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# New evidence of a dynamic fascial maintenance and self-repair process

Dittmore et al. (2016) have described experimental evidence that collagen operates a self-healing process involving what they term *"cleavage-vulnerable binding regions"*.

These sites are arrayed periodically at ~1 μm (one millionth of a meter) intervals, along collagen fibrils.

They note that the triple-helix of fibrillary collagen, in its most common form, assembles into highly organized networks that provide the scaffolding for the extracellular matrix, tendons, bones, and other load-bearing structures.

The essence of the model that emerges from the Dittmore et al. experiments is that, when collagen fibrils are in what are termed an '*intact*' phase, molecules are in a straight conformation. This is a '*high-energy*' state, that periodically results in the accumulation of internal strain, relieved by the collagen uncoiling to form 'buckled' molecular configurations (termed 'cleavage sites').

This buckling process exposes the unloaded collagen, allowing enzymes, such as specialized matrix metalloproteinases (MMPs), to bind to it, before initiating proteolysis — followed by subsequent repair and remodeling.

The data provided by Dittmore et al. suggests that fibrillar collagen self-regulates its own maintenance in this way — by a constant process of repairing collagen fibrils, on a cellular level.

## The importance of tissue tension

Importantly, Dittmore et al. also note that tension-dependent stabilization against degradation by MMPs, has been demonstrated in normal tissue.

Others, such as Susilo et al. (2016) have also reported that: *"mechanical loading induces stabilizing changes internal to the fibrils themselves, or in the fibril-fibril interactions."*

This suggests that the self-repair, remodeling sequence may be delayed (i.e. made less necessary) by the presence of appropriate levels of tension, since, as has been explained *"contractile forces of the cell, stresses exerted through changes during development, interstitial fluid pressure, and physical activity, alter the strain on fibrils and reinforce collagen in the direction of loading."* (Bhole et al., 2009).

## Summary

- Collagen fibrils contain billions of minute sites that are vulnerable to buckling — if internally or externally derived forces fail to maintain optimal tension.
- A triple helix collagen fibril that is not under external tension spontaneously forms buckling sites — at approximately 1 μm intervals. However, if the fibril is under appropriate tension, the number of buckling sites decreases, and if tension is sufficiently high, there are no buckling (cleavage) sites (Lotz et al., 2008).
- Buckling exposes collagen to specific enzymes (MMPs) at these cleavage site, initiating the enzyme-related degradation and subsequent repair process.
- Dittmore et al. explain *"The underlying dynamic molecular changes in collagen structure, which may be on the order of single atoms* (Perumal et al., 2008), *have evaded detection by conventional structural approaches but were readily observed through tracking of enzyme binding."*
- The presence of strain-driven defects may have general and widespread regulatory repair and maintenance functions in self-assembled biological (collagen) filaments — with the possibility that externally applied load — via exercise, or the imposition of compression/shear force/stretching etc — might be capable of influencing this apparently constant process.
- It is of interest to note that these self-regulating processes operate via mechanisms that are independent of the nervous system. In reality the process is dependent on force transmission/load transfer, fluid dynamics and mechanotransduction mechanisms (amongst others) (Humphrey et al., 2014)

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## Significance

Dittmore et al. describe the significance of their findings as follows:

> *"Collagen fibrils resemble nanoscale cables that self-assemble and constitute the most prevalent protein structure in the body. Our experiments reveal unanticipated defects that form along collagen fibrils. These defects are the initiation sites of collagenase activity and represent a strain-sensitive thermally-labile mechanism for regulating tissue remodeling. The emergence of defects, their spatial periodicity, and fluctuations are quantitatively accounted for with a buckling model in which defects spontaneously form, repulsively interact, and self-heal."*

## Questions?

The Dittmore et al. findings have important clinical implications for manual and movement therapies, and raise a number of questions, such as:

