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Journal club

MOVING INTO THE THIRD DIMENSION

Anyone researching cell adhesion and motility knows about focal adhesions — actin filament and integrin-rich molecular assemblies that mediate cell attachment to the extracellular matrix (ECM) and cell migration over substrata. After decades of studying these structures in cells migrating on two-dimensional (2D) surfaces, some scientists read the first description of focal adhesions in a 3D environment, by Cukierman *et al.*, with glee and relief. At last the nagging worry that these structures were an artefact of 2D culture could be put to bed.

Now, the same can be concluded for the second class of adhesions: podosomes and invadopodia. In the mid 1980s, several actively migrating cell types of monocytic lineage were shown to display podosomes on their basal surfaces as they moved on planar substrata. Although they contained many of the same proteins as focal adhesions, they had a distinct morphology owing to the presence of additional molecules (such as Wiskott–Aldrich syndrome protein). Invadopodia were identified a few years later in invasive cancer cells. As well as being recognized as adhesive structures distinct from focal adhesions, podosomes and invadopodia were found to deliver proteolytic enzymes for the focal degradation of the ECM — ideal for tissue-invasive cell types. Despite the interest in these structures as modulators of cell migration, no one had shown that they existed *in vivo* or in 3D culture, but two recent papers provide evidence for this.

> “podosomes and invadopodia mediate the transmigration of cells through barriers such as basement membranes.”

First, Rottiers *et al.* described the generation of podosomes in the endothelium of native mouse arterial vessels when exposed to the inflammatory cytokine transforming growth factor-β; podosomes form protrusions through the underlying basement membrane, and evidence of ECM degradation can be seen underneath them. Then, Cougoule *et al.* showed that loss of haematopoietic cell kinase (HCK), a key Src-family kinase in macrophages, reduces the ability of these cells to form podosome rosettes and degrade the ECM in 3D migration and degradation assays. Together, these studies suggest that podosomes and invadopodia mediate the transmigration of cells through barriers such as basement membranes. It is not yet clear whether these structures are necessary for the continued migration of cells once they have broken through the barrier. My educated guess, based upon a few isolated observations, is probably not, but we'll see.

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ORIGINAL RESEARCH PAPERS Cukierman, E. *et al.* Taking cell-matrix adhesions to the third dimension. *Science*, **294**,1708–1712 (2001) | Rottiers, P. *et al.* TGFβ-induced endothelial podosomes mediate basement membrane collagen degradation in arterial vessels. *J. Cell Sci.* **122**, 4311–4318 (2009) | Cougoule, C. *et al.* Three-dimensional migration of macrophages requires Hck for podosome organization and extracellular matrix proteolysis. *Blood* **115**, 1444–1452 (2010)