文章编号:1004-7220(2023)03-0451-07

树突状细胞的生物力学与力学生物学研究进展

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摘要:树突状细胞(dendritic cells, DCs)是目前已知机体内功能最为强大的抗原提呈细胞,具有高效的抗原摄取、加工和处理能力,能够在二级淋巴组织向幼稚 T 细胞提呈抗原,从而诱导免疫应答或耐受,在启动和放大先天性及适应性免疫中发挥关键作用。DCs 在发挥其生理学功能的过程中经历复杂的化学和力学微环境变化,并表现出不同力学表型和免疫表型,深入理解调控 DCs 力学表型和免疫表型的化学和力学因素是利用其治疗免疫相关疾病的先决条件。本文主要介绍 DCs 生物力学与力学生物学研究的进展,并探讨其在免疫相关疾病治疗中的潜在应用和未来发展方向。

关键词: 树突状细胞; 力学表型; 免疫表型; 生物力学; 力学生物学
中图分类号: R 318.01 **文献标志码**: A
DOI: 10.16156/j.1004-7220.2023.03.004

Progress in Biomechanics and Mechanobiology of Dendritic Cells

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Abstract: Dendritic cells (DCs) are now known as the most powerful antigen-presenting cells *in vivo*, with efficient antigen uptaking, and processing capabilities. They can present antigens to naïve T cells in secondary lymphoid tissues, thereby induce immune response or tolerance, and play a key role in initiating and amplifying innate and adaptive immunity. DCs experience complex chemical and mechanical microenvironment changes and show different mechanophenotypes and immunophenotypes in the process of exerting their physiological functions. Deeply understanding the chemical and mechanical factors that regulate the mechanophenotypes and immunophenotypes of DCs is a prerequisite for using DCs to treat immune related diseases. In this review, the progress in the biomechanics and mechanobiology research of DCs was mainly introduced, and their potential applications and future development directions in the treatment of immune related diseases were explored.

Key words: dendritic cells (DCs); mechanophenotypes; immunophenotypes; biomechanics; mechanobiology

收稿日期:2023-05-29; **修回日期**:2023-06-02
基金项目:国家自然科学基金项目(12132006, 31771014, 11762006)
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树突状细胞(dendritic cells, DCs)是已知功能最强大的专职抗原提呈细胞(antigen presenting cells, APCs),在先天性和适应性免疫应答的启动过程中发挥着关键作用。从功能上来说,DCs 在执行其免疫调节功能的过程中分为未成熟 DCs(immature DCs, imDCs)和成熟 DCs(mature DCs, mDCs)两个分化阶段。在机体内,imDCs 通常巡游于皮肤和黏膜等外周组织,当遭遇并识别抗原后,通过吞噬、胞饮等方式摄取并加工、处理抗原,逐渐降低其抗原吞噬能力,上调主要组织相容性复合体(major histocompatibility complex, MHC)、CD40、CD80、CD83、CD86、趋化因子受体 7(chemokine receptor 7, CCR7)等免疫表型分子的表达,沿着淋巴管内皮细胞分泌的趋化因子配体(CC chemokine ligand, CCL)19 和 21 浓度梯度,迁移至二级淋巴组织,分化为 mDCs;在淋巴结内,mDCs 与幼稚 T 细胞(naïve T cells)发生动态的物理性相互作用,形成免疫突触,向其提呈所获抗原,刺激幼稚 T 细胞抗原特异性增殖,从而启动适应性免疫应答或耐受。由于 DCs 在免疫系统中的特殊地位,使其成为免疫相关疾病(肿瘤、自身免疫性疾病等)治疗的逻辑靶点[1-4]。目前,基于 DCs 的肿瘤疫苗(DCs-based tumor vaccination, DCBTV)在临床抗肿瘤免疫治疗方面虽然取得了重大的进展,但是该疗法目前的临床治疗效率较低,还有许多问题需要解决,例如肿瘤的免疫逃逸和 DCs 的迁移能力低下等[1]。研究发现,imDCs 和 mDCs 的迁移能力分别是保证它们在外周组织巡游并摄取抗原以及在二级淋巴组织内与幼稚 T 细胞相互作用并提呈抗原的必要条件,即 DCs 的免疫调节功能高度依赖于其迁移能力[5-7]。细胞的生物力学特性可以反映其结构和功能的关系,也被称为力学表型(mechanophenotype),包括细胞的黏弹性、变形能力、膜流动性、电泳率、渗透脆性和骨架结构等[8-9],与其周期、分化、代谢和迁移等密切相关[10-15]。近年来,免疫细胞的力学表型和免疫表型(immunophenotypes)间的关系及其潜在的力学-化学耦合分子机制越来越受到人们的关注[16-17]。自 2000 年以来,本课题组一直从生物力学(Biomechanics)与力学生物学(Mechanobiology)角度研究影响不同分化阶段 DCs 力学表型的化学(肿瘤微环境来源的抑制性细胞因子)和物理(细胞外基质硬度等)因素,以期深入理解 DCs 的免疫调节功能,为基于 DCs 的免疫相关疾病的临床治疗提供理论依据。

