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侵袭性伪足形成-基质硬度调控肿瘤侵袭转移的关键一环

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Invadopodia formation: An important step in matrix stiffness-regulated tumor invasion and metastasis

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Abstract

Highly motile and invasive abilities are symbolic

features of metastatic tumor cells. Being a critical molecular event for maintaining the highly migratory and invasive capabilities of tumor cells, invadopodia formation undoubtedly determines the progression of tumor invasion and metastasis. Growing numbers of studies suggest that increased matrix stiffness, as a notable property of physical mechanics in solid tumors, participates in the regulation of tumor invasion and metastasis *via* different molecular mechanisms. However, to date the relevant mechanisms of matrix stiffness-induced invadopodia formation and activity in tumor cells remain largely unclear. This paper is to make a review on the structure and function of invadopodia, the stages and inductive factors of invadopodia formation, the regulatory mechanisms of matrix stiffness-induced invadopodia formation and so on, with an aim to reveal the important roles of invadopodia in matrix stiffness-regulated tumor invasion and metastasis.

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Key Words: Invadopodia; Matrix stiffness; Tumor; Invasion and metastasis

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摘要

高运动、侵袭能力是转移性肿瘤细胞的标志性特征, 而侵袭性伪足(invadopodia)形成则是维持肿瘤细胞高迁移、侵袭能力的关键, 也是决定肿瘤侵袭转移进程的重要分子事件之一. 基质硬度增加是实体肿瘤显著的物理力学特征, 其通过不同调控机制参与肿瘤侵袭转移报道逐渐增多, 而基质硬度诱导肿瘤

细胞侵袭性伪足形成、活性的相关机制探讨目前尚处起步阶段. 本文将从侵袭性伪足结构与功能, 侵袭性伪足形成及诱导因素, 基质硬度参与侵袭性伪足形成的调控机制等方面进行综述, 探讨侵袭性伪足在基质硬度调控肿瘤侵袭转移病理进程中所扮演的重要角色.

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关键词: 侵袭性伪足; 基质硬度; 肿瘤; 侵袭转移

核心提要: 本文从侵袭性伪足(invadopodia)结构与功能、侵袭性伪足形成及诱导因素、基质硬度参与侵袭性伪足形成的调控机制等方面进行综述, 探讨侵袭性伪足在基质硬度调控肿瘤侵袭转移病理进程中所扮演的重要角色.

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0 引言

肿瘤微环境参与肿瘤侵袭转移调控逐渐成为肿瘤领域的研究热点. 对肿瘤微环境调控信号的认识已不再局限于基质细胞、浸润免疫细胞、细胞因子、外泌体等生化信号, 一些物化信号包括缺氧、酸碱pH、温度、基质硬度等研究也取得明显进展. 其中, 基质硬度作为实体肿瘤显著物理力学特征, 调控肿瘤侵袭转移机制报道近年逐渐增多, 基质硬度增加通过影响肿瘤细胞上皮间质转化^[1,2]、迁移模式改变^[3,4]、侵袭转移关联基因表达^[5-7]、肿瘤细胞干性维持^[8]、预转移龛形成^[9]等恶性特征改变, 促进肿瘤侵袭转移. 高迁移、侵袭能力是转移性肿瘤细胞的标志性特征, 而侵袭性伪足(invadopodia)形成则是维持肿瘤细胞高迁移、侵袭能力的关键, 也是决定肿瘤侵袭转移进程的重要分子事件之一. 在侵袭转移早期阶段, 从原发瘤脱落的肿瘤细胞必须降解胞外基质, 穿越基底膜、基质层、血管壁等物理屏障^[10], 才能进入血管实现远端转移, 侵袭性伪足在实现上述基质降解及突破的侵袭转移病理进程中扮演重要角色. 已有研究显示, 生长因子、细胞外基质(extracellular matrix, ECM)、细胞间接触、缺氧、外泌体等因素可诱导侵袭性伪足形成. 而胞外基质硬度增加可显著改变肿瘤细胞形态结构^[11]、增强肿瘤细胞运动^[4]、上调肿瘤细胞基质金属蛋白酶(matrix metalloproteinases, MMPs)表达分泌^[12], 提示基质硬度与肿瘤细胞侵袭性伪足形成可能存在较强

