貌变化带来的影响, 并在几分钟内恢复到圆柱形[10].

细胞膜上有许多水通道蛋白(aquaporins)、离子通道(ion channel)和离子泵(ion transporter)(如图2所示). 因此细胞膜对水、离子和小分子都有很好的渗透性[9], 同时细胞膜两边的静水压差与渗透压差可以直接控制这些水和离子的跨膜输运. 水是不可压缩的, 因此水的跨膜输运会直接影响细胞体积. 与此同时, 离子的跨膜输运会改变细胞内外的渗透压差, 从而影响细胞对水的输运. 因此, 通过协同调节水和离子的跨膜输运, 细胞可以很好地调控自身的体积. 细胞对离子的输运主要由两种膜蛋白控制, 力敏感通道和离子泵. 力敏感通道的蛋白质构象在细胞膜张力的作用下会发生变化[11], 从而引起力敏感通道的开合. 力敏感通道的开合概率与细胞膜张力的关系

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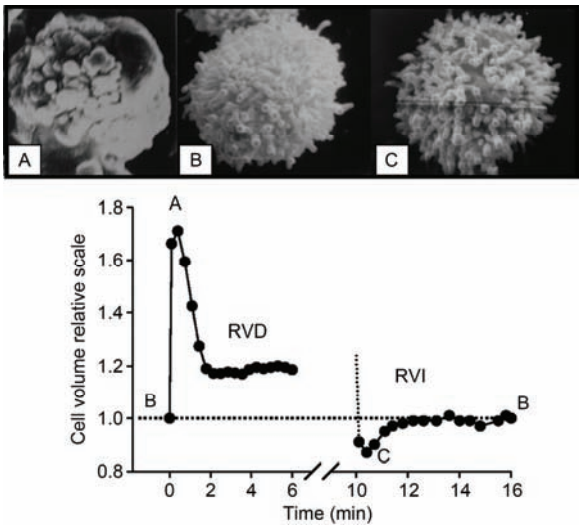

图 1 在渗透压作用下, 埃利希腹水瘤细胞(Ehrlich ascites tumor (EAT) cells)的调节性体积减小(regulatory volume decrease (RVD))和调节性体积增大(regulatory volume increase (RVI))过程. RVD: EAT细胞首先在等渗培养液中培养(300 mOsm), 在 0 时刻转移到低渗培养液(150 mOsm). 细胞体积以初始体积作归一化. RVI: EAT细胞首先在低渗培养液中 (225 mOsm) 培养 10 min, 之后转移到等渗培养液(300 mOsm)中[9]

Figure 1 Regulatory volume decrease (RVD) and regulatory volume increase (RVI) in EAT cells. RVD: EAT cells, preincubated in isotonic (300 mOsm) medium for 40 min, were at zero time transferred to hypotonic medium (150 mOsm). Cell volume is given relative to the initial isotonic volume. RVI: cells preincubated in hypotonic (225 mOsm) medium for 10 min were returned to isotonic medium[9]

可以用波尔兹曼函数来表示[11,12]. 由于力敏感通道是在离子浓度梯度的作用下被动输运离子, 所以力敏感通道输运离子的驱动力主要是来源于细胞内外的渗透压差. 不同于力敏感通道, 离子泵则是通过消耗三磷酸腺苷(adenosine triphosphate, ATP)水解的能量来抵消浓度梯度的能垒, 主动向细胞内部输运离子[13,14].

在细胞膜下有一层厚度200 nm[15]左右的肌动蛋白皮层(actin cortex, 图2). 肌动蛋白皮层主要是由肌动蛋白细丝(actin filaments)、肌球蛋白马达(myosin motors)和结合蛋白(actin-binding proteins)组成[16]. 肌动蛋白皮层能在一定程度上起到类似植物细胞和细菌中细胞壁的作用, 它是动物细胞的表面机械强度的主要来源并且能承受一定的机械力. 与普通的高分子聚合物网架不同, 由于连接蛋白(crosslinker)的循环和肌球蛋白产生的收缩, 整个肌动蛋白皮层会不断地重构自身的网架结构[16]. 因此在短时间内(<1 min), 肌动蛋白皮层主要表现为弹性[17], 弹性模量的量级为10^3 Pa[18]; 而在较长时间尺度下, 由于自身结构的重组以及连接蛋白的脱开, 肌动蛋白皮层表现为黏性[17]. 在肌球蛋白马达的作用下, 肌动蛋白皮层会主动产生收缩力, 从而能影响细胞膜的张力与细胞内部的静水压, 最终影响细胞体积的调控. 实验上已经观测到肌动蛋白皮层收缩力的震荡会引起悬浮细胞的体积震荡[19~21].

