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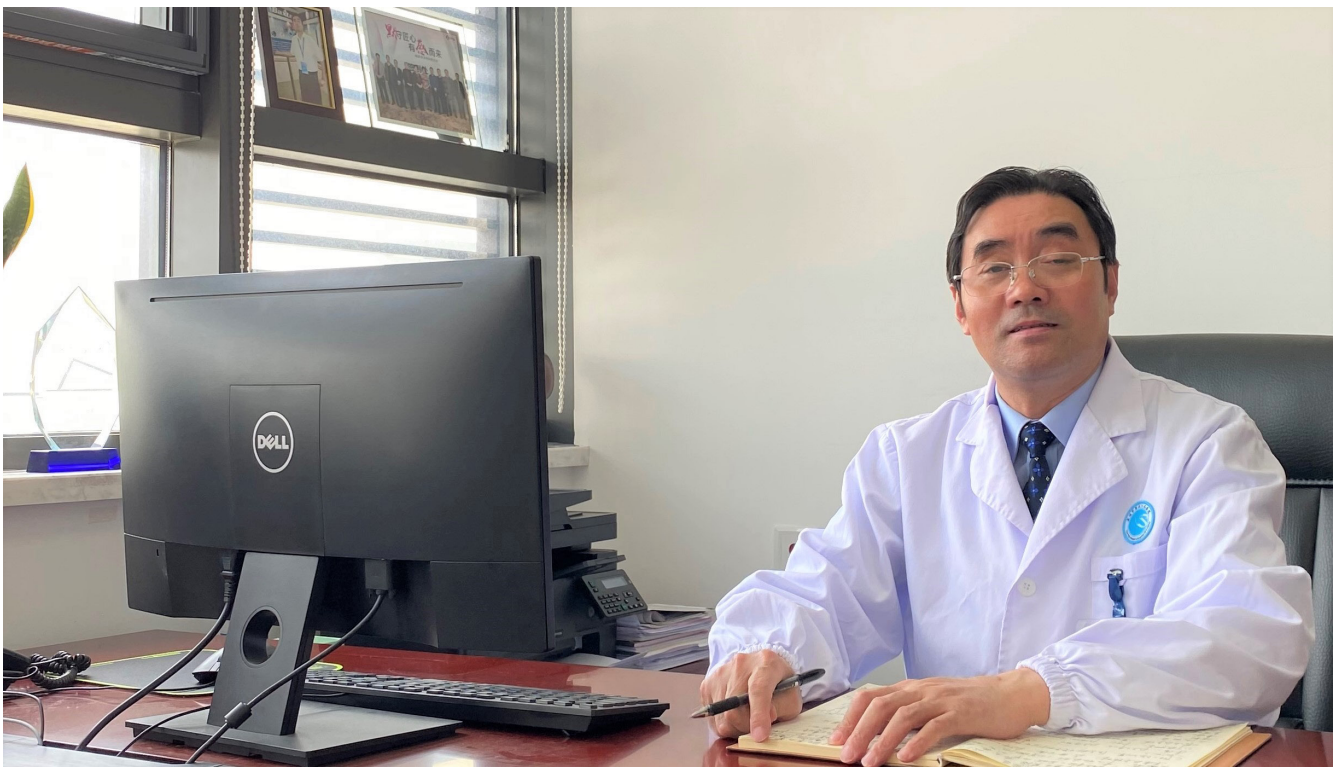

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述评 EDITORIAL

机械敏感性离子通道蛋白Piezo1在肿瘤研究中新进展

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王咪咪, 博士研究生, 研究方向为肝癌侵袭转移机制的基础研究.

基金项目: 机械敏感通道蛋白Piezo1感应硬度力学信号调控肝癌转移新机制, 国家自然科学基金资助项目, No. 81972910.

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Role of mechanosensitive ion channel Piezo1 in tumors

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Abstract

A better understanding of mechanotransduction mechanisms is the key to exploring biomechanical signal-regulated tumor malignant characteristics, and it is also the theoretical and practical basis for effective intervention from the upstream of mechanical cues. The discovery of the novel mechanosensitive ion channel protein Piezo1 (piezo type mechanosensitive ion channel component 1) provides a new perspective for the study of mechanotransduction mechanism in tumors. This article summarizes some of the latest research progress of Piezo1 in modulating tumor progression, including inducing cell carcinogenesis; regulating cell cycle, proliferation, invasion, and metastasis; influencing tumor stemness and angiogenesis; as well as reprogramming tumor immune microenvironment, *etc.*

Key Words: Piezo1; Mechanical signals; Digestive system tumors

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摘要

生物力学信号传递机制是从生物力学角度探讨其调控肿瘤恶性特征的关键, 也是力学信号源头干预的理论实践基础. 近期新型机械敏感离子通道蛋白Piezo1(piezo type mechanosensitive ion channel component 1, Piezo1)感应力学信号新途径的出现, 为肿瘤细胞力学传递机制研究提供了新的视角. 本文归纳总结了Piezo1介导力学信号参与肿瘤发生进展调控的新进展, 包括诱导细胞癌变, 调控细胞周期、增殖和侵袭转移, 影响肿瘤细胞干性, 血管新生, 调控肿瘤免疫微环境等.