的关联. 零星报道也显示^[3,13], 基质硬度改变可影响肿瘤细胞侵袭性伪足形成及活性. 但是, 针对硬度力学信号诱导肿瘤细胞伪足膜突起结构形成的机制目前依然知之甚少. 本文将从侵袭性伪足结构功能、侵袭性伪足形成诱导因素、以及基质硬度调控侵袭性伪足形成机制等方面进行综述, 以探讨侵袭性伪足在基质硬度调控肿瘤侵袭转移过程中发挥的重要作用.

1 侵袭性伪足结构与功能

依据形态、结构及功能特征的不同, 细胞膜突起结构被分为丝状伪足、片状伪足、侵袭性伪足和足体. 片状伪足在细胞迁移运动中起主导作用, 丝状伪足则感受胞外趋化因子, 控制运动方向, 在肿瘤侵袭起始阶段, 丝状伪足与片状伪足也发挥黏附作用^[14-16]. 侵袭性伪足多见于高侵袭性肿瘤细胞, 为富含丝状肌动蛋白(F-actin)的胞膜突起结构^[17], 电镜下呈细长突起状, 长约0.5-2 μm, 直径约50 nm^[18-21]. 除肌动蛋白外, 侵袭性伪足中还聚集许多肌动蛋白调控蛋白, 包括cortactin、神经源性Wiskott-Aldrich综合征蛋白(neural Wiskott-Aldrich syndrome protein, N-WASP)、Arp2/3复合体、cofilin、Mena、fascin和formin等^[18,22-27]. 此外, 侵袭性伪足可募集分泌多种蛋白酶, 如MT1-MMP(也称MMP14)、MMP2、MMP9、seprase、cathepsin B、ADAM12和uPAR等^[28-35], 促进ECM降解, 部分蛋白酶还能激活释放ECM中贮存的生长因子^[10,36-40]. 侵袭性伪足组分及其调控因子参与细胞黏附^[28,41]、ECM降解^[42]、膜运输^[43-45]、信号转导^[22,46,47]等病理生理过程. 足体(podosome)存在于树突状细胞、巨噬细胞、内皮细胞、血管平滑肌细胞、破骨细胞等正常细胞中, 为富含肌动蛋白且具有基质重塑功能的亚细胞结构^[48-56]. 一般将侵袭性伪足、足体和Src诱导的侵袭性伪足样结构统称为侵袭体(invadosome)^[57]. 尽管结构形态相似, 侵袭性伪足与足体之间依然存在差异, 如侵袭性伪足以长突起状结构为主, 存在时间长达数小时; 而足体结构更为短平, 仅存在数分钟时间^[48]; 其次, 两种膜突起结构中表达的关键性调控蛋白不同, 如Nck1和Mena在侵袭性伪足中表达, 在足体中不表达; WASP和Grb2在足体中表达, 在侵袭性伪足中则不表达^[58-60].

2 侵袭性伪足的形成及其诱导因素

2.1 侵袭性伪足的形成 侵袭性伪足形成是肿瘤细胞侵袭转移进程中早期形态改变. 侵袭性伪足形成一般分三个阶段: 侵袭性伪足前体核心形成, 侵袭性伪足前体的稳定和侵袭性伪足成熟^[61]. 侵袭性伪足前体核心由N-WASP、Arp2/3复合体和cofilin募集至actin-cortactin复合体周围而形成, 前体核心在数秒内即可形成, 但并