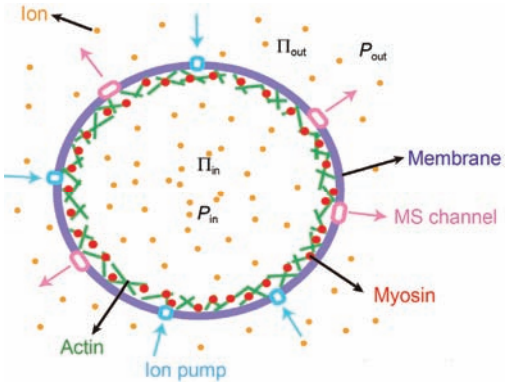

图 2 (网络版彩色)细胞的结构示意图. 细胞的外围是由actin皮层与细胞膜组成, 在细胞膜中, 会有许多的离子通道和离子泵[22]

Figure 2 (Color online) A spherical cell enclosed by an actomyosin cortex and the cell membrane. Embedded in the membrane are several families of passive MS ion channels and active ion pumps[22]

1.2 理论模型

要研究细胞体积调控的力学机制就必须综合考虑上面的几个因素, Jiang等人[22]提出了一个耦合了以上因素(水的渗透, 离子的主动与被动运输, 细胞皮层的力学影响)的力学生物学模型来研究动物细胞体积和压力的调控. 在他们的模型中, 悬浮细胞的半径r与细胞内部的离子数n随时间t的变化由以下方程描述:

$$\frac{\mathrm{d}r}{\mathrm{d}t}=J_{\mathrm{water}}=-\alpha(\Delta P-\Delta\Pi), \tag{1}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t}=4\pi r^2(J_{\mathrm{out}}+J_{\mathrm{in}}), \tag{2}$$

其中, α是细胞膜对水的渗透常数, ΔP是细胞内外的静水压差, $\Delta\Pi$是细胞内外的渗透压差; J_{out}与J_{in}分别是通过离子通道流出细胞和通过离子泵流入细胞的离子流量. 通过力敏感通道流出细胞的离子流量J_{out}与细胞的渗透压差$\Delta\Pi$和肌动蛋白皮层的应力σ成正比

$$J_{\mathrm{out}}=\begin{cases}0, & \text{if } \sigma<\sigma_{\mathrm{c}},\\ -\beta(\sigma-\sigma_{\mathrm{c}})\Delta\Pi, & \text{if } \sigma_{\mathrm{c}}\leqslant\sigma\leqslant\sigma_{\mathrm{s}},\\ -\beta(\sigma_{\mathrm{s}}-\sigma_{\mathrm{c}})\Delta\Pi, & \text{if } \sigma>\sigma_{\mathrm{s}},\end{cases} \tag{3}$$

其中, β是速率常数, σ_c和σ_s分别是力敏感通道打开与饱和的临界肌动蛋白皮层应力. 通过离子泵向细胞内部输运离子的流量为

$$J_{in} = \gamma(\Delta\Pi_c - \Delta\Pi), \quad (4)$$

其中, γ是速率常数, $\Delta\Pi_c$是离子泵能正常工作的临界渗透压差($\Delta\Pi<\Delta\Pi_c$). 如图3所示, Jiang等人[22]发现细胞在受到渗透压刺激之后能够通过水和离子的跨膜输运很好地自适应维持自身体积, 而且细胞最终的稳定体积与外界渗透压无关(图3(e)). 但是细胞内部的离子总数会随着外界的渗透压强度变化而变化(图3(g)).