1 不同分化阶段 DCs 的力学表型

不同分化阶段的 DCs 具有不同的力学表型。DCs 的分化成熟过程伴随着细胞骨架 F-actin 重塑导致的显著形态变化[18],从其分化前体-单核细胞(monocytes, MOs)经 imDCs 分化为 mDCs 的过程中,树枝状突起的数量和长度逐步增加,F-actin 结构由致密变疏松且表达量减少,变形能力与迁移能力增强,这与细胞骨架结合蛋白的时空表达差异密切有关[19-20]。细胞膜流动性能够反映膜脂分子的运动情况,从 MOs 到 mDCs 的分化过程中,膜流动性逐渐增加,膜脂分子运动加快[18,21]。imDCs 膜流动性的增加有利于其在外周组织巡游并识别、吞噬和加工处理抗原;mDCs 膜流动性的增加有利于其在二级淋巴组织内与幼稚 T 细胞相互作用,形成免疫突触并进行抗原提呈,进而诱导幼稚 T 细胞抗原特异性活化和增殖[22],这与 DCs 细胞膜胆固醇等脂质分子成分的动态变化相关[21]。生理状态下,细胞膜糖蛋白携带的唾液酸水解赋予其表面携带负电荷,可以用细胞电泳率来反映[23],这种负电屏障的存在影响细胞间相互作用和迁移等生物学行为。MOs 到 mDCs 分化过程中,细胞电泳率显著增加,即膜表面带有更多的负电荷,意味着细胞间斥力增大[18],这可能是 mDCs 相较于 MOs 和 imDCs 低黏附特性的原因之一[24]。渗透脆性是指细胞抵抗低渗透压环境的能力,可以反映细胞膜抗张强度[25-27]。不同渗透压下,MOs、imDCs 和 mDCs 的渗透脆性曲线变化趋势基本一致,但 imDCs 和 mDCs 抗低渗能力明显高于 MOs[18],说明 imDCs 和 mDCs 能抵抗更大的渗透压,更能适应体内不同渗透压微环境,与二者较好的变形能力有关。这些研究结果表明,不同分化阶段的 DCs 具有不同的力学表型,且与其免疫表型相适应。另外,本课题组对 DCs 诱导的免疫应答启动过程中外周组织和淋巴结内 DCs 和 T 细胞的动态结合进行数值模拟,该数学模型可准确模拟 imDCs、mDCs 和 T 细胞的数量变化和适应性免疫应答启动所需要的时间[28]。

