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REVIEW

Active Contractile Properties of Fascia

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The ubiquitous network of fascial tissues in the human body is usually regarded as a passive contributor to musculoskeletal dynamics. This review aims to highlight the current understanding of fascial stiffness regulation. Notably the ability for active cellular contraction which may augment the stiffness of fascial tissues and thereby contribute to musculoskeletal dynamics. A related narrative literature search via PubMed and Google Scholar reveals a multitude of studies indicating that the intrafascial presence of myofibroblasts may enable these tissues to alter their stiffness. This contractile tissue behavior occurs not only in several pathological fibrotic contractures but has also been documented in normal fasciae. When viewed at time frames of seconds and minutes the force of such tissue contractions is not sufficient for exerting a significant effect on mechanical joint stability. However, when viewed in a time-window of several minutes and longer, such cellular contractions can impact motoneuronal coordination. In addition, over a time frame of days to months, this cellular activity can induce long-term and severe tissue contractures. These findings tend to question the common clear distinction between active tissues and passive tissues in musculoskeletal dynamics. Clin. Anat. 32:891–895, 2019.

Key words: myofibroblast; fascia; connective tissue; contracture; stiffness; fibrosis

INTRODUCTION

Myofibroblasts play a crucial role in the development of several disorders, particularly in fibrotic pathological conditions such as hypertrophic scars, frozen shoulder, and Dupuytren's contracture. Among other features, myofibroblasts exhibit a significant cellular contractility and an increased synthesis of extracellular matrix components, such as collagen Types I and III (Gabbiani, 2003; Hinz et al., 2012). In addition to their well-established occurrence in pathological conditions, their presence has also been revealed in normal (i.e., nonpathological) ligaments and tendons, as well as several other connective tissues (Tomasek et al., 2002; Schleip et al., 2005). Recent investigations suggest that myofibroblasts are also present in normal intramuscular (Hoppe et al., 2014) and extramuscular fasciae as well (Schleip et al., 2005; Bhattachary et al., 2010). It has been proposed that their presence and activity may be able to influence fascial stiffness and thereby influence musculoskeletal dynamics (Yahia et al., 1993; Schleip et al., 2008; Schleip et al., 2006).

MATERIALS AND METHODS

A narrative literature search was conducted using PubMed and Google Scholar from their start date to January 2019. The used search terms included "fascia"

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in addition to either "contraction," "contractility," "contracture," or "stiffness." From the more than 600 findings, only those relating to the basic question of this review were selected and reviewed. Review papers, case reports, and publications of non-peer reviewed journals were excluded.

RESULTS

Of the 69 analyzed articles 29 were in vitro observations, 21 human clinical studies, 12 animal studies, and the rest mixed investigations. Most studies confirm the presence of myofibroblasts—considered as a specialized connective tissue cell with augmented contractile properties— not only in pathological fasciae (Tomasek et al., 2002; Desmoulière et al., 2005) but also in normal fasciae (Battacharya et al., 2010; Hoppe et al., 2014; Dawidowicz et al., 2015; Schleip et al., 2019). When compared with human plantar fascia or with human fascia lata as well as with rat lumbar fascia, the human lumbar fascia contains a significantly higher density of myofibroblasts (Schleip et al., 2019). Interestingly, an apparently increased density of these cells has been observed in the perimysium (Hoppe et al., 2014; Fig. 1). In one investigation examples of histological sections of lumbar fascia from low-back-pain patients were documented which expressed an augmented myofibroblast density comparable to that found in frozen shoulder (Willard et al., 2012).

An increased fascial thickness in the lumbar area from older humans compared with younger humans was reported by Wilke et al. (2019). Although a trend toward an increased density of myofibroblasts with increasing age was observed by Schleip et al. (2019) in both human lumbar fascia as well as in rat lumbodorsal fascia, neither of these trends was statistically significant.

A contractile response of fascial tissues in vitro in response to pharmacological stimulation has been documented with rat lumbodorsal fascia as well as with human lumbar fascia (Hoppe et al., 2014; Schleip et al., 2019). Observed maximal contraction forces in these experiments ranged from 220 to 445 $\mu N/mm^2$. The most potent contractions were observed with transforming growth factor beta 1 (TGF-β1). Stimulation with botulinum toxin Type C3—used as a Rho kinase inhibitor—provoked mild relaxation. In contrast, fascial tissues were unresponsive to stimulation with angiotensin and caffeine. A positive correlation between myofibroblast density and contractile force was found (Schleip et al., 2019; Figure 2).

