frontiers | Frontiers in Mechanical Engineering

TYPE Editorial
PUBLISHED 09 May 2023
DOI 10.3389/fmech.2023.1211250

OPEN ACCESS

EDITED AND REVIEWED BY
Stanislav N. Gorb,
University of Kiel, Germany

*CORRESPONDENCE
Ehsan Ban,
ehsan.ban@gmail.com

RECEIVED 24 April 2023
ACCEPTED 02 May 2023
PUBLISHED 09 May 2023

CITATION
Ban E, Freedman BR, Smith LR and Wells RG (2023), Editorial: The mechanobiology of collagen remodeling in health and disease.
Front. Mech. Eng 9:1211250.
doi: 10.3389/fmech.2023.1211250

Editorial: The mechanobiology of collagen remodeling in health and disease

Ehsan Ban[1]*, Benjamin R. Freedman[2], Lucas Robert Smith[3] and Rebecca G. Wells[4]

[1]Department of Biomedical Engineering, Yale University, New Haven, CT, United States, [2]Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center Harvard Medical School, Boston, MA, United States, [3]Department of Neurobiology, Physiology and Behavior, University of California, Davis, CA, United States, [4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

KEYWORDS

collagen, tissue remodeling, fibrosis, extracellular matrix (ECM), cardiovascular mechanobiology

Editorial on the Research Topic
The mechanobiology of collagen remodeling in health and disease

Extracellular matrices composed of collagen provide structural support to soft tissues and have an impact on cellular behavior, including the cells responsible for producing and modifying the matrix. The mechanobiological effects of matrix on cells have emerged as important factors in driving the behavior of pathogens, immune cells, neurons, stem cells, and cancer cells. Improving our understanding of collagen mechanobiology has the potential to advance research across organ systems in health and the myriad of fibrotic disease conditions which disrupt the collagen network.

This Research Topic includes articles that reflect the major challenges and open questions in the collagen mechanobiology field today: the impact of mechanics on collagen degradation and synthesis, the relationship between collagen structure and function, and the best modalities for imaging collagen at different length scales.

Ita and Winkelstein studied collagen function and degradation, specifically in the perception of pain during the deformation of collagen-rich ligaments above the threshold of injury. They devised a unique experimental approach that combined analysis of the degradation of collagen matrices by matrix metalloproteinases, biaxial mechanical testing, and analysis of collagen fiber kinematics with the factors involved in signaling pain. Their results uncover a new mechanistic connection between matrix metalloproteinases, collagen degradation, and pain in the context of injury to the facet ligament of the spine. Using a neuron-fibroblast co-culture collagen gel model, the researchers found that a sub-failure equibiaxial stretch induced a significant re-organization of collagen fibers, and doubled the expression of substance P, a nociceptive neuropeptide. Treatment with the MMP inhibitor ilomastat prevented the stretch-induced increase in substance P expression, but did not affect MMP-1 and MMP-9 expression. The study suggests that MMPs may play a role in ligamentous injury and pain, and may be involved in nociceptive-related signaling pathways.

On the side of collagen synthesis, van Haasterecht et al. carried out a meta-analysis of the existing literature on the *in vitro* response of human dermal fibroblasts to mechanical strain. They searched research databases and analyzed 48 existing studies, assessing the correlation

between collagen production and cell proliferation and factors including the frequency of tissue stretching, the presence of vitamin C, and strain. The study finds that mechanical stretch does not affect fibroblast proliferation in neonatal fibroblasts but significantly increases proliferation in adult fibroblasts. Collagen production is significantly increased in response to mechanical stimulation, with Vitamin C stimulation as the most important covariate. Stretching frequency is positively associated with fibroblast proliferation and negatively associated with collagen production. The results have important implications for mechanobiology in collagen-rich tissues, showing that mechanical stimulation is a key regulator of collagen production by fibroblasts but that age plays a major role in other responses, particularly proliferation.

Neave et al. make an important contribution to the complex question of the relationship between collagen structure and function. Previous research has underscored the important role of collagen remodeling in the formation of aortic aneurysms and its vital role in preventing aneurysm ruptures (Schriefl et al., 2012; Jana et al., 2019). The authors carried out a variety of measurements–including uni- and biaxial tensile testing–of vascular collagen within the aortic media and adventitia in human patients, then determined the correlation between age, gene expression, collagen content, and the strength and stiffness of the vascular wall. The study found that collagen-I content was related to improved mechanical properties, while total collagen content does not show an overt relationship with biomechanics. Gene expression (COL1A1 and COL3A1) related to collagen-I content but not total collagen content or biomechanical performance. Together, this study provides novel insight into the relationship between collagen remodeling in aortic aneurysms and patient age and location (media, adventitia) within the wall, emphasizing the importance of location and this collagen in particular in driving the mechanical properties of the aortic wall in health and during aneurysmal disease.

Finally, Iannucci et al. reviewed techniques to image the dynamic processes involving collagen in health and disease. The review discusses the optical properties of collagen and the different optical imaging approaches that can be used to monitor, sense, and diagnose changes in collagen dynamics. Techniques used in cell-scale research (second harmonic generation imaging and confocal microscopy) as well as methods such as photoacoustic imaging that can be employed at the scale of tissues are discussed. The review concludes with a description of recent efforts applying machine learning to imaging collagen, suggesting that microscopy provides a direct means of visualizing the collagen-related phenomena underlying changes in cellular phenotype.

While there remain many outstanding questions about the mechanisms and implications of collagen deposition and organization, the current Research Topic highlights state-of-the-art and provides insight into directions for future research and the potential for leveraging knowledge about collagen in fighting disease, engineering tissue, and devising novel therapeutics.

Author contributions

EB, BF, LS, and RW wrote the article. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Jana, S., Hu, M., Shen, M., and Kassiri, Z. (2019). Extracellular matrix, regional heterogeneity of the aorta, and aortic aneurysm. *Exp. Mol. Med.* 51 (12), 1–15. doi:10.1038/s12276-019-0286-3

Schriefl, A. J., Collins, M. J., Pierce, D. M., Holzapfel, G. A., Niklason, L. E., and Humphrey, J. D. (2012). Remodeling of intramural thrombus and collagen in an Ang-II infusion ApoE−/− model of dissecting aortic aneurysms. *Thrombosis Res.* 130 (3), e139–e146. doi:10.1016/j.thromres.2012.04.009