2　肿瘤微环境化学因素对 DCs 力学表型和免疫表型的影响

肿瘤微环境由肿瘤细胞、基质细胞、免疫细胞和细胞外基质(extracellular matrix,ECM)等组成,是肿瘤细胞增殖、生存、侵袭和转移等的主要场所,具有弱酸性,缺氧、高间质压和纤维化等特征。肿瘤浸润部位有 DCs 存在,且 DCs 的数量与肿瘤浸润程度呈负相关,与肿瘤患者的临床治疗预后呈正相关[29],但是潜在的机制还不清楚。本课题组先后发现,Jurkat 细胞(急性 T 细胞白血病细胞系)培养上清[30]、肝癌细胞(hepatocellular carcinoma cells,HCCs)[31]和 K562[32]细胞(髓性白血病细胞系)等能够异常重塑 DCs 的力学表型和免疫表型;肿瘤细胞培养上清中存在大量的血管内皮生长因子(vascular endothelial growth factor,VEGF)、转化生长因子-β1(transform growth factor-β1,TGF-β1)和白介素 10(interleukin-10,IL-10)等抑制性细胞因子,VEGF 和 TGF-β1 分别通过 VEGFR2-RhoA-cofilin1 和 Smad2/3 通路损伤 DCs 力学表型和免疫表型[7,33-35];酸性微环境[36]和渗透压[37]也同样能够异常重塑 DCs 的力学表型和免疫表型。因此,肿瘤来源的化学因素对 DCs 力学表型的异常重塑可能是肿瘤免疫逃逸机制的一个方面,建议临床施行 DCBTV 疗法前阻断抑制性细胞因子的信号通路,提高 pH 值,降低间质压力,以提高该疗法的临床治疗效率。

3　力学因素对 DCs 力学表型和免疫表型的影响

力学生物学的观点认为,在整个生命周期中,细胞、组织、器官始终处于复杂的力学因素作用下,且几乎所有的细胞都具有力学刺激敏感性。细胞从个体到群体对生物力学环境变化做出响应,参与调控机体各种生理及病理生理过程[38],如动脉粥样硬化[39]、纤维化[40-41]和癌症[42-43]等。临床上,基于吡非尼酮和尼达尼布等抗纤维化药物改变病理状态下力学微环境的相关疗法有效性反映了生物力学因素对调控细胞生物学行为的重要性[44-45]。近年来,生物力学因素对 DCs 等免疫细胞的力学表型和免疫表型的调控及其潜在力学-化学耦合分子机制越来越受到人们的关注。

一般认为,imDCs 通过模式识别受体(pattern recognition receptor,PRR)识别并结合病原体表面病原体相关模式识别分子(pathogen associated molecular pattern,PAMP)识别并吞噬抗原,从而分化为 mDCs,进而有效提呈抗原信息,刺激 T 细胞抗原特异性增殖,启动适应性免疫应答[46]。然而,有研究发现,在无病原体提供抗原信息的情况下,生物力学因素也能调控 DCs 免疫表型。Craig 等将 imDCs 暴露于 40 mmHg 的压力环境中 12 h 后,细胞共刺激分子 CD80、CD86 和 MHC-II 的表达明显上调,IL-12、IL-6、TNF-α、IFN-γ 等炎性细胞因子的分泌增加[47]。Chakraborty 等[48]发现,硬度为 50 kPa 的 ECM 能够上调 DCs 的免疫表型分子(CD80、CD86)、MHC-II 和促炎性细胞因子(IL-6、IL-12、TNF-α)的表达,表现出 mDCs 的生物学特征,Mennens 等[49]的研究也发现了相似的结果。而 Lewis 等[50]研究发现,心血管系统或肺中普遍存在的基质拉伸力虽然上调了 DCs 免疫表型分子的表达,但细胞因子的分泌不受影响。本课题组最近发现,二维和三维纤维蛋白原水凝胶能够显著改变 DCs 的力学表型,在 RhoA 和 CDC42 信号通路介导下,imDCs 和 mDCs 的免疫表型分别受到负调控和正调控[51-52]。Moura 等[53]研究发现,流体剪切力可调控 DCs 与 T 细胞的互作过程,且剪切力作用下 $CD4^+$T 细胞与 DCs 的结合力明显强于 $CD8^+$ T 细胞。此外,基质拉伸也能促进 DCs 诱导的 $CD4^+$ T 细胞增殖[50]。体内实验也证实,在硬基底上培养的 DCs 回输到体内,将介导 $CD4^+$和 $CD8^+$ T 细胞活化,引起更强的抗肿瘤免疫应答[48]。流体剪切力、基质拓扑结构的不同也可调控 DCs 的分化成熟过程[54-55]。Mathaes 等[56]研究发现,抗原的几何大小及表面形貌的可以影响 DCs 的分化程度,球形纳米颗粒诱导的 DCs 免疫表型分子的表达高于椭圆形纳米颗粒,导致 mDCs 有较强的刺激 T 细胞活化的能力[57-58],促进炎症反应的发生[48]。这些研究结果表明,生物力学因素在调控 DCs 的免疫表型方面发挥着重要作用。

