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FASCIA SCIENCE AND CLINICAL APPLICATIONS: EXTENSIVE REVIEW

A unifying neuro-fasciagenic model of somatic dysfunction — Underlying mechanisms and treatment — Part I

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Summary This paper offers an extensive review of the main fascia-mediated mechanisms underlying various dysfunctional and pathophysiological processes of clinical relevance for manual therapy. The concept of somatic dysfunction is revisited in light of the diverse fascial influences that may come into play in its genesis and maintenance. A change in perspective is thus proposed: from a nociceptive model that for decades has viewed somatic dysfunction as a neurologically-mediated phenomenon, to a unifying fascial model that integrates neural influences into a multifactorial and multidimensional interpretation of dysfunctional process as being partially, if not entirely, mediated by the fascia.

The fascia

Fascia is an ubiquitous tissue permeating the entire body. It surrounds, supports, suspends, protects, connects and divides muscular, skeletal and visceral components of the organism (Kumka and Bonar, 2012). The fascia plays different physiological and functional roles related to joint stability, general movement coordination, proprioception, nociception (Tozzi, 2012), transmission of mechanical forces (Huijing, 2009); and is associated with wound healing, tissue repair and many connective tissue pathologies such as Dupuytren contracture and the effects of post-operative adhesions (Gabbiani, 2003). By investing each tissue at multiple hierarchical levels, the fascia embodies the element of structural interconnectedness around, within and between body constituents, whilst allowing simultaneous sliding and gliding motions. Since it appears to shape every body constituent, it has been referred to as both an 'organ of form' (Varela and Frenk, 1987) and as an 'organ of innerness' due to its phenomenological dimension of 'in between' the 'outer' (skin) and the 'inner' (visceral

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endothelium) boundaries of the body (Van der Wal, in preparation). Instead of consisting of different superimposed layers, gliding on each other, it has been proposed as a single architecture with various levels of form and complexity (Guimbertau, 2012). It has been defined as an 'ectoskeleton' (Wood Jones, 1944), in relation to its continuity and function of muscle attachment, enveloping, force transmission and body-wide proprioception. Even at a cellular level, fascia displays an interconnected arrangement with soft tissue fibroblasts within the ECM forming an extensive reticular network, via their cytoplasmic expansions, that permeates the whole body (Langevin et al., 2004). Fibroblasts may actually form adherens and gap junctions at the intercellular levels of contact, allowing also for a more concerted response to mechanical loading (Ko et al., 2000). Furthermore, each fibroblast's cytoskeleton is structurally connected to the external environment, either directly with contiguous cells or through the extracellular matrix (ECM) constituents (Hinz and Gabbiani, 2003a; Fletcher and Mullins, 2010). The entirety of this system may indeed represent a body-wide signaling network (Langevin, 2006) that depends on the relationship between cells and surrounding matrix. Mechanical tension signals from the ECM are transferred through transmembrane mechanoreceptors to the cytoskeleton and cell nuclei, while being transduced into chemical information — via mechanotransduction - so impacting on various aspects of cell behavior and metabolism via the modulation of gene expression (Wang et al., 2009). On the one hand, cells synthetize, secrete, modify and degrade ECM constituents, and on the other, mechanical properties of the ECM affect cytoskeletal organization and cell behavior (Chiquet et al., 2009; Guilak et al., 2006). Cell growth, differentiation, metabolism, contractility, proliferation and apoptosis are under the influence of forces transmitted from the extracellular matrix to the cell via 'focal adhesion' proteins (Goldmann, 2014; Chicurel et al., 1998), and from the cytoskeleton to the nucleus via linker complexes (Isermann and Lammerding, 2013). Focal adhesions are highly flexible and dynamic complexes that are constantly changing and reassembling in response to tensional forces on both sides of the cell membrane. Under increases in tension, these adhesion contacts can become stronger (Parsons et al., 2010) or be released (Liu et al., 2011), and can initiate biochemical signaling cascades for cytoskeletal remodeling and actin polymerization (Machesky and Hall, 1997). Thus they represent a clear pathway for active tensional regulation, whilst mediating vital cell functions, as well as playing a role in disease development (Hoffman, 2014). Indeed, defects in cellular and extracellular mechanics, caused by protein misregulation (Jaalouk and Lammerding, 2009), mutations and/or changes in the expression of proteins linking the cell nucleus with the cytoskeleton (Isermann and Lammerding, 2013), may be implicated in the etiology and development of multiple diseases such as cardiomyopathies and cancer.