不稳定,前体核心形成约20 s后,Tks5结合于前体核心上^[62]。Tks5介导前体复合物与位于细胞膜上的PI(3, 4)P₂结合,稳定前体结构^[62-64]。而lamellipodin蛋白使Mena-Arg-SHIP2复合体募集至前体^[63,64]。SHIP2促进PI(3, 4)P₂生成,利于前体固定于细胞膜上,增强前体稳定性,cofilin和Arp2/3复合体分别介导两条不同的肌动蛋白聚合通路,两条通路协同作用,大大增强肌动蛋白进一步的聚合^[65]。最终,肌动蛋白聚合使侵袭性伪足延长并形成突起,募集MMPs并降解ECM,完成侵袭性伪足成熟^[61,62,66]。侵袭性伪足形成三阶段模型来源于人、大鼠和小鼠腺癌细胞研究,该模型是否适用于其它肿瘤细胞类型目前仍不清楚^[67]。

2.2 诱导侵袭性伪足形成的因素及其分子机制 以往认为,侵袭性伪足形成在一定程度上受肿瘤驱动基因突变(driver mutations)的调控。如: Src和Ras基因异常激活可使正常细胞发生恶性转化并诱导侵袭性伪足前体形成^[68,69]。而近来证据表明,肿瘤驱动基因突变并不足以决定体内肿瘤表型或肿瘤细胞行为,来自肿瘤微环境刺激信号同样可决定肿瘤表型改变^[70]。目前,肿瘤微环境信号生长因子、ECM、细胞间接触、肿瘤缺氧、外分泌体均已显示可诱导、促进侵袭性伪足形成。

2.2.1 生长因子: 多种生长因子如转化生长因子- β (transforming growth factor- β , TGF- β)^[71]、表皮生长因子(epidermal growth factor, EGF)^[46]、肝素结合-表皮生长因子(heparin-binding EGF-like growth factor, HB-EGF)^[35]、血管内皮生长因子(vascular endothelial growth factor, VEGF)^[72]、血小板衍生生长因子(platelet derived growth factor, PDGF)^[73]、肝细胞生长因子(hepatocyte growth factor, HGF)^[74]和基质细胞衍生因子1 α (stromal-derived factor1- α , SDF1 α)^[75]等被发现可诱导促进肿瘤细胞侵袭性伪足形成和(或)活性。虽然不同生长因子诱导侵袭性伪足形成的机制各异,但生长因子通路常汇聚至胞内共同的信号枢纽,如Src激酶、磷酸肌醇3-激酶(phosphoinositide 3-kinases, PI3Ks)等,来调控肌动蛋白聚合及侵袭性伪足形成,从而左右肿瘤细胞侵袭与转移^[66,76]。Ke等^[71]研究显示, TGF- β 1诱导肝细胞癌HepG2细胞侵袭性伪足形成及活性增强, TGF- β 1降低膜相关鸟苷酸激酶家族成员Dlg5(discs large homolog 5)表达, Dlg5能抑制Girdin与Tks5结合,进而降低侵袭性伪足形成及活性,进一步机制探讨发现, Dlg5下调可经Girdin依赖性FAK/Src活性介导增强Tks5磷酸化,说明TGF- β 1通过Dlg5/Girdin/Tks5通路调节增强侵袭性伪足形成及活性。Mader等^[46]发现, EGF与EGFR结合可激活乳腺癌细胞非受体酪氨酸激酶Arg使cortactin磷酸化,引发侵袭性伪足肌动蛋白聚合和成熟,侵袭性伪足中Src和Arg共

存,敲除Src后,过表达Arg可部分恢复EGF诱导的侵袭性伪足肌动蛋白聚合,而敲除Arg后,过表达Src并无补偿作用,说明Arg为Src激活的下游分子,EGFR-Src-Arg-cortactin通路可参与调控乳腺癌细胞侵袭性伪足形成及活性。Malek等^[77]研究乳腺癌发现,生长因子EGF激活 I 类PI3K(Class I PI3K), I 类PI3K催化底物PI(4, 5)P₂生成PI(3, 4, 5)P₃,后者在5-磷酸酶作用下发生去磷酸化从而产生PI(3, 4)P₂, PI(3, 4)P₂激活其下游效应因子Tks5,从而促进Tks5依赖性侵袭性伪足形成。