2 体积调控对细胞迁移的影响

细胞迁移是很多生理和病理过程发生的基础, 如组织形态发育、伤口愈合、免疫应答和癌症转移. 目前, 我们对细胞迁移机制的了解大都来源于体外二维(2D)基底上细胞迁移的研究[23,24]. 如图3所示, 在2D平面基底上, 细胞迁移的经典模式是不断循环重复着4个步骤: (1) 肌动蛋白(actin) 聚合生成突触(protrusion)[23]; (2) 在细胞前部形成与整合素有关的新的黏附点; (3) 细胞后部的脱黏与回缩; (4) 肌球蛋白II(myosin II)引起的收缩使得细胞整体前移(图4)[25]. 因此, actin的聚合以及myosin II产生的收缩力对细胞在2D基底上的迁移是必不可少的. 目前, 已经有不少研究表明, 在2D基底上, 细胞可以感受到基底的药物梯度[26]、硬度梯度[27,28]以及黏附能梯度[29], 从而向药物浓度更高(趋药性), 基底更硬(趋硬性)和更黏(趋触性)的区域迁移. 虽然在2D基底上的细胞迁移与体内的某些生理过程是相类似的, 例如沿着内皮迁移的中性粒细胞或上皮细胞的伤口愈合, 但是大多数体外的2D迁移实验都不能很好地模拟细胞在生物体内迁移所遭遇的生理环境.

在生物体内, 细胞通常是在三维(3D)的细胞外基质中迁移, 此外细胞也会通过在三维管道内迁移[30]来穿越不同的组织. 这些3D管道通常是在结缔组织和肌肉、神经和上皮的基底膜之间形成. 在纤维间隙组织中, 相邻的胶原纤维之间也可以形成3D纵向管道. 这些体内的3D管道的横截面积的范围一般在10~300 μm^2[31], 这表明在生物体内迁移的细胞会受到不同程度的物理限制. 由于这些限制, 在3D管道内迁移的细胞无法与在2D基底上迁移的细胞一样形成板状伪足[32,33]. 同时还有实验发现, 即使抑制了actin的聚合以及myosin II的收缩, 细胞仍然能在3D管道内迁移[33]. 这些研究表明细胞在受限空间内存在一个与actin聚合、myosin活性以及细胞黏附无关的迁移机制.

有研究表明离子通道和水通道蛋白会影响细胞的迁移[9]. 通过药物抑制钠离子/氢离子通道-1(NHE-1)抑制细胞对离子的跨膜输运会降低内皮细胞和上皮细胞的迁移速度[34], 而水通道蛋白在肿瘤细

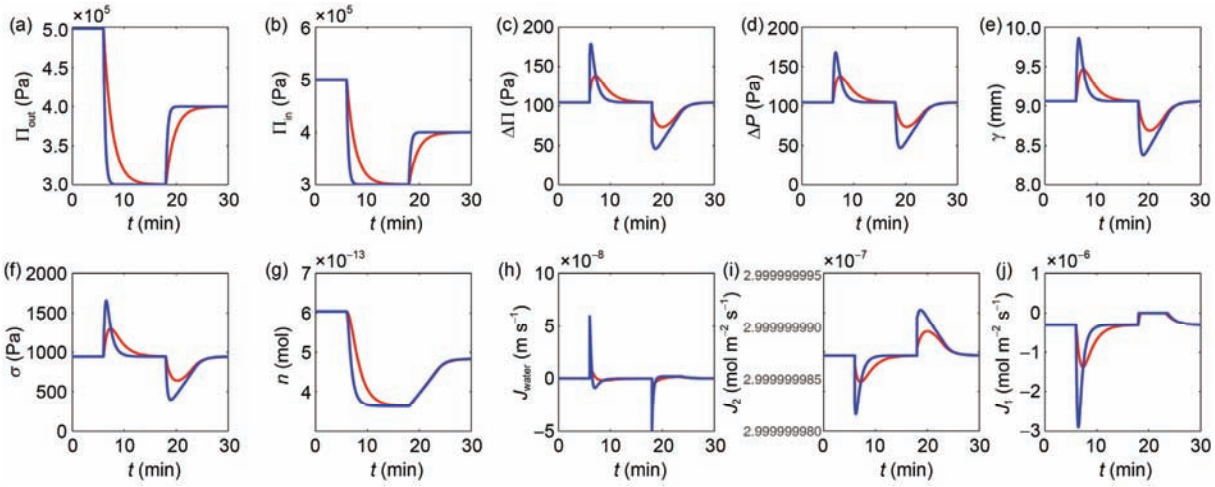

图 3 (网络版彩色)细胞在渗透压冲击下的体积调节[22]. (a) 在t=6 min引入一个低渗冲击, 接着在t=18 min引入一个高渗冲击, 两条曲线是两种不同波形的渗透压冲击; (b)~(j) 细胞的响应. 可以发现细胞稳定的半径总是保持一致

