DOI: 10.1002/cbin.12156

COMMENTARY

Cell Biology International WILEY

Durotaxis: A cause of organ fibrosis and metastatic cancer?

Wolfgang H. Goldmann

Department of Biophysics, Friedrich-Alexander-University, Erlangen-Nuremberg, Erlangen, Germany

Correspondence
Wolfgang H. Goldmann, Department of Biophysics, Friedrich-Alexander-University, Henkestr. 91, 91052 Erlangen, Germany.
Email: wolfgang.goldmann@fau.de

Directional migration, in which cells move up matrix stiffness gradients independent of soluble factors (chemotaxis) or matrix-bound ligands (haptotaxis), is termed durotaxis (Lo et al., 2000). Advances in the development of bioengineered matrices with stiffness gradients have facilitated the study of cell durotaxis in vitro (Sunyer et al., 2016) and demonstrated the durotactic capacity of stem (Tse & Engler, 2011), tumor (DuChez et al., 2019), stromal (Kawano & Kidoaki, 2011), vascular (Isenberg et al., 2009), epithelial (Happe et al., 2017), and immune cells (Phillipson et al., 2009). These studies suggested a potential role for durotaxis in cell development, homeostasis, and disease; however, the relevance and biological role of durotaxis in vivo remained speculative (Shellard & Mayor, 2021).

The study of durotaxis in vivo has long been limited by the lack of high-resolution measurements of spatial variations in matrix stiffness observed in organs and tissues. Recently, the application of atomic force microscopy (AFM) in biological studies has enabled the measurement of stiffness gradients in mouse limb buds (Zhu et al., 2020), developing Xenopus brains (Barriga et al., 2018), fibrotic organs (Berry et al., 2006), and desmoplastic tumors (Plodinec, et al., 2012). These reports demonstrated spatiotemporal associations between the presence of stiffness gradients and directional cell migration in vivo. Thus, the lack of genetic and pharmacological tools that target durotaxis-specific pathways without affecting other forms of directional cell migration has limited the study of durotaxis and did not allow solid conclusions to be drawn regarding the existence and biological relevance of this process in vivo.

Important new work has identified molecular pathways involved in the detection of stiffness gradients (Acerbi et al., 2015; Lange & Fabry, 2013), a process commonly known as "mechanosensing," which is regulated by integrins and focal adhesion-associated proteins (Goldmann, 2012a, 2012b, 2014). These durotactic sensing mechanisms appear to be dispensable for chemotaxis or haptotaxis (Plotnikov et al., 2012), and provided an opportunity to investigate the role of durotaxis in vivo by specifically targeting these integrin-dependent mechanosensitive pathways (Lagares et al., 2015; Santos & Lagares, 2018). These researchers investigated the biological role of durotaxis in in vivo disease models of lung fibrosis and metastatic pancreatic cancer, both of which are characterized by the presence of stiffness gradients. In addition, they demonstrated in preclinical mouse models a selective antidurotactic therapy to modulate disease severity.

The pathological recruitment of stromal cells to sites of tissue injury and their subsequent activation into scar-forming myofibroblasts are critical steps in the progressive scarring that underlies organ fibrosis. While the role of chemotaxis in directing the recruitment of fibrocytes (Reilkoff et al., 2011), immune cells (Misharin et al., 2017), and fibroblasts (Kadry et al., 2021; Lagares et al., 2017a) to sites of fibrosis is well established, the contribution of durotaxis to tissue fibrogenesis has not been investigated. Areas of active fibrosis were characterized by extracellular matrix deposition and localized matrix stiffening, creating stiffness gradients extending from healthy soft to fibrotic stiff tissues. To characterize the local spatial distribution of matrix stiffness in fibrotic tissues with nanoscale precision, in situ AFM nanoindentation was applied with post hoc image coregistration and picrosirius red staining (Lattouf et al., 2014) to healthy and fibrotic tissues from mouse models in lung, skin, and kidney (Guo et al., 2022; Herrera et al., 2018). Consistent with previous work by Lagares et al. (2017b), mouse fibrotic tissues exhibited an overall increase in collagen content and matrix stiffness compared to healthy controls. In lung and kidney fibrosis, the stiffness gradients are believed to be significantly higher, which suggests that cell durotaxis may contribute to the onset and progression of tissue fibrosis in vivo. Further, the genetic targeting of durotaxis with CRISPR-Cas9 or pharmacological inhibition of the FAK-paxillin protein–protein interaction with the molecule JP-153 are assumed to affect the disease severity of lung fibrosis and

metastatic pancreatic cancer (Espina et al., 2022; Hinz & Lagares, 2020; Vincent et al., 2013).

