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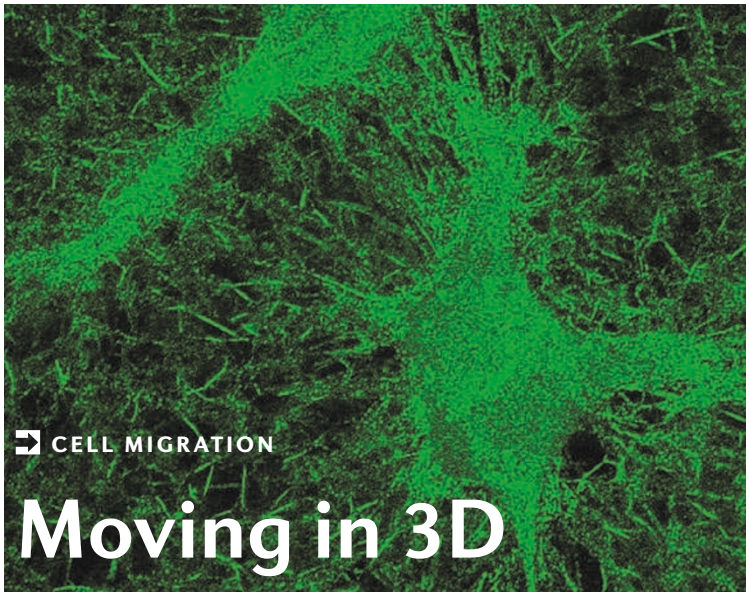

Reflection confocal image showing collagen fibres of a three-dimensional matrix in which HT-1080 cells are embedded and cellular protrusion dynamics are regulated by focal adhesion proteins. Image courtesy of D. Wirtz, Johns Hopkins University, Baltimore, USA.

Cells use focal adhesions — actin- and integrin-rich protein assemblies that mediate cell adhesion to the substrate, cell signalling and force transduction — to migrate in two dimensions (2D), but little is known about their role *in vivo* or during migration in a 3D matrix. In *Nature Cell Biology*, Fraley *et al*. now report that cells in 3D matrices, which best mimic a physiological environment, do not form stable focal adhesions, but focal adhesion proteins regulate motility by controlling the formation of pseudopodia.

Previous studies reported that focal adhesions are not readily detected *in vivo*. Indeed, using confocal microscopy to image a human sarcoma cell line that was embedded in a 3D matrix, the authors were not able to see any focal adhesions, suggesting that they might not form or might be too small and/or have too short a lifetime to allow detection. Nevertheless, knock down of the main focal adhesion proteins (including vinculin, α-actinin, zyxin, paxillin, vasodilator-stimulated phosphoprotein, the adaptor protein p130Cas (also known as BCAR1) and focal adhesion kinase) affected cell motility. Interestingly, measurements of cell speed and persistence of migration (the distance a cell travels and the time it takes before it changes direction) in knockdown cells migrating in 2D and 3D showed that these proteins regulate migration in a 3D matrix in a different manner to that on a 2D surface.

So how do focal adhesion proteins control cell motility in a 3D matrix without forming mature and stable focal adhesions? Cells did not form a wide protruding lamella (which is typical of the leading edge of cells migrating on a 2D substrate) but instead extended thinner protrusions called pseudopodia, the formation of which was affected by focal adhesion proteins. Cell speed and persistence in 3D strongly correlated with the number and growth rate of pseudopodia, but not with the lifetime or length of the protrusions.

These results suggest that when cells are embedded in a 3D matrix they modulate migration speed and persistence by regulating protrusion dynamics. Rather than producing long-lived elongated protrusions, cells form adhesive pseudopodia as frequently as possible to probe the environment, and such protrusions require focal adhesion proteins.

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ORIGINAL RESEARCH PAPER Fraley, S. I. *et al.* A distinctive role for focal adhesion proteins in three-dimensional cell motility. *Nature Cell Biol.* **12**, 598–604 (2010)
FURTHER READING Geiger, B., Spatz, J. P. & Bershadsky, A. D. Environmental sensing through focal adhesions. *Nature Rev. Mol. Cell Biol.* **10**, 21–23 (2009)

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