Figure 3 (Color online) Cells adapt to osmotic shocks[22]. (a) A hypotonic shock is introduced at t=6 min followed by a hypertonic shock at t=18 min. Two curves are two wave forms of the osmotic shock; (b)–(j) the response of the cell. We can find that cells can maintain a constant cell radius at different osmotic pressures

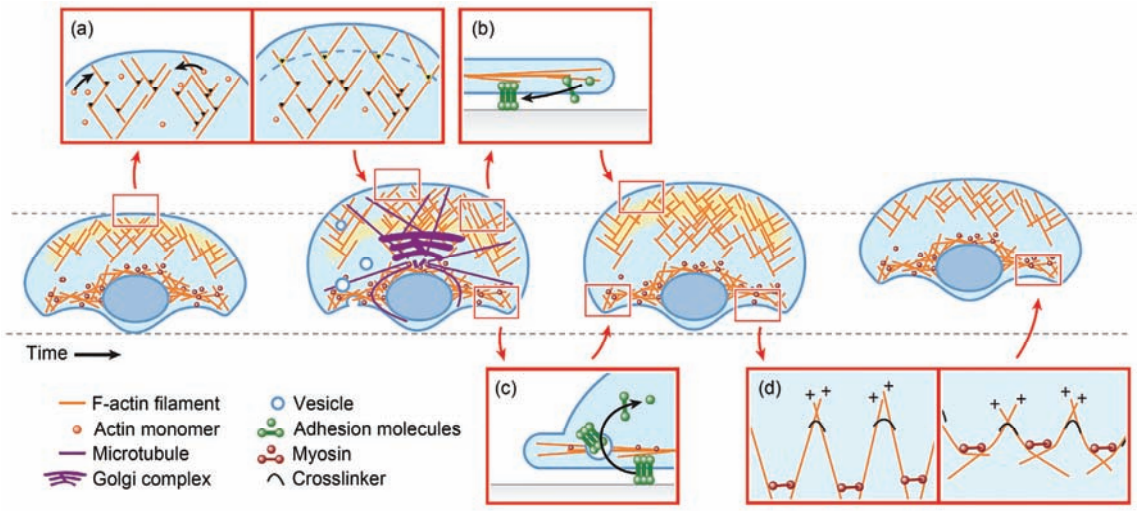

图 4 (网络版彩色)细胞迁移分为 4 个步骤. (a) Actin聚合产生聚合力促使细胞生成突触; (b) 在细胞前端形成新的黏附; (c) 细胞后部黏附的脱开; (d) myosin 产生的收缩力驱使细胞体发生位移[25]

Figure 4 (Color online) Cell migration is divided into four discrete steps. (a) Protrusion based on actin growth and polymerization force; (b) formation of new adhesions at the front; (c) release and recycling of adhesions at the rear; (d) actin myosin powered contraction of the cytoplasm, resulting in forward translocation of the cell body[25]

胞中的过表达能促进肿瘤细胞的迁移[4,35,36]. 实验还发现钠离子通道主要集中在迁移细胞的前端, 而钙离子通道和钾离子通道主要集中在迁移细胞的后部[37~39], 这意味着细胞前后端离子输运的差异可能会与细胞的极性有很大的关联. 对细胞施加渗透压冲击也会影响细胞的迁移, 嗜中性细胞的迁移在高渗冲击下会受到很大的抑制[40,41], 而肾上皮细胞的迁移在低渗或者高渗冲击下都会受到抑制[42,43]. Stroka等人[3]最近发现, 细胞在三维管道内迁移时, 钠离子通道和水通道蛋白主要集中在迁移细胞的前端. 从而导致了在细胞前端水和离子流入细胞, 而在细胞的后端水和离子流出细胞. 如图5(a)所示, 细胞前后两端水和离子跨膜输运的差异能够给细胞在受限空间内的迁移提供一个与细胞黏附和收缩无关的驱动力, 这个机制被称为“渗透压引擎模型”(osmotic engine model). 通过这个机制, 我们可以通过调控细胞迁移前端和后端的渗透压强度来控制细胞的迁移方向与速度(图5(b)~(d)).