关键词: Piezo1; 力学信号; 消化系统肿瘤

核心提要: 本文归纳总结了Piezo1作为机械敏感性离子通道在消化系统肿瘤中的研究进展, 包括其介导力学信号诱导肿瘤细胞癌变, 参与调控细胞周期、增殖, 侵袭转移, 干性, 血管新生, 及免疫微环境等.

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0 引言

从细胞形态维持到组织发育驱动, 力学信号的影响无处不在. 与在正常组织发挥的生理调节不同, 力学信号在实体肿瘤发生、生长、侵袭转移等恶性进展中起着不可忽视的促进作用[1-3]. 生物力学信号常来自于基质硬度、挤压力、牵拉力、流体剪切力等力学刺激, 上述力学刺激可显著改变细胞生物学功能, 同时细胞亦会通过改造胞外微环境以适应周边力学压力, 以此形成一个反馈循环, 而阐明生物力学调控反馈循环机制, 尤其是细胞如何感应力学信号无疑为疾病干预提供了新的研究方向.

将机械力学信号转化为生物信号或电信号的过程称为生物力学信号转导. 力学信号转导途径常分为三类: 细胞膜受体和表面的离子通道, 细胞骨架(应力纤维、微管等), 核骨架和细胞骨架连接体复合体[1]. 离子通道为包埋在质膜中的蛋白质孔道. 当通道受力学信号刺激打开时, 离子沿电化学梯度方向从孔道进入细胞内部, 不需要ATP水解提供能量. Piezo1通道就是典型的机械敏感性离子通道[4,5].

1 Piezo1结构与功能, 及其通道活化影响因素

Piezo1是机械力敏感性离子通道Piezo家族成员之一, 2010年由Bertrand Coste团队发现, 并以希腊文"πίεση" (píesi)命名-意为压力[5]. 该团队使用钙离子通道阻滞剂钌红证实Piezo1蛋白可在细胞膜表面组成特定电导的孔状通道, 非选择地传导阳离子[4]. Syeda等[6]则明确力学信号直接调节Piezo1通道开关. Piezo1可感应生理病理过程中多种机械力刺激, 包括脉管血压[7,8]、流体剪切应力[9]、骨骼系统微重力[10]、红细胞内渗透压[11-13]、胞外基质硬度[14], 触觉、本体感觉[15]等.

人Piezo1基因位于染色体16, 其蛋白由2521个氨基酸组成. 小鼠PIEZO1基因与人类高度同源. 研究者利用蛋白质工程、X射线晶体学、单粒子冷冻电子显微镜及活细胞免疫染色等多种技术, 成功揭示了小鼠Piezo1通道结构[4,16,17]. 小鼠Piezo1蛋白由2547个氨基酸组成[16], 具有独特的38跨膜螺旋拓扑结构. 三个Piezo1蛋白组装成一个三叶螺旋桨状的功能结构, 其中, 侧边螺旋桨叶片是力学信号感应关键区域[17]. 该蛋白结构的解析为理解Piezo1离子传导和门控机制提供了基础.

Piezo1在机械力调控下可切换封闭与开放构象, 以控制不同种类(离子选择性)及流量(电导)的离子通过通道. Piezo1被瞬时性力学信号激活后, 能在50-100 ms内迅速完全失活[18]. 同时, 特定情况下也展现慢失活或无失活状态[19,20]. 多数研究以瞬时机械力学信号解析通道特征, 而对持续机械力学信号刺激研究较少.

机械力敏感性离子通道的门控机制包括"横向膜张力"模型(来自脂质双分子层的力)和"系绳弹簧模型"(来自细胞骨架的力), 分别对应"从外到内"和"从内到外"两种力学信号传导方向[21, 22]. 因此, 影响Piezo1门控的因素主要包括细胞膜张力、硬度, 细胞膜骨架蛋白, 及与Piezo1相互作用的其他通道或蛋白.