These studies discussed the novel and innovative mechanistic insight into the role of durotaxis in the development of human disease identifying durotaxis as a unique disease mechanism driving lung fibrosis and metastatic pancreatic cancer in mouse disease models. A major conceptual advance of in vivo durotaxis studies was mentioned by Berry et al. (2006) during Xenopus embryonic development. While studies suggest that durotaxis may be a widespread phenomenon in vivo during embryonic development, homeostasis, and disease, further research is still required, particularly to characterize the task durotaxis plays in mammals and to understand how it is regulated in vivo. In this regard, the identification of durotaxis-specific inhibitors such as JP-153 targeting the FAK-PaxillinY31/118 pathway may provide answers to the long-standing hypothesis that stiffness gradients in fibrotic tissues and desmoplastic tumors drive cell durotaxis and disease pathology in vivo (Barriga et al., 2018; Sunyer & Trepat, 2020; Zhu et al., 2020). These studies gave reason to believe that genetic or pharmacological inhibition of durotaxis attenuate lung fibrosis and impair pancreatic cancer metastasis in vivo, suggesting selective antidurotaxis therapy as a novel approach for the treatment of a variety of human diseases. More recently, Fan et al. (2024) showed that changes in extracellular matrix viscoelasticity promote hepatocellular cancer progression through an integrin-β1–tensin-1–YAP mechanotransductive pathway in animal studies.

In conclusion, more novel biophysical and imaging methods are needed to dissect the temporal and spatial regulation of durotaxis in vivo. It may also be possible that other cell types undergo durotaxis via yet unidentified mechanosensing pathways and play an unexpected role in cell development, physiology, and disease. Further, the generation of novel genetic models that modulate durotaxis-specific pathways in a cell-specific manner may allow the field to further elucidate the biological role and relevance of durotaxis in vivo.

ACKNOWLEDGMENTS

Open Access funding enabled and organized by Projekt DEAL.

ORCID

Wolfgang H. Goldmann http://orcid.org/0000-0003-0738-2665

REFERENCES

Acerbi, I., Cassereau, L., Dean, I., Shi, Q., Au, A., Park, C., Chen, Y. Y., Liphardt, J., Hwang, E. S., & Weaver, V. M. (2015). Human breast cancer invasion and aggression correlates with ECM stiffening and immune cell infiltration. *Integrative Biology*, *7*, 1120–1134.

Barriga, E. H., Franze, K., Charras, G., & Mayor, R. (2018). Tissue stiffening coordinates morphogenesis by triggering collective cell migration in vivo. *Nature*, *554*, 523–527.

Berry, M. F., Engler, A. J., Woo, Y. J., Pirolli, T. J., Bish, L. T., Jayasankar, V., Morine, K. J., Gardner, T. J., Discher, D. E., & Sweeney, H. L. (2006). Mesenchymal stem cell injection after myocardial infarction improves myocardial compliance. *American Journal of Physiology-Heart and Circulatory Physiology*, *290*, H2196–H2203.

DuChez, B. J., Doyle, A. D., Dimitriadis, E. K., & Yamada, K. M. (2019). Durotaxis by human cancer cells. *Biophysical Journal*, *116*, 670–683.

Espina, J. A., Marchant, C. L., & Barriga, E. H. (2022). Durotaxis: The mechanical control of directed cell migration. *The FEBS Journal*, *289*, 2736–2754.