The mean maximal contraction force of myofibroblasts has been estimated as 4.1 μN/cell (Wrobel et al., 2002). A hypothetical mathematical prediction of the contraction forces to the human lumbar region—based on the reported myofibroblast densities and the registered forces in pharmacological contraction tests—yielded a maximal contraction force between 0.95 and 2.63 N (Schleip et al., 2019). While being below the threshold for exerting an impact on mechanical joint stability (Cholewicki and McGill, 1995), these force magnitudes are above the much lower threshold for mechanosensory stimulation and subsequent motoneuronal coordination (Krauspe et al., 1992).

DISCUSSION

The reviewed literature suggests that the presence and density of myofibroblasts play an active role in influencing fascial tissue stiffness in both pathological as well as normal conditions. Although the short-term contraction forces of these cells might permit an

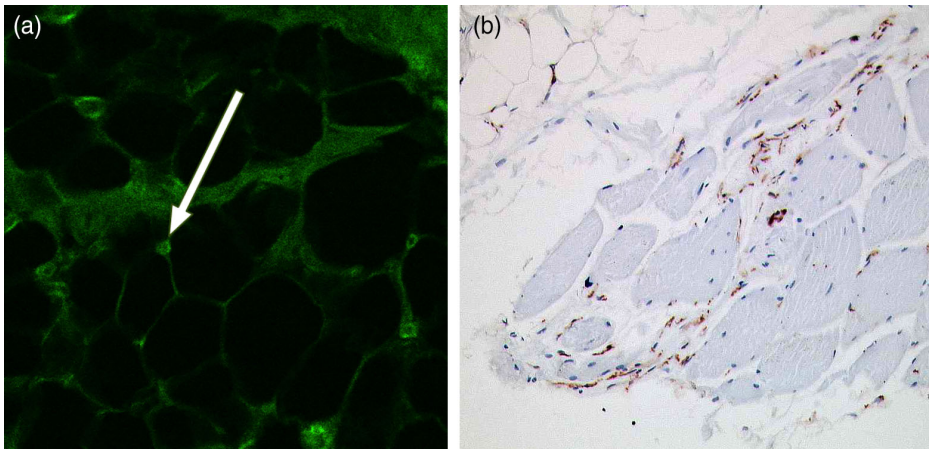

Fig. 1. Histological slides of rat fascia. (a) Immunofluorescence imaging of intramuscular fascia. Bright green: alpha-smooth muscle actin labeling, indicative for the presence of myofibroblast. Note the clearly stained line from the upper right toward the upper left side, indicating a high density of contractile cells in this perimysium. Example of a typical myofibroblast is marked with an arrow. Image length 550 μm. (b) Example of perimysial fascia in regular immunohistochemical imaging. Dark red: alpha-smooth muscle actin stained elements. Image length 400 μm. Illustration with friendly permission from Hoppe et al. (2014). [Color figure can be viewed at wileyonlinelibrary.com]

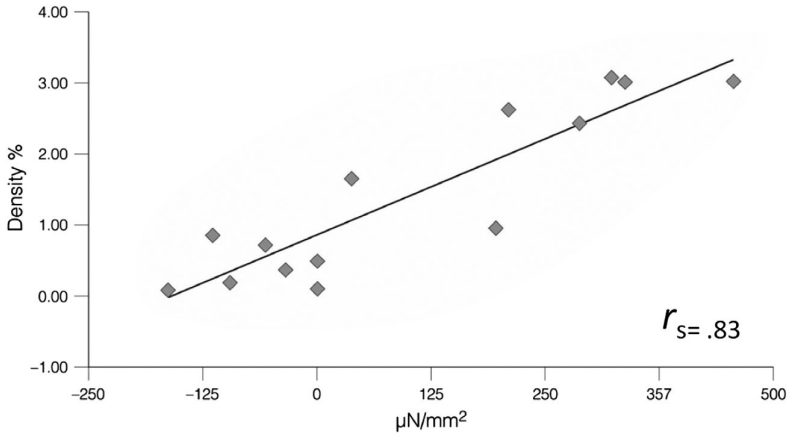

Fig. 2. Statistical analysis of the contractile force of rat lumbar fascia in response to pharmacological stimulation in vitro revealed a positive correlation with the inherent myofibroblast density (n = 14; data and illustration from Schleip et al., 2019).

influence on motoneuronal regulation, they do not appear to be strong enough to influence spinal stability or other important aspects of human biomechanics when viewed at a time frame of several minutes or hours. Predicted contraction forces of fascial tissues are then at least two orders of magnitude below that of skeletal muscle tissue of comparable cross-sectional area (Schleip et al., 2019).