DCs 的免疫功能发挥高度依赖于其高效的迁移能力。在不同的维度下 DCs 表现出不同的形态特征[51]和迁移模式。2D 环境下,DCs 以整合素依赖

的模式迁移,与细胞骨架结构及其结合蛋白肌动蛋白相关蛋白 2/3(actin-related protein 2/3, Arp2/3)和肌球蛋白 myosin 的分布有关,而在 3D 环境下,DCs 以非整合素依赖的方式迁移,与 Arp2/3 和 Myosin 的分布无关[59]。Choi 等[60]研究发现,随着 ECM 硬度的增加,DCs 迁移速度变慢,迁移范围缩小,这可能与高硬度下 DCs 伪足小体的减少和 CCR7 的表达下调有关[61]。此外,ECM 的拓扑结构也能调控 DCs 的迁移[62]。

现有研究表明,免疫细胞主要通过其膜上的力学感受器感知胞外力学环境的变化,T 细胞受体等免疫受体和整合素等黏附分子等都是力学刺激敏感分子[63]。近年来,有研究发现,机械力敏感的钙离子通道 Piezo1 是巨噬细胞(macrophage, Mφ)一种力学感受器,它能通过上调胞内钙离子浓度、活化钙蛋白酶 2(calpain 2)和焦点黏附激酶(focal adhesion kinase, FAK)等来应答硬度、拓扑结构、空间束缚、流体剪切力和渗透压等力学刺激的变化,进而影响细胞骨架的动态重塑过程,导致细胞生物学行为的改变[64]。在 DCs 向 T 细胞提呈抗原的过程中,DCs 和 T 细胞之间的黏附力能够激活 T 细胞表面的 Piezo1 离子通道,驱动钙内流和 Calpain 2 的活化,进而调控 T 细胞骨架的重塑,利于 T 细胞与 DCs 之间免疫突触的形成[65]。有学者发现,细胞局部钙离子振荡的形成依赖于机械力激活的瞬时受体电位钙离子通道(transient receptor potential melastatin7, TRPM7)的活性。在 2D 条件下,游离钙离子信号通过钙调蛋白(calmodulin)-肌球蛋白轻链激酶(myosin light chain kinase, MLCK)-Myosin II 通路使内皮细胞前部形成片状伪足收缩[66]。Solanes 等[67]发现,钙离子信号与 DCs 的迁移速度呈正相关。在受限环境下,DCs 快速、高效迁移伴随着三磷酸肌醇受体(inositol 1,4,5-triphate receptor, IP3R)-Myosin II 依赖的胞内钙离子浓度波动。另外,本课题组用荧光共振能量转移(fluorescence resonance energy transfer, FRET)技术初步证明,DCs 能够通过 G 蛋白偶联受体(G protein coupled receptor, GPCR)-Src 通路对 1 Pa 流体剪切力的刺激产生应答,而且剪切力的刺激应答早于 GPCR 的激动剂去甲肾上腺素的作用,说明力学刺激的效果早于化学刺激(未发表数据)。

4 总结与展望

生物力学与力学生物学研究旨在通过生物医学和力学的理论与技术方法相融合,实现对生命过程中的力学因素及其作用进行定性与定量研究,从而认识生命过程规律,解决生物学、医学领域科学问题[68],阐明细胞对力学微环境感知并应答的力学-化学耦合分子机制是其中的重要内容。深入理解生理和病理生理状态下的免疫细胞对整体或局部力学微环境刺激的应答及其潜在的力学-化学耦合分子机制以及力学表型和免疫表型的相互关系会进一步丰富力学免疫学(mechanoimmunology)和免疫力学生物学(immuno-mechanobiology)的内涵,甚至可能会催生力病理学(mechnopathology)和力医学(mechanomedicine)的概念,为相关疾病的临床治疗提供新的思路和理论基础。

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