3 体积调控对细胞黏附和脱黏的影响

细胞黏附对细胞迁移、细胞识别、硬度感知等起到十分重要的作用. 细胞黏附一般可以分为两大类: 特异性黏附与非特异性黏附. 特异性黏附主要来源于受体与配体的特异性结合, 这种特异性结合可以动态地脱开和重连[44]; 非特异性黏附主要来源于正负分子间的静电力[45,46], 以及溶质分子的排空作用[47,48]. 有实验发现在分裂细胞由黏附状态变圆时, 细胞体积可以增大30%[49], 这一过程可视为细胞动态铺展的反过程. 此外, 对于黏附在两个平行板之间的细胞, 在铺展过程中, 细胞的体积可以增大约30%[50].

最近Yang等人[51]的研究发现在细胞特异性地黏附到两平行板之间时(其中一个板易变形, 另一个则很难变形), 细胞除了能达到外凸和内凹的稳定黏附状态之外, 细胞还会出现自动破裂(细胞膜张力急剧增大)以及崩塌(细胞高度降为零)的不稳定黏附行为(图6(a)). 细胞的形貌主要是由细胞与平行板之间的黏附能密度Γ_0、两平行板的间隔H_0、细胞大小r_i、可变形板的刚度k决定(图7). 对于较大的细胞和较硬的可变形板, 细胞很难发生自动破裂这种不稳定现象(图7(a)). 在此基础上保持可变形板的刚度不变而减小细胞的大小, 在比较大的黏附能密度下细胞就会出现自动破裂这种不稳定现象(图7(b)). 至于崩塌这种不稳定现象, 只有在很软的平行板和较大的黏附能密度的情况下才会出现(图7(c)和(d)). 在黏附能密度很大时, 非常软的可变形板不足以抵抗细胞黏附产生的收缩力, 最终会使得细胞的高度降为零. 有趣的是, 自动破裂和崩塌的不稳定黏附行为在细胞

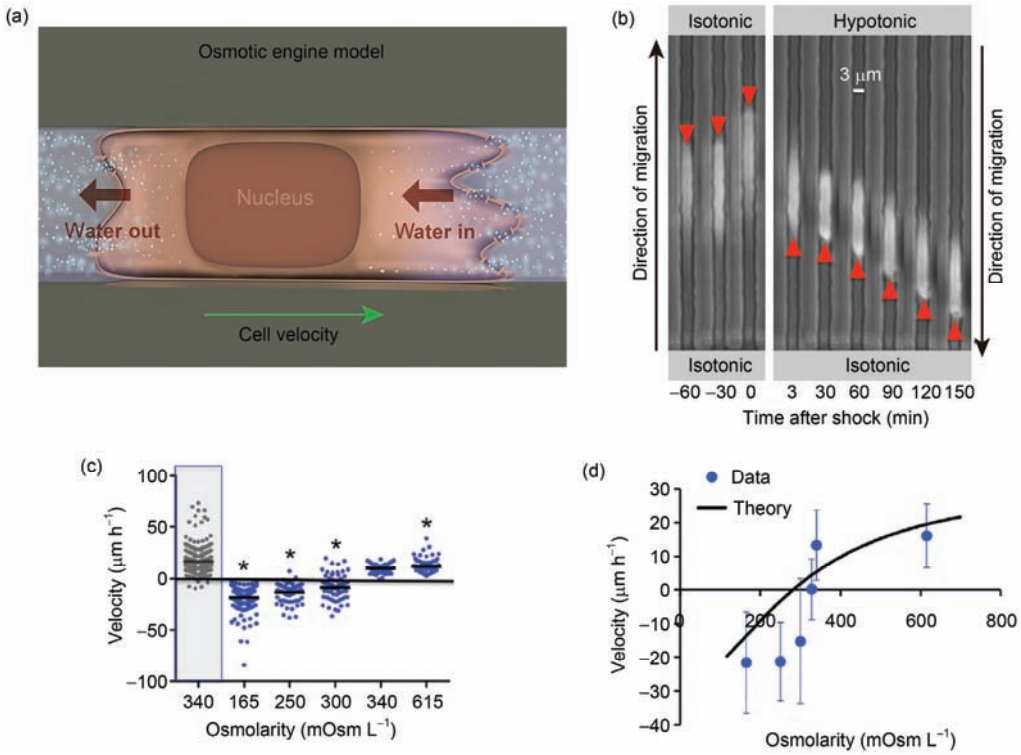

图 5 (网络版彩色)渗透压引擎模型[3]. (a) 细胞前后水的跨膜输运会驱使细胞在受限空间内迁移; (b) 在迁移细胞前端施加低渗冲击会改变细胞的迁移方向; (c), (d) 细胞迁移的速度与细胞前端的渗透压强度有关

