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Mechanochemical Force-Structure Causality in the Matrix: Making bones from soup

Abstract. Shockingly, there exists no established model that can explain how a cluster of vertebrate cells, which are expressing matrix proteins manage to produce, refine and grow load-bearing structures that are organized over much longer length scales than the cells themselves. The current best guess model, which was proposed in the mid-1980s by David Birk and Robert Trelstad (subsequently carried forward by Karl Kadler's group) suggests that cells extrude formed collagen fibrils into the extracellular space via structures which are termed "fibripositors". Thus, one imagines that the cells, working together, somehow weave the collagen into the matrix, thread by thread with the necessary exposed loose ends finding each other and fusing to form long-range, organized connective tissue. However, gathering evidence to support this model is severely hampered because it is nearly impossible to observe cells in the act of producing matrix while observing the collagen fibril deposition directly at the nanoscale. In addition, the fibripositor model does not contemplate either matrix refinement or growth. Thus, we are not only in need of experimental evidence to support the fibripositor theory, we are short of a comprehensive testable hypothesis in general for how tissue is built. To address this gap, we have chosen to make a simple (and risky) assumption: We reject the idea that the cells directly manipulate individual collagen monomers make tissue. Instead, we assume the cell has spent much of its time (~billion years) refining specific molecular systems (secretomes) that are designed to "settle" into their appropriate configuration simply by "reading" the energetic landscape. To generate load-bearing connective tissues, we suggest that the cells provide appropriate geometry by self-organizing and then produce an appropriate secretome that has been designed to assemble in opposition to the locally and globally applied mechanical forces which threaten to dissipate animal structure. In effect, we predict that mechanical strain is a short and long-range structure producing signal which works via mechanical allostery to modulate both collagen fibril assembly and retention. Because collagen is generally found resisting tension in load-bearing soft-connective tissue, we expect that the mechanical environment directly shifts the molecular energetics such that collagen's inherent stability and assembly kinetics are enhanced in the direction of applied tensile forces. I will present the current state and limitations of our investigation of this risky assumption and entertain your thoughts, concerns and comments. As an epilogue, I will present some of our plans to take advantage of this energy-based view of matrix formation.