However, in contrast to skeletal or smooth muscle fibers, myofibroblasts exert a relatively long-lasting Rho/RHOCK/myosin chain phosphatase pathway-dependent contractile activity that induces more permanent tissue contractures which include tissue remodeling (Hinz, 2013). Their incremental minute cellular contractions, combined with tissue remodeling can generate severe tissue contractures of ~1 cm per month (Follonier Castella et al., 2010) when viewed at a larger time-frame. Some of the induced tissue contractures, such as in frozen shoulder, develop a tissue stiffness and strength which requires the combined forces of several surgeons to break them up under anesthesia (Karas et al., 2016). Active fascial contractility may, therefore, be strong enough to impact spinal stability and other important aspects of biomechanical behavior when viewed at larger time frames, such as several days to months.

While myofibroblast contractile activity is already considered as a well-known contributory factor in specific fibrocontractile pathologies, such as Dupuytren contracture, Morbus Ledderhose, or frozen shoulder, it may also play a role in other pathological musculoskeletal conditions which are associated with an augmented myofascial stiffness. An increased fascial thickness and/or stiffness has been reported in ulnar nerve compression syndrome (Klingler et al., 2014) and in myofascial neck pain (Stecco et al., 2013, 2014. An increased fascial stiffness has also been suggested as a contributing factor in iliotibial band syndrome (Fairclough et al., 2007; Tateuchi et al., 2016). It might, therefore, be an interesting field for future research, to examine the potential role of active fascial contractility in these conditions.

The reported increased myofibroblast density in the perimysium could be of clinical significance (Fig. 1). Food scientists report about a correlation between meat toughness and perimysial thickness (Bendall, 1967; Rowe, 1974). Because an increased perimysial collagen density has been observed in tonic muscles when compared with more phasic muscles (An et al., 2014; Roy et al., 2018), it seems justified to assume that a related perimysial stiffening could—at least in some cases—contribute to myofascial tonicity in human erector spinae muscles, and particularly to the deep multifidus layer (Mannion et al., 1997; MacDonald et al., 2006). In fact, several myofascial pathologies associated with increased myofascial stiffness are associated with changes in the perimysium (Williams and Goldspink, 1984; De Deyne et al., 2000; de Bruin et al., 2014). In contrast, these described changes have not been found in the endomysium. Similarly, aging tends to be associated with an increased perimysial thickness (Nishimura, 2010; Csapo et al., 2014). Future research into this dimension, including the newly developed myofibroblast quantification method based on needle biopsy extracts (Schleip et al., 2018), appears as a promising direction.

The potential influence of myofibroblast contractility in back stability and low back pain merits special consideration. This is supported by the increased density of myofibroblasts in the human lumbar fascia, reported above. It is also corroborated by the histological tissue sections reported by Willard et al. (2012) from a patient who expressed an augmented myofibroblast density comparable to that found in frozen shoulder.

The involved cellular contractility seems independent from a direct synaptic signal transmission from the central nervous system, such as via acetylcholine or adrenaline (Schleip et al., 2008). Instead, the contractile activity of these cells is influenced via the expression of various cytokines within the ground substance. For

one of these cytokines, TGF-β1, a clear influence of the sympathetic nervous system onto their activity has recently been documented (Bhowmick et al., 2009; Liao et al., 2014). This influence appears to support the hypothesis of Staubesand and Li (1996,1997), which proposed a close connection between fascial stiffness and chronic sympathetic activation. In light of the reported large contribution of psychosocial factors in low back pain (Yang et al., 2016; Burgel and Elshatarat, 2017), this connection appears to offer an interesting field for future investigation.

Besides the influence of TGF-β1 and of other cytokines on myofibroblast contractility, the pH level in the ground substance might exert an enhancing influence on tissue stiffness. This consideration is supported by the reported augmenting effect of an acidic pH condition on myofibroblast contractions in vitro by Pipelzadeh and Naylor (1998) as well as well as by the documented lactic acid-induced myofibroblast differentiation in lung fibrosis which is mediated by the pH-dependent activation of latent TGF-β1 (Kottmann et al., 2012). If verified, therapeutic strategies to modify the acidity of the ground substance—such as via moderate exercise and nutritional modifications—might be explored as potential avenues in conditions with an enhanced fascial stiffness.

The reliability of tissue stiffness assessment via ultrasound elastography as well as via myometry and indentometry has been recently documented (Pruyn et al., 2016; Salavati et al., 2017; Wilke et al., 2018). Because mechanoadaptation of collagenous tissues does not always go along with the adaptation of related skeletal muscles (Mersmann et al., 2017), it is suggested to enhance the incorporation of fascial tissue assessments in future therapeutic as well as scientific investigations in the field of sports medicine (Zuegel et al., 2018).

To conclude, the reported capacity of fascial tissues actively to contract question the common clear distinction between active tissues and passive tissues in musculoskeletal dynamics (Panjabi, 1992). Myofibroblast-driven fascial tissue stiffness regulation deserves to be considered as an additional important element in the complexity of musculoskeletal interactions.

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