Figure 5 (Color online) Osmotic Engine Model[3]. (a) Water permeation through the cell membrane at leading and trailing edges drives cell migration in confined microenvironments; (b) a hypotonic shock at the leading edge can change the direction of cell migration; (c), (d) cell velocity as function of the osmolarity at cell leading edge

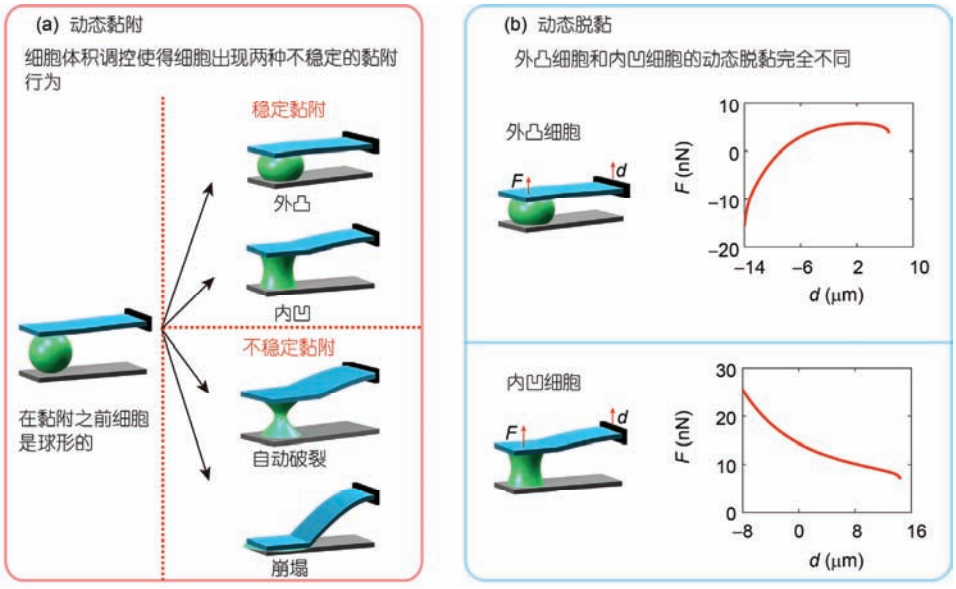

图 6 (网络版彩色)细胞体积调控对细胞动态黏附与动态脱黏的影响. (a) 由于体积的调控细胞可以稳定地(外凸或者内凹)或者不稳定地(自动破裂或者崩塌)黏附到两平行板之间; (b) 稳定黏附的外凸细胞和内凹细胞的动态脱黏过程有显著性差异

Figure 6 (Color online) The influences of cellular volume regulation on the dynamic adhesion and dynamic detachment. (a) The adherent cells can be either stable (convex or concave) or unstable (spontaneous rupture or collapse); (b) the detachments of convex cells and concave cells are very different