2.2.2 ECM: ECM不仅是结构性基质,其组分、硬度、排列及拓扑结构等信息也可经细胞-ECM接触表面传递至细胞中。ECM通过特异性细胞表面黏附受体可调控侵袭性伪足形成及活性^[78]。侵袭性伪足成熟需要整合素介导的ECM黏附。多种特异性整合素受体如 α 2 β 1、 α 3 β 1、 α 5 β 1和 α 6 β 1等,存在于侵袭性伪足中^[61,79-81]。ECM中的基质蛋白如纤维连接蛋白(fibronectin), I 型胶原蛋白(type I collagen)和层黏连蛋白(laminin)等能激活侵袭性伪足整合素受体^[61,66,81,82]。Fibronectin与整合素 α 5 β 1结合与肿瘤侵袭性增强和患者预后不良相关^[61,82-84]。Laminin的分泌可抑制侵袭性伪足形成,而抑制laminin受体 α 3 β 1则能促进侵袭性伪足形成^[66]。整合素 β 1对促进侵袭性伪足成熟起重要作用。整合素 β 1激活Arg激酶,使cortactin 421和466位点酪氨酸磷酸化,从而诱导侵袭性伪足成熟^[65,82,85,86]。整合素 β 1将talins和moesins募集至侵袭性伪足核心,使Na⁺-H⁺反向转运蛋白NHE1贴附于侵袭性伪足^[83]。NHE1使侵袭性伪足核心处PH值升高,激活cofilin依赖的肌动蛋白聚合^[83,87];同时降低细胞外PH值,使可溶性MMP2和MMP9及不溶性MT1-MMP蛋白酶向侵袭性伪足运输^[88]。另外,ECM交联程度变化通过整合素 β 1-ECM结合位点介导,非线性调控侵袭性伪足活性^[89]。侵袭性伪足相关MMPs降解ECM过程可释放许多生物活性蛋白片段,如laminin-111衍生肽AG73和C16,可增强整合素 β 1依赖性侵袭性伪足形成^[90]。CD44可介导肿瘤细胞黏附于透明质酸、I 型及IV型胶原蛋白、laminin和fibronectin^[91,92]。CD44在fibronectin作用下可增强整合素 α 5 β 1活性,促进侵袭性伪足成熟^[82]。在淋巴瘤细胞中,CD44参与募集MMP9至细胞腹侧面过程^[93]。

2.2.3 细胞间接触: 从原发灶向外播散过程中,肿瘤细胞与基质细胞间存在持续较久的直接接触。单个肿瘤细胞、促血管生成巨噬细胞和血管内皮细胞之间直接接触形成的细胞复合体称为TMEM(tumor microenvironment of metastasis)^[94-96]。TMEM通过巨噬细胞诱导的肿瘤细胞侵袭性伪足来破坏内皮细胞间黏附,从而增强血管通透性和跨内皮迁移,促使肿瘤细胞侵入血管^[60,97-99]。乳腺癌组织标本中TMEM数目是转移性复

发独立预后指标^[94,98,99]. TMEM中巨噬细胞-肿瘤细胞接触诱导Notch1信号通路, 促使RhoA和Mena依赖性侵袭性伪足形成^[59,97].

2.2.4 肿瘤缺氧: 肿瘤快速生长与血液供应不足导致肿瘤微环境缺氧. 在多种类型肿瘤细胞中, 缺氧诱导的侵袭性伪足形成受转录因子缺氧诱导因子1 α (hypoxia inducible factor 1 α , HIF-1 α)调控^[100]. Diaz等^[35]对头颈部鳞状细胞癌、肺癌和胰腺癌细胞研究发现, 在缺氧条件下HIF-1 α 可激活Notch信号通路上调金属蛋白酶ADAM12表达及活性, 促进EGFR配体HB-EGF胞外结构域脱落, HB-EGF的释放诱导肿瘤细胞侵袭性伪足形成. 此外, 缺氧促进NADPH氧化酶系统产生活性氧(reactive oxygen species, ROS), 诱导侵袭性伪足形成^[85].

