Directing cell migration is critical for both tissue engineering/regeneration and controlling cancer metastasis. Cell migration has been guided directly via physical structures and gradients. However, cell migration control is also an emergent property of fibrous extracellular matrix (ECM) and scaffolds in which cells can rearrange fibers to generate their own guidance cues. This positive feedback system in which cells simultaneously follow and align fibers has typically been studied in the context of multi-cell masses and large-scale, permanent ECM deformations. However, such systems do not accurately recapitulate single, autonomous cell invasion. Here, we asked whether the positive feedback afforded by flexible substrate fibers influences individual cell migration decisions.

Timelapse imaging of HT-1080 fibrosarcoma and NIH3T3 fibroblast cells in 3D collagen type I matrices and electrospun polycaprolactone fiber scaffolds revealed that cell polarity in fibrous environments is determined at the level of individual protrusions, which are individually guided by local fiber orientation. The co-alignment of multiple protrusions along co-aligned fibers polarizes the entire cell. However, if the fibers are not aligned and cannot be aligned by cells, contact guidance of individual protrusions still occurs along fibers, but does not produce overall cell polarization. This inability to align randomly oriented fibers in turn decreases cell migration persistence relative to cells in substrates with deformable fibers. These findings suggest that the autonomous migration of individual cells is affected by the microenvironment’s responsiveness to remodeling and offer a means to impact cell invasion by modulating cells’ ability to generate their own contact guidance cues.