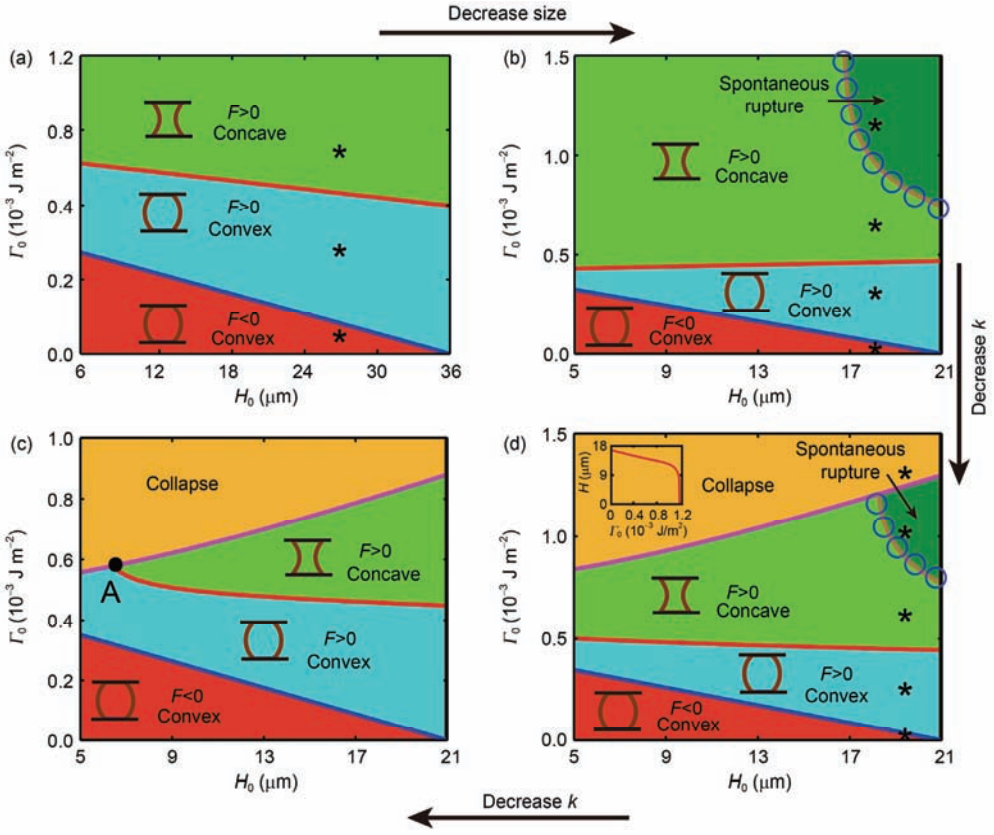

图 7 (网络版彩色)细胞黏附的形貌会受到细胞与两平行板之间的黏附能密度Γ_0, 两平行板间的间隔H_0, 细胞大小r_i, 和可变形板的硬度k的影响[51]. (a) r_i=18 μm, k= 0.5 N m^{-1}; (b) r_i=10.5 μm, k=0.5 N m^{-1}; (c) r_i=10.5 μm, k=0.005 N m^{-1}; (d) r_i=10.5 μm, k=0.01 N m^{-1}

Figure 7 (Color online) The shape of the adherent cells is determined by the adhesion energy density Γ_0, the separation of two parallel microplates H_0, the cell size r_i, and the stiffness of the flexible microplate k[51]. (a) r_i=18 μm, k= 0.5 N m^{-1}; (b) r_i=10.5 μm, k=0.5 N m^{-1}; (c) r_i=10.5 μm, k=0.005 N m^{-1}; (d) r_i=10.5 μm, k=0.01 N m^{-1}

体积恒定时消失了. 这些结果表明, 自动破裂和崩塌这两个独特的不稳定黏附行为是直接由黏附过程中细胞体积的变化引起的. 此外, 由于脱黏过程中体积变化趋势的不同, 稳定黏附的外凸和内凹细胞在受拉脱黏时的动力学行为存在着明显的差异. 外凸细胞脱黏过程中所受的拉力随着拉伸距离的增大而增大, 但是内凹细胞脱黏过程中受到的拉力则是随着拉伸距离的增大而减小(图6(b)). 最后, 作为一个开放系统, 细胞从基底脱开的黏附强度和断裂力还与加载速度和加载历史有关.

上述发现对指导细胞力学实验非常重要. 即使针对同一种细胞做测量, 如果细胞大小、细胞与平行板之间的黏附能密度、两平行板的间隔、可变形板的刚度、加载速度和加载历史有所不同, 则得到的结果会有很大差别, 甚至会得到互相矛盾的结果. 因此, 实验中需要谨慎选择上述的实验参数, 才能得到真正有意义的结果.