Fan, W., Adebowale, K., Váncza, L., Li, Y., Rabbi, M. F., Kunimoto, K., Chen, D., Mozes, G., Chiu, D. K. C., Li, Y., Tao, J., Wei, Y., Adeniji, N., Brunsing, R. L., Dhanasekaran, R., Singhi, A., Geller, D., Lo, S. H., Hodgson, L., … Török, N. J. (2024). Matrix viscoelasticity promotes liver cancer progression in the pre-cirrhotic liver. *Nature*, *626*, 635–642.

Goldmann, W. H. (2012a). Mechanotransduction in cells. *Cell Biology International*, *36*, 567–570.

Goldmann, W. H. (2012b). Mechanotransduction and focal adhesions. *Cell Biology International*, *36*, 649–652.

Goldmann, W. H. (2014). Mechanosensation: A basic cellular process. *Progress in Molecular Biology and Translational Science*, *126*, 75–102.

Guo, T., He, C., Venado, A., & Zhou, Y. (2022). Extracellular matrix stiffness in lung health and disease. *Comprehensive Physiology*, *12*, 3523–3558.

Happe, C. L., Tenerelli, K. P., Gromova, A. K., Kolb, F., & Engler, A. J. (2017). Mechanically patterned neuromuscular junctions-in-a-dish have improved functional maturation. *Molecular Biology of the Cell*, *28*, 1950–1958.

Herrera, J., Henke, C. A., & Bitterman, P. B. (2018). Extracellular matrix as a driver of progressive fibrosis. *Journal of Clinical Investigation*, *128*, 45–53.

Hinz, B., & Lagares, D. (2020). Evasion of apoptosis by myofibroblasts: A hallmark of fibrotic diseases. *Nature Reviews Rheumatology*, *16*, 11–31.

Isenberg, B. C., Dimilla, P. A., Walker, M., Kim, S., & Wong, J. Y. (2009). Vascular smooth muscle cell durotaxis depends on substrate stiffness gradient strength. *Biophysical Journal*, *97*, 1313–1322.

Kadry, H., Lagares, D., & Al-Hilal, T. A. (2021). Method for investigating fibroblast durotaxis. *Methods in Molecular Biology*, *2299*, 227–236.

Kawano, T., & Kidoaki, S. (2011). Elasticity boundary conditions required for cell mechanotaxis on microelastically-patterned gels. *Biomaterials*, *32*, 2725–2733.

Lagares, D., Ghassemi-Kakroodi, P., Tremblay, C., Santos, A., Probst, C. K., Franklin, A., Santos, D. M., Grasberger, P., Ahluwalia, N., Montesi, S. B., Shea, B. S., Black, K. E., Knipe, R., Blati, M., Baron, M., Wu, B., Fahmi, H., Gandhi, R., Pardo, A., … Kapoor, M. (2017a). ADAM10-mediated ephrin-B2 shedding promotes myofibroblast activation and organ fibrosis. *Nature Medicine (New York, NY, United States)*, *23*, 1405–1415.

Lagares, D., Liu, F., Auernheimer, V., Adams, D. C., Ludovic, V., Kapoor, M., Suter, M. J., Goldmann, W. H., Engler, A. J., Tschumperlin, D. J., & Tager, A. M. (2015). Feedback amplification of lung fibrosis through matrix stiffness gradient-induced fibroblast durotaxis via alpha tatl-mediated microtubule acetylation. *American Journal of Respiratory and Critical Care Medicine*, *191*:A5329.

Lagares, D., Santos, A., Grasberger, P. E., Liu, F., Probst, C. K., Rahimi, R. A., Sakai, N., Kuehl, T., Ryan, J., Bhola, P., Montero, J., Kapoor, M., Baron, M., Varelas, X., Tschumperlin, D. J., Letai, A., & Tager, A. M. (2017b). Targeted apoptosis of myofibroblasts with the BH3 mimetic ABT-263 reverses established fibrosis. *Science Translational Medicine*, *9*, 3765.

Lange, J. R., & Fabry, B. (2013). Cell and tissue mechanics in cell migration. *Experimental Cell Research*, *319*, 2418–2423.