GsMTx4和Yoda1是Piezo1通道常用拮抗剂和激动剂. GsMTx4为蜘蛛毒液中提取的一种肽毒素, 可阻断牵拉激活性通道[23]. GsMTx4能插入脂质双分子层抑制各种阳离子机械敏感通道, 包括Piezo1、双孔钾离子通道家族成员KCNK2(potassium two pore domain channel subfamily K member 2, KCNK2)、和大电导机械敏感性离子通道(mechanosensitive channel of large conductance, MscL)[24], 通过调节局部膜张力而非直接作用Piezo1蛋白而发挥作用[23]. Yoda1是Piezo1第一种化学活化剂. Yoda1增强Piezo1机械敏感性并减慢失活而充当门控修饰剂. 其可直接与Piezo1蛋白结合, 在没有外在机械力刺激情况下激活通道[25]. 此外, Jedi1和Jedi2两种新型低亲和力水溶性化学激活剂, 可特异性激活Piezo1; 比Yoda1介导的电流呈现更快爆发和衰变; Jedi1和Yoda1激活Piezo1位点不同, 可协同应用[26].

2 Piezo1感应力学信号调控肿瘤恶性特征研究进展

肿瘤组织与正常组织的硬度力学特征明显不同, 临床许多常见实体肿瘤也多依据上述物理特征进行鉴别与诊断, 如肝细胞肝癌[27]、胰腺导管细胞癌[28,29]和乳腺癌[30-32]等. 本课题组前期相继报道基质硬度增加调控肝癌侵袭转移的系列新机制, 包括独立诱导肝癌上皮间充质转化(epithelial-mesenchymal transition, EMT)的发生[33]; 加速肝癌肺预转移龛形成[34-36]; 上调肝癌细胞血管内皮生长因子(vascular endothelial growth factor, VEGF)表达[37]和血管内皮细胞生长因子受体2(vascular endothelial growth factor receptor 2, VEGFR2)表达[38], 促进肿瘤血管新生, 说明硬度力学信号在增强肝癌细胞恶

性特征方面发挥重要作用. 而机械敏感性离子通道蛋白Piezo1在胃肠道系统中均有表达, 包括胃、小肠、结肠组织等[5], 作为传递力学信号的新途径, 其在消化系统肿瘤癌变、生长、侵袭转移等相关恶性特征调控中同样发挥作用.

2.1 Piezo1介导力学信号诱导细胞癌变 部分具有正常生理功能的健康细胞也携带致癌突变基因[39,40]. 单个基因的突变可增加癌变易感性, 但致癌基因并非驱动细胞癌变的唯一因素, 细胞与其周边微环境交流也是重要决定因素, 包括微环境中生物力学因素.

在小鼠和人乳腺管腔分化细胞中转染编码HER2的慢病毒, 使其具有癌变易感性, 细胞及动物实验显示HER2+的管腔细胞在高基质硬度条件下能成瘤[41]. 表明力学信号的增强对癌基因启动、肿瘤发生至关重要. 正常组织基质偏软, 在一定程度上削弱癌基因驱动力. 研究显示, 在Apc突变小鼠结肠, 微环境压力可激活结肠上皮细胞Ret信号, 诱导β-catenin Y654位点磷酸化, 阻断其与E-cadherin结合, 使其从粘附连接处释放[42], 在胞质累积发生核转位, 促进相关靶基因表达增加, 进而诱导结肠肿瘤恶变[43].

感应机械力学信号Piezo1的发现, 为力学信号调控细胞癌变机制研究与源头干预提供了基础. Gudipaty等[44]在犬肾上皮细胞(Madin-Darby canine kidney, MDCK)、人结肠上皮细胞、斑马鱼表皮细胞进行研究, 发现Piezo1可介导牵拉力促进上皮细胞分裂, 同时又可介导挤压力在细胞密度达到一定程度后, 通过1-磷酸鞘氨醇(sphingosine-1-phosphate, S1P), 诱导Rho介导的肌动球蛋白环收缩, 从而在细胞密度最高的地方将活细胞挤出, 最终诱导离巢细胞死亡[45]. 上述过程保持细胞数量维持上皮稳态, 而破坏Piezo1力学信号传导会阻止活细胞挤出, 导致上皮细胞团块大量堆积, 说明Piezo1介导力学信号在癌变发生尤其是上皮类肿瘤癌变中扮演重要角色. Liu等[46]用DEN诱发Piezo1+/-小鼠与Piezo1+/+小鼠癌变, 发现Piezo1+/-小鼠的肿瘤大小和恶化程度明显低于Piezo1+/+小鼠, 同样说明Piezo1与细胞癌变密切相关.