2.2.5 外泌体: 外泌体促进非生长因子依赖性侵袭性伪足形成, 延长其存在时间, 诱导侵袭性伪足MT1-MMP胞外分泌, 不同于EGF对侵袭性伪足的快速诱导, 外源性外泌体诱导侵袭性伪足形成长达1 h, 提示两种诱导因素引发侵袭性伪足形成过程可能不同^[29]. Mallawaarachthy等^[101]对六种胶质母细胞瘤细胞系分泌的囊泡(extracellular vesicles, EVs, 主要为外泌体)进行蛋白质组学分析, 共鉴定公共蛋白145个, 通过侵袭性伪足实验及高、低侵袭性肿瘤细胞表达比对分析, 发现14种EV差异候选蛋白与侵袭性伪足形成呈显著正相关, 其中某些蛋白如整合素 β 1、肌动蛋白相关蛋白3等, 可能参与调控肌动蛋白聚合及侵袭性伪足形成. 外泌体也可促进足体形成^[102], 对外泌体调控侵袭性伪足形成研究有一定的借鉴作用.

3 基质硬度参与侵袭性伪足形成的调控机制

除前述基质蛋白自身生化信号诱导侵袭性伪足形成及活性外, 由基质蛋白沉积交联形成的基质硬度力学信号也参与侵袭性伪足形成及活性调控. 由于理想基质硬度实验平台缺乏及伪足检测手段局限, 目前对于硬度力学信号诱导肿瘤细胞侵袭性伪足形成的相关调控机制依然知之甚少.

报道显示, 基质硬度增加可诱导多种肿瘤细胞侵袭性伪足数目增多、活性增强. Parekh等^[13]发现基质硬度在一个宽硬度弹性范围内可调控乳腺癌细胞侵袭性伪足数量及活性, 硬度弹性系数为30 kPa时, 乳腺癌细胞侵袭性伪足相关ECM降解及侵袭性伪足数目均达峰值, 该硬度弹性系数位于肿瘤基质硬度范围内; 当硬度弹性系数达到2 GPa时, 侵袭性伪足数目再次达到峰值, 出现基因表达改变, 说明细胞可识别基质硬度上限高达GPa级. Alexander等^[3]在乳腺癌研究中发现, 抑制非肌性肌球蛋白II、肌球蛋白轻链激酶和Rho相关激酶

(rho-associated kinase, ROCK)活性均可降低侵袭性伪足相关ECM降解, 表明基质硬度信号传导依赖于细胞收缩装置, 尽管非肌性肌球蛋白II A、II B及磷酸化肌球蛋白轻链均不定位于侵袭性伪足中, 但力学传感蛋白p130Cas(Cas)和黏着斑激酶(focal adhesion kinase, FAK)活性磷酸化形式却均存在于活跃降解ECM的侵袭性伪足中, 且其磷酸化水平受肌球蛋白抑制剂影响, Cas或FAK过表达可增强高硬度基底表面生长的肿瘤细胞侵袭性伪足活性, 说明基质硬度增加可通过活化非肌性肌球蛋白II-FAK/Cas通路促使乳腺癌细胞侵袭性伪足数目增多、活性增强. Jerrell等^[103]对头颈部鳞状细胞癌和乳腺癌研究发现, 基质硬度增加可激活Rho/ROCK信号通路从而增强侵袭性伪足活性, 但ROCK1和ROCK2在基质硬度调控侵袭性伪足活性的过程中发挥不同作用, ROCK1通过激活非肌性肌球蛋白II调控肌动球蛋白收缩, 而ROCK2通过激活LIM激酶(LIM kinase, LIMK)直接调控cofilin磷酸化, 二者以收缩性和非收缩性机制调控侵袭性伪足活性. Sedgwick等^[11]在黑色素瘤、结肠癌和前列腺癌研究中发现, 不同基质硬度表面生长的肿瘤细胞可显示两种不同的侵袭模式, 在硬基质表面, 肿瘤细胞形成侵袭性伪足, 以间质细胞样表型发生侵袭, Rac1激活及其下游信号促进侵袭性伪足形成; 但在软基质表面, 肿瘤细胞释放微囊泡而不形成侵袭性伪足, 以阿米巴样表型发生侵袭, 抑制Rac1可激活RhoA/ROCK信号通路, 从而促进微囊泡形成分泌并抑制侵袭性伪足形成, 该研究说明, 基质硬度增加可激活Rac1, 通过抑制RhoA/ROCK信号通路促进侵袭性伪足形成. Zhao等^[12]报道, 在涎腺腺样囊性癌中, 基质硬度增加导致肿瘤细胞侵袭性伪足数量增多, MMP2、MMP9和MMP14表达增多, MMP组织抑制剂TIMP1、TIMP2和TIMP4表达减少, 与Sedgwick^[11]报道的调控机制不同, 本研究发现基质硬度增加可上调RhoA、Rac1、ROCK1和ROCK2表达, 提示基质硬度增加可能激活RhoA/ROCK信号通路促进侵袭性伪足形成及MMPs活性, 而影响肿瘤细胞侵袭迁移能力. Chakraborty等^[104]发现, 与正常肝细胞相比, 肝癌细胞可过表达和分泌蛋白多糖Agrin, 促进Arp2/3复合物依赖性侵袭性伪足形成. 进一步研究显示^[105], 基质硬度增加促进Agrin表达, Agrin经整合素-Lrp4/MuSK受体通路激活转录因子YAP, 从而增强肝癌恶性表型. 由此推测基质硬度可能通过影响Agrin-YAP途径调控肝癌细胞侵袭性伪足形成.

