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# Journal Club

## THE NEEDLE IN THE ECM HAYSTACK

Mary L. Stearns phrased it succinctly in her 1940 paper when she wrote, "The problem of the source, development and orientation of the intercellular fibers of connective tissue, although the subject of investigation for many years, is still unsettled." She was referring to the collagen fibrils that account for 60% of the mass of most tissues and are so long (they are several millimetres in length) that investigators at the time questioned the role of the cell in their synthesis. Stearns used a camera lucida (an optical device used by artists as a drawing aid) to look into a glass chamber implanted into a rabbit's ear, and thereby watched cells synthesising collagen fibrils. Her paper contains 46 hand-drawn figures showing cytoplasmic connections between cells, striations within cells, 'vacuoles de segregation' and fibres growing from the cell surface. She had discovered the importance of cells as the architects of extracellular matrix (ECM) synthesis and connective tissue organization.

> "75 years since Stearns published her paper … the mechanism of collagen fibril assembly *in vivo* remains elusive."

During the 75 years since Stearns published her paper, scientists have discovered the structure of DNA and learnt how to clone animals, but the mechanism of collagen fibril assembly *in vivo* remains elusive. The reason for this is that, as Graham *et al.* showed, the sites of rapid fibril growth are located at the needle-shaped ends of the fibrils, which are extremely sparse in adult tissue. However, Trelstad and Hayashi demonstrated that these sites are always found at the surfaces of embryonic fibroblasts, and Canty *et al.* expanded on this observation to reveal that they are specifically located at the base of fibripositors (actin-rich plasma membrane protrusions). Rapid improvements in high-resolution imaging, as well as genetic and biochemical approaches, mean that the study of embryonic fibroblast surfaces is now more accessible and that it is unlikely to take another 75 years to understand the dynamic interface between the ECM (specifically collagen fibril assembly) and the actin cytoskeleton — or will it?

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**ORIGINAL RESEARCH PAPERS** Stearns, M. L. Studies on the development of connective tissue in transparent chambers in the rabbit's ear. II. *Am. J. Anat.*, **67**, 55–97. doi: 10.1002/aja.1000670104 (1940) | Graham, H. K, Holmes, D. F., Watson, R. B. & Kadler, K. E. Identification of collagen fibril fusion during vertebrate tendon morphogenesis. The process relies on unipolar fibrils and is regulated by collagen-proteoglycan interaction. *J. Mol. Biol.* **295**, 891–902 (2000) | Trelstad, R. L. & Hayashi, K. Tendon collagen fibrillogenesis: intracellular subassemblies and cell surface changes associated with fibril growth. *Dev Biol.* **71**, 228–242 (1979) | Canty, E. G., Lu, Y., Meadows, R. S., Shaw, M. K., Holmes, D. F. & Kadler, K. E. Coalignment of plasma membrane channels and protrusions (fibripositors) specifies the parallelism of tendon. *J Cell Biol.* **165**, 553–563 (2004)