- In what ways may internally generated forces — for example — associated with rhythmic pulsations, contractions, peristalsis, respiratory activity etc — influence the tension-status of associated collagen fibrils?
- To what extent can we influence the tension status of collagen fibrils via hydration? For example, Masic et al. have noted that: *"We find major water-induced conformational changes of the collagen molecule, which are very inhomogeneous along its length. We also show that the resulting shortening is capable of producing tensile stresses, which—depending on osmotic pressure—may get up to 100 MPa, much larger than that generated by muscles."* They add: *"From the experiments and from the model calculations, we conclude that water plays a crucial role in stabilizing the structure of the collagen molecule and is an essential and active part of the protein unit."* This supports many studies, such as Leikin et al. (1997) who observed: "Tightly bound waters are believed to stabilize the triple helix by participating in the Hbond backbone". (See also Bella 2016, De Simone A et al., 2008).
- How does force-transmission, via muscle-fascial connections, influence the tension status of associated collagen fibrils?
- In what ways might exercise, and/or movement therapies (Yoga, Tai chi, Pilates, Feldenkrais etc) influence the tension status of associated collagen fibrils?
- In what ways do externally applied loads, via manual therapies (massage, osteopathy, chiropractic, physiotherapy etc) influence the tension status of associated collagen fibrils?
- If collagen self-repair is tension-dependent — as suggested by Dittmore et al. — in what ways might the 'unloading' of excessively tense tissues (as in osteopathic functional, or counterstrain methodology, or forms of kinetic taping, as examples) — or relaxation of tense tissues via massage, for example — influence tension (and thermally) related self-repair processes?

Other questions raised include consideration of optimal therapeutic manual or movement dosages?

We have some clues as to answers:

For example in their study of the effects of different forces (degree, direction etc) required for optimal healing of damaged tendons, Wang and Guo (2012) note that:

> *"Tendons are … mechanoresponsive … they have the capacity to adapt themselves to altered mechanical loading"*

and that:

> *"Repetitive mechanical stretching has two opposite effects—anti-inflammatory at small magnitudes, pro-inflammatory at large magnitudes."*

In regard to the *degree* of load, this translates in clinical settings as follows:

- Low levels (2%) of mechanical load to damaged tendons were found to retard tensile strength and reduce collagen production (among other factors)
- High levels of mechanical load (8%) to damaged tendons interfered with collagen organization, and increased inflammatory mediators, while increasing Tendon Stem Cell (TSC) differentiation into non-tenocytes.
- In contrast, moderate mechanical load (4%) to damaged tendons increases tensile strength and collagen synthesis, while increasing TSC differentiation into tenocytes and decreasing inflammatory mediators

This *in vivo* evidence is supported by Cao et al. (2015), who have demonstrated that similar degrees of force/load described above, promoted healing in damaged bioengineered tendons.

- Cao et al. combined human dermal fascia fibroblasts with bovine collagen to create bioengineered tendons (BET)
- After creating a wound in a BET — different degrees and durations of uniaxial strain were applied, in the direction of the long axis of the structure, simulating Myofascial Release (MFR)
- Wounded bioengineered tendon were treated with 0% (non-strain), 3%, 6%, 9%, or 12% of simulated MFR, for 90 s. It was found that the most rapid healing occurred with a 3%—6% load — whereas in contrast 12% of load retarded healing 48 h after the load application.

In regard to the optimal *duration* of load in their studies, Cao et al., reported that:

- Wounded bioengineered tendons were then treated with 6% load beyond the initial resting length, for either 1, 2, 3, 4, or 5 min, so mimicking myofascial release stretch. All durations of this load resulted in different degrees of healing of the wounded tendon, with 4—5 min being optimal, 48 h after the load application.

In a different study it has been observed that not only the degree, and duration of load, influenced outcomes — but direction.

Zein-Hamoud and Standley (2015) note that fibroblasts respond to different types of strain by secreting anti-inflammatory chemicals and growth factors, thus improving wound healing and muscle repair processes:

- "heterobiaxial but not equibiaxial strain affects fibroblast morphology …. [likely due to] … actin, which mediates strain-induced cellular Ca++ release. "

Duration, direction and degree of load are all features that need to be identified, if manual and movement interventions are to be optimally applied to assist the self-regulating functions, described by Dittmore et al., and others.

**Note**: For related discussion, see Serge Gracovetsky's article *Can fascial characteristics be influenced by manual therapy*? In the *Fascia Science and Clinical Applications*, section of this issue.

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Leon Chaitow, Editor-in-Chief, Honorary Fellow, ND, DO
*University of Westminster, United Kingdom*

*E-mail address:* chaitow1@gmail.com