Somatic dysfunction

Nowadays, the aim of manual therapy is to promote health and to support the inherent self-regulatory capacities within a dynamic interaction of body, mind and spirit (Rogers et al., 2002) and this is achieved in the osteopathic field by focusing on the musculoskeletal system as the interface of the body's homeostatic potential (Hruby, 1992). Therefore, it is paramount to identify and resolve any dysfunction that may compromise health. As such, the term 'somatic dysfunction' has been defined as any "impaired or altered function of related components of the somatic (body framework) system: skeletal, arthrodial and myofascial structures" (E.C.O.P., 2011), related to neural and/or vascular elements, that might underlie pathophysiologic conditions. The observational and palpatory features include objective findings such as local changes in tissue texture and temperature, structural and/or functional asymmetries and restriction of motion (DeStefano, 2011b), and subjective elements such as tenderness on palpation and/or altered sensitivity to touch (DiGiovanna, 2005).

Since its origins, osteopathic research has focussed on the mechanisms underlying somatic dysfunction and on its features by exploring related neurological interactions. Louisa Burns (1907) was the first to conduct proper scientific studies to investigate the dysfunctional visceral and somatic reflexes associated with 'osteopathic lesions' (the old term for 'somatic dysfunction'). Through animal autopsy, she found vascular changes in the fascial tissues — 'hemorrhage per diapedesin' — associated with vertebral dysfunctions that showed signs of inflammation, exudation and altered tissue texture (Burns, 1925). These findings confirmed the idea that tissue motion restrictions or alterations associated with 'lesions' were a result of connective tissue inflammation as previously suggested by Marion Clark (1906). Experiments by Cole (1951), Denslow et al. (1947) and Korr (1979) then demonstrated the presence of aberrant somato-visceral reflexes as the basis for the existence of facilitated areas in the spine that corresponded with the palpable features of the 'osteopathic lesion'. Hix (1976), Beal (1985), Kelso et al. (1982), and more recently Fryer et al. (2010, 2006, 2004) continued the research in a similar direction; and most of these findings became organized into the nociceptive model as formulated by Van Buskirk (1990) (Box 1.1).

This model primarily interprets somatic dysfunction from a neurological perspective and as the result of a neurogenic inflammation caused by the release of proinflammatory neuropeptides (such as substance-P and somatostatin) from primary afferent nociceptors following mechanical, chemical or thermal noxious stimulus. If persistent, as in the case of tissue damage, the activation of these nerve fibers alters their own thresholds to produce an area of primary hyperalgesia (peripheral sensitization). The latter, and the associated edematous response, are proposed to underlie respectively the increased sensitivity to touch and the tissue texture changes found in somatic dysfunction. Excessively active primary afferent fibers also relay action potentials into the dorsal horn of the spinal cord and release excitatory amino acids and substance-P. This, in turn, may induce phosphorylation events, altered membrane properties, subsequent gene inductions and the release of facilitatory compounds such as dynorphin — that produces lowered thresholds of activation — up to pathologic changes in the

Box 1.1. Fascia in osteopathic history.

From the very beginnings of osteopathy (1870's), assessment of the role of connective tissue has been considered fundamental in the treatment of a wide variety of conditions, and essential to achieving the most desirable clinical outcomes (Lee, 2006). As the founder, Andrew Taylor Still stated, *"Fascia is the place to look for the cause of disease and the place to consult and begin the action of remedies in all diseases"* (Still, 1899a). The role of fascia in osteopathic practice has been traditionally covering such a key position that *"... this philosophy (of Osteopathy) has chosen the fascia as a foundation of which to stand ..."* (Still, 1899b).