尽管多数报道认为基质硬度增加促进侵袭性伪足数量增多、活性增强, 但也有研究提出不同观点. Gu等^[106]对人成纤维细胞、脐静脉内皮细胞、乳腺癌细胞和纤维肉瘤细胞的研究发现, 排除细胞因子、趋化因子和ECM蛋

白类型等的影响, 柔软ECM(低硬度)可抑制细胞间稳定黏附连接形成、促进MMP分泌及ECM降解、以及诱导侵袭体样突起(invadosome-like protrusion, ILP)形成, 在两维和三维定向侵袭实验中, 柔软基质均更易促进ILP形成, 成纤维细胞仅在很窄基质硬度范围内(0.1-0.4 kPa)自发形成ILP, 该过程受Src家族激酶调控; 而乳腺癌细胞和纤维肉瘤细胞可在很宽的基质硬度范围内自发形成ILP, 但同样发现低硬度基质更易促进ILP形成的现象, 说明柔软ECM促进细胞侵袭. 肿瘤细胞异质性、硬度体外培养平台标准化、以及模拟实体瘤硬度区间范围的不统一可能部分地解释上述研究结果间的差异.

此外, 基质硬度与细胞收缩性在调控侵袭性伪足形成过程中关系密切. 细胞通过肌动球蛋白收缩产生的细胞内张力识别ECM力学特性, 这些收缩力传递至基质表面形成牵引应力, 介导细胞与ECM间力学相互作用^[107]. Jerrell等^[108]利用不同硬度基底培养头颈部鳞状细胞癌并检测细胞侵袭和收缩特性, 发现ECM降解和细胞牵引应力均与基质硬度呈线性正相关, 且牵引应力可预测ECM降解情况, 说明细胞力学在基质硬度参与侵袭性伪足形成及活性的调控作用中发挥重要作用.

4 结论

从基质硬度角度解析侵袭性伪足形成及活性的相关研究尚处起步阶段, 许多问题目前依然无法解决, 如硬度及其它诱导因素在调控侵袭性伪足形成与活性时是否存在协同作用? 不同诱导因素在侵袭性伪足形成中所占权重及各自调控靶点及途径? 动物体内不同组织硬度模拟困难及侵袭性伪足示踪检测手段有限, 体外类组织硬度模型缺乏等. 未来随着高分辨率活体内显微成像、高分辨率荧光原位杂交、体内硬度相关肿瘤模型和体外硬度实验技术平台等的发展和完善, 相信基质硬度调控侵袭性伪足形成机制的研究将会获得更多进展, 从而为肿瘤侵袭转移新型诊疗手段的出现提供重要帮助.

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