2.2 Piezo1介导力学信号调控细胞增殖、周期与凋亡 研究显示牵拉力可激活MDCK上皮细胞Piezo1通道, 促进钙离子内流, 激活细胞外调节蛋白激酶1/2(extracellular regulated protein kinases 1/2, ERK1/2)通路, 增加细胞Cyclin B表达, 促进上皮细胞从G2期进入有丝分裂, 从而加速细胞增殖[44]. 而挤压力激活Piezo1通道, 则诱导上皮细胞失巢凋亡[45]. 说明Piezo1对细胞增殖、凋亡的影响取决于机械力种类和方向. 然而, Piezo1对不同种类的细胞增殖和周期的影响也不同, 如Piezo1敲除可显著抑制胶质瘤细胞生长, 但对正常脑组织细胞无影响[14]. 在前列腺癌[47]、胃癌[48]、肝细胞肝癌[46]中, 下调Piezo1抑制肿瘤细胞增殖, 促进肿瘤细胞凋亡. 而Yoda1可诱导结肠癌细胞凋亡[49]. 此外, 不论药物抑制还是基因干预Piezo1表达与活化都不影响胰腺导管细胞癌生长[50]. 因此, 脱离细胞类型及细胞力学环境讨论Piezo1功能是不可取的, 但目前多数研究将Piezo1作为原癌基因或抑癌基因对其下调或过表达, 忽略力学信号对Piezo1活性影响, 且机械力对细胞增殖影响并非线性, 而当机械力刺激超过一定范围后, 细胞增殖速率随之降低[51,52], 甚至会出现损伤及死亡, 此时药物抑制Piezo1通道, 可保护细胞免于病理水平机械力刺激的影响[53-55].

2.3 Piezo1介导力学信号影响肿瘤细胞干性 力学信号可显著影响肿瘤细胞干性特征. Liu等[56]用21 kPa, 70 kPa, 105 kPa三种不同硬度水平的海藻酸盐凝胶, 对头颈部鳞状细胞癌细胞进行培养, 发现70 kPa硬度培养体系中, 癌细胞干性标记物表达最高, 成瘤能力和药物耐受性最强. 本课题组前期研究也显示基质硬度增加增强肝癌细胞干性特征[57], 说明适宜的基质硬度环境的确可影响肿瘤细胞干性. Piezo1介导力学信号调控肿瘤细胞干性研究尚未见报道, 但已有研究显示: 随年龄增加导致大脑硬度增加, 通过激活Piezo1降低大脑多功能干细胞活性, 抑制Piezo1能够抵消衰老中枢神经系统中力学信号对多功能干细胞干性的削弱[58]; 果蝇胃扩张可通过激活Piezo1促进肠内分泌前体细胞自我增殖和分化[59]. 上述结果均为Piezo1介导力学信号影响肿瘤细胞干性研究提供了启示.

2.4 Piezo1介导力学信号影响肿瘤侵袭和转移 肿瘤细胞从原发瘤脱落、基质侵袭、进入血管、血管免疫逃逸、出血管、定植扩增形成转移灶的整个转移过程中, 都会感应到不同机械力刺激, 包括基质力学信号和流体力学信号[60,61]. 而Piezo1作为机械敏感性离子通道可以感应多种种类的力学信号刺激. 因此, 通过Piezo1研究力学信号对肿瘤侵袭转移的影响具有代表性.

Piezo1表达与肿瘤细胞侵袭转移密切相关. Piezo1蛋白与三叶因子1(trefoil factor 1, TFF1)结合, 能够增强胃癌细胞运动性[62]; 敲低Piezo1可诱导胃癌细胞内GTP-Rac1积累, 降低细胞运动能力[48]. Piezo1在结肠癌组织中高表达, 体外Piezo1过表达或者Yoda1刺激可通过线粒体钙单向转运体(mitochondrial calcium uniporter, MCU)-缺氧诱导因子1α(hypoxia inducible factor 1α, HIF-1α)-VEGF通路促进结肠癌细胞迁移; 沉默Piezo1则相反[49]. 肿瘤细胞转移需要具备在限制性空间迁移的能力, 细胞从狭窄通道穿行需要钙离子内流, 而Piezo1激活可诱发大量钙离子内流. 研究显示, 下调仓鼠卵巢细胞CHO中Piezo1表达, 对其在非限制空间的迁移速度无明显影响,

但明显降低了细胞在限制空间的迁移速度[63]. 细胞核是细胞中最硬的结构, 当通过的周边基质或孔道硬度高于核硬度时, 细胞核需要变形以适应迁移通道尺寸, 才能顺利通过通道. 细胞核大小、可塑性是肿瘤细胞在限制性空间迁移的重要限制因素[64]. 基质硬度影响细胞核形状, 在硬的基质表面生长的细胞呈现较薄且伸展的细胞核, 而在软基质表面生长细胞的细胞核相对更厚、延展面积小[65]. 胞外基质硬度改变核膜硬度、染色体解聚、小叶化, 使细胞更易于向周围基质浸润[66]. 此外, 流体剪切应力激活Piezo1通道, 钙离子内流, 介导肌动蛋白收缩, 使细胞核缩小[67]. 上述结果提示空间限制、牵拉力、流体剪切应力等, 均可激活Piezo1通道, 调控细胞核大小, 影响肿瘤细胞迁移.