4 总结与展望

细胞作为一个开放系统, 可以与外界的生理环境进行水和离子的交换, 从而调控自身的体积和压力. 这种调控机制可以使得细胞能够很好地维持合适的体积和压力来保证细胞的活性以及行使自身的生理功能. 目前, 虽然已经发现细胞的体积变化会对癌细胞在受限空间内的迁移[3]和细胞黏附[51]等生理过程有重要的影响. 但是在很多其他生理过程中也会伴随着明显的细胞体积变化, 例如在果蝇胚胎发育过程中的背部愈合时细胞体积会明显减小[52], 在细胞受到剪切时体积也会明显减小[53,54]. 因此, 还有很多问题有待进一步地研究. 例如, 在细胞动态铺展的过程中细胞体积是如何变化? 细胞培养的基底的力学性质如何调控细胞的体积? 细胞体积在

伤口愈合、细胞趋硬、趋触等迁移行为中又是起到什么作用？细胞体积调控是否对细胞的硬度感知、力学信号的传递以及细胞分化有明显的影响？详细地了解细胞体积在上述生理过程中的调控机制，我们将来就有可以通过改变细胞的体积大小来调控细胞的生理功能.

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Summary for “细胞体积对细胞生理功能的调控作用”

The effect of cellular volume regulation on cell physiological functions

Yuehua Yang & Hongyuan Jiang*

CAS Key Laboratory of Mechanical Behavior and Design of Materials, Department of Modern Mechanics, University of Science and Technology of China, Hefei 230027, China
* Corresponding author, E-mail: jianghy@ustc.edu.cn

As an open system, cells can exchange water, ions and energy with the environment, thus the cellular volume and pressure are not constant. In the last decade, cellular volume regulation has attracted intense attention. It has been found that the changes of cell volume can impact many cell physiological processes, such as cell mechanical properties, cell metabolic activities, cell viability and cell growth. However, the mechanisms of cellular volume regulation and how the changes of cell volume affect cell physiological functions are still unclear. In this paper, we will briefly review the mechanisms of cellular volume and pressure regulation, as well as the roles of cellular volume regulation in cancer cell migration, cell adhesion and cell mechanics.

The regulation of cellular volume includes the combined effects of the transport of water and ions, as well as the mechanical properties of cytoskeleton. The membrane is permeable to water and the flow of water is driven by the osmotic pressure difference and the hydrostatic pressure difference across the membrane. Since water is incompressible, the transport of water is directly related to the changes in cellular volume. And cells can regulate the ion number (the osmotic pressure) inside the cells by the ion efflux through ion channels and ion pumps. The properties of cytoskeleton can control the activity of ion channels, and then affect the cellular volume regulation. Experiments found that when cells migrate in narrow channels, they can undergo persistent movement in one direction for several hours, and this persistent movement occurs spontaneously in the absence of external gradients. Inhibition of adhesion complexes and cortical contractility do not affect cell migration in narrow channels. In contrast, the adhesion complexes and cortical contractility are the prerequisite of the cell migration on two dimensional substrates since they can provide the traction force for cell migration. Recent theoretical studies and experiments have showed that the water permeation through the cell membrane at leading and trailing edges can provide the driving force for the cell migration in the 3D confined microenvironments. Furthermore, the changes in cell volume can affect the morphology and mechanics of cells adhered between two surfaces. Depending on the cell size, adhesion energy density, the separation of two adhesive surfaces, and the stiffness of the flexible surface, cells can be convex or concave. Furthermore, the changes in volume can directly lead to two unstable adhesion states, i.e., spontaneous rupture and collapse. The changes in cell volume can also affect the detachment of adherent cells. Different changes in cell volume would lead to different detachment behavior for convex cells and concave cells. The cell volume of convex cells decreases during detachment, which is accompanied by a decrease in stretch force. However, the volume of concave cells increases during detachment, and then leads to an increase in stretch force. Moreover, as an open system, the mechanical responds of cells is related to the loading history and the loading rate.

This review summaries the mechanisms of cellular volume regulation, emphasizes the importance of water and ion transport in cellular volume regulation, and discusses the regulating roles of cellular volume changes in cancer cell migration, cell adhesion and cell detachment. In conclusion, this review provides an overview of the experimental and theoretical developments on cellular volume regulation, and discusses the current challenges and further prospects of how cellular volume changes affect the cell physiological processes, such as wound healing, cell spreading, membrane trafficking, rigidity sensing, haptotaxis, durotaxis and cell fate determination.

ion channels, water and ion transport, volume regulation, cancer cell migration, cell adhesion, mechanobiology

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