Lattouf, R., Younes, R., Lutomski, D., Naaman, N., Godeau, G., Senni, K., & Changotade, S. (2014). Picrosirius red staining: A useful tool to appraise collagen networks in normal and pathological tissues. *Journal of Histochemistry & Cytochemistry*, *62*, 751–758.

Lo, C. M., Wang, H. B., Dembo, M., & Wang, Y. L. (2000). Cell movement is guided by the rigidity of the substrate. *Biophysical Journal*, *79*, 144–152.

Misharin, A. V., Morales-Nebreda, L., Reyfman, P. A., Cuda, C. M., Walter, J. M., McQuattie-Pimentel, A. C., Chen, C. I., Anekalla, K. R., Joshi, N., Williams, K. J. N., Abdala-Valencia, H., Yacoub, T. J., Chi, M., Chiu, S., Gonzalez-Gonzalez, F. J., Gates, K., Lam, A. P., Nicholson, T. T., Homan, P. J., … Perlman, H. (2017). Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span. *Journal of Experimental Medicine*, *214*, 2387–2404.

Phillipson, M., Heit, B., Parsons, S. A., Petri, B., Mullaly, S. C., Colarusso, P., Gower, R. M., Neely, G., Simon, S. I., & Kubes, P. (2009). Vav1 is essential for mechanotactic crawling and migration of neutrophils out of the inflamed microvasculature. *The Journal of Immunology*, *182*, 6870–6878.

Plodinec, M., Loparic, M., Monnier, C. A., Obermann, E. C., Zanetti-Dallenbach, R., Oertle, P., Hyotyla, J. T., Aebi, U., Bentires-Alj, M., Lim, R. Y. H., & Schoenenberger, C. A. (2012). The nanomechanical signature of breast cancer. *Nature Nanotechnology*, *7*, 757–765.

Plotnikov, S. V., Pasapera, A. M., Sabass, B., & Waterman, C. M. (2012). Force fluctuations within focal adhesions mediate ECM-rigidity sensing to guide directed cell migration. *Cell*, *151*, 1513–1527.

Reilkoff, R. A., Bucala, R., & Herzog, E. L. (2011). Fibrocytes: Emerging effector cells in chronic inflammation. *Nature Reviews Immunology*, *11*, 427–435.

Santos, A., & Lagares, D. (2018). Matrix stiffness: The conductor of organ fibrosis. *Current Rheumatology Reports*, *20*, 2.

Shellard, A., & Mayor, R. (2021). Durotaxis: The hard path from in vitro to in vivo. *Developmental Cell*, *56*, 227–239.

Sunyer, R., Conte, V., Escribano, J., Elosegui-Artola, A., Labernadie, A., Valon, L., Navajas, D., García-Aznar, J. M., Muñoz, J. J., Roca-Cusachs, P., & Trepat, X. (2016). Collective cell durotaxis emerges from long-range intercellular force transmission. *Science*, *353*, 1157–1161.

Sunyer, R., & Trepat, X. (2020). Durotaxis. *Current Biology*, *30*, R383–R387.

Tse, J. R., & Engler, A. J. (2011). Stiffness gradients mimicking in vivo tissue variation regulate mesenchymal stem cell fate. *PLoS One*, *6*, e15978.

Vincent, L. G., Choi, Y. S., Alonso-Latorre, B., del Álamo, J. C., & Engler, A. J. (2013). Mesenchymal stem cell durotaxis depends on substrate stiffness gradient strength. *Biotechnology Journal*, *8*, 472–484.

Zhu, M., Tao, H., Samani, M., Luo, M., Wang, X., Hopyan, S., & Sun, Y. (2020). Spatial mapping of tissue properties in vivo reveals a 3D stiffness gradient in the mouse limb bud. *Proceedings of the National Academy of Sciences of the United States of America*, *117*, 4781–4791.

How to cite this article: Goldmann, W. H. (2024). Durotaxis: A cause of organ fibrosis and metastatic cancer? *Cell Biology International*, 1–3. https://doi.org/10.1002/cbin.12156