2.5 Piezo1介导力学信号影响肿瘤血管新生 Piezo1为内皮细胞剪切应力感受器, 是胚胎发育及生理过程中血管发育形成、维持结构功能的决定因素[9, 68-71]. 小鼠Piezo1全部敲除或内皮特异性破坏会严重扰乱脉管系统发育而致胚胎死亡[9,70]. 而Yoda1激活Piezo1可诱导内皮细胞发芽及管腔形成[69]. 因此, Piezo1与肿瘤血管新生、功能、完整性等之间存在密切关系, 但相关研究目前较少. Piezo1在结肠癌组织中高表达, 与差的预后密切相关. 沉默Piezo1表达可抑制HIF-1α和VEGF的表达. 而VEGF是肿瘤血管新生的强诱导因子[49]. 我们研究数据也显示, 基质硬度激活肝癌细胞Piezo1通道增加钙离子内流, 促进促血管因子表达, 诱导肝癌血管新生(未发表结果).

3 Piezo1感应力学信号调控肿瘤免疫微环境

肿瘤免疫微环境重塑可显著影响肿瘤恶性特征及其进展, Piezo1是否会通过诱导肿瘤免疫抑制微环境形成促进肿瘤进展? 研究显示, Piezo1低表达胰腺导管腺癌患者5年存活率为20%, 而Piezo1高表达患者则未发现长期存活, 利用小鼠胰腺导管腺癌原位模型, 发现GsMTx4可有效地抑制肿瘤生长, 且使肿瘤组织中髓系抑制细胞明显减少, Yoda1则增加肿瘤中髓系抑制细胞的数量; 髓系细胞经Piezo1感知机械压力, 抑制组蛋白去乙酰基酶2(histone deacetylase 2, HDAC2), 减少视网膜母细胞瘤基因(retinoblastomal transcriptional corepressor 1, *Rb1*)表达, 而使髓系细胞大量扩增, 抑制肿瘤T细胞活化, 形成肿瘤免疫抑制微环境, 促进肿瘤发展[50]. 此外, Piezo1可介导周期性静水压刺激肺单核细胞内HIF-1α聚集, 诱导促炎表型形成[72]; 高基质硬度力学信号也可激活Piezo1, 加速树突状细胞糖酵解速率, 增强促炎功能[73]; 力学信号感应蛋白Piezo1也可参与T细胞激活[74]. 因此, Piezo1在机体固有免疫和适应性免疫方面都具有调节作用.

Piezo1离子通道也可被超声激活, 介导钙离子内流, 激活钙调神经磷酸酶, 去磷酸化转录因子活化T细胞核因子(nuclear factor of activated T cells, NFAT), 促进其核转位, 进而激活NFAT反应元件, 驱动设计的靶基因表达. 研究者们利用这一原理进行合成遗传电路设计, 使用远程超声激活Piezo1控制嵌合抗原受体(chimeric antigen receptor, CAR)转录表达, 进而识别根除靶肿瘤细胞. 该方法是模块化的, 具有高时空精度、远程控制和非侵入性等优势, 用于优化免疫治疗[75].

4 结论

Piezo1介导力学信号调控肿瘤细胞恶性特征、血管新生、免疫微环境等相关研究目前尚处起步阶段, 相关实验研究仍具有较大局限性, 包括体外精准模拟力学微环境困难, 尤其三维层面的精准模拟; 此外, 用于力学信号研究的理想动物模型缺乏, 对干预反证实验的开展形成制约. Piezo1研究多聚焦其表达及活化对肿瘤细胞恶性特征的调控, 忽视肿瘤与胞外基质或流体力学信号的相互作用. 另一方面, Piezo1研究也面临一些新问题, 包括除钙离子内流通路外, Piezo1是否与其他机械转导通路存在协同? 贴壁和悬浮细胞Piezo1感应和传递力学信号刺激的区别? Piezo1是否影响细胞骨架、核骨架进而影响细胞形态表型? 相信上述问题提出必将推动Piezo1介导力学信号调控肿瘤进展机制的完整阐明.

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