The importance of fascia for the body fluid dynamics was highlighted by A.T. Still in more than one statement, as in this example: *"Suppose venous blood to be suspended by cold or other causes in the lungs to the amount of oedema of the fascia, another mental look would see the nerves of the fascia of the lungs in a high state of excitement, cramping fascia on veins which is bound to stop flow of blood to heart."* (Still, 1899c). Thus, it is plausible that the ability of fascia to contract was implicitly considered as a possible contributor to the pumping mechanism for the venous return. This contractile property was proposed to be influenced by nerves that may get 'overexcited' in dysfunctional conditions, hence producing 'fascial cramps'. Conversely, normal fascial function is seen to be essential for maintaining good nervous function (Still, 1899d).

Still's students continued to propose fascia as a fundamental excretory system, rich in lymphatic vessels, to be addressed in order to remove metabolic and inflammatory wastes, as in respiratory tract infections (Hazzard, 1901a) or in cutaneous diseases such as eczema (Murray, 1918). Furthermore, due to its nerve supply and to the possibility that nerves may get inflamed, fascia was already considered as related to musculoskeletal conditions, including low back pain, more than 100 years ago (Hazzard, 1901b). While Littlejohn (1902) emphasized how life is based on the body's structural framework and on its fascial elements that *"make up the complete physical organism"*, William Neidner, in the early '20s, was the first to describe fascial torsion patterns in healthy and unhealthy individuals and one of the first to introduce to the osteopathic field a specific fascial approach, defined as *fascial twist* (Centers et al., 2003). By observing and palpating the entire fascial organization of the body, he noticed that people in good health tend to show clockwise fascial torsional patterns from head to feet (Frymann, 2004). He then proposed that various types of direct manipulative techniques could globally release such myofascial torques, through the use of the limbs as long levers for the untwisting manoeuvre (DeStefano, 2011a).

Still's concept of fascia continued to be developed by the early osteopaths and created the basis for much of our clinical understanding of this tissue, which is increasingly recognized as the unifying structural element of the body, and key to understanding the reciprocal interrelation between structure and function, and the body's innate ability to self-regulate (Page, 1952; Snyder, 1956). These principles then led to the development of manual approaches that went beyond the structural model of treating articular joints.

In the 1980s, Ward's biomechanical model emphasized the muscular-fascial relationship and their interdependent neural influences, and led to *Myofascial Release* and *Integrated Neuromusculoskeletal Release* techniques (Ward, 2003); while Chila's fascial continuum model of the 'big bandage' introduced *Fascial Release* and *Fascial Ligamentous Release* techniques, based on the integrity of the fascial continuum (Chila, 2003). The same period also saw a gradual shift towards other methods based on oscillatory motion as an intrinsic tissue property, with Sutherland's model of cranial and balanced ligamentous tension treatment (Sutherland, 1998); and Frymann's approach to fascia as the primary tissue to unwind any traumatic force imposed in the organism. Fulford's vibratory model (Fulford and Stone, 1997) and Becker's fluid approach then developed these further: *"... allow the fluid to resume its normal tidal mechanism ... 'bend to the oar' through the fascia and 'ride the tide to the shore' by way of the fluid"* (Becker, 2000). In addition, the respiratory-circulatory model of Zink (1977) implied the assessment of compensated and uncompensated fascial patterns together with the opening of fascial pathways to restore and maintain homeostatic balance (Zink and Lawson, 1979); and the bioenergetic model of O'Connell considered the bioresponsive electric potentials of fascia as changing holographically, as a result of the intention, attention and activation processes that occur during assessment and treatment (O'Connell, 2000).

tissue such as terminal sprouting and inhibitory neuron death (Willard, 1995). The whole series of these events may result in spinal grey matter changes leading to spinal facilitation (central sensitization). This involves an altered activity in the ventral roots and visceral efferent fibers causing respectively muscle tone and vasomotor/sudomotor/organ changes in the associated spinal segments. These changes suggest the neurophysiologic basis for the altered motion and positional asymmetry as well as for the aberrant reflexes (such as somato-visceral and viscero-somatic) found in somatic dysfunction. In addition, an adaptive response of the whole body may follow via the interaction of neuro-endocrine pathways (Willard, 1995), which affect autonomic, immune and hormonal activities, leading to a sustained shift of the organism towards allostasis. Despite the lack of strong evidence, this neurologically-based model has for decades been the dominant explanation of the features found in dysfunctional tissue and of some beneficial results obtained by manual intervention. This model proposes that appropriate treatment should decrease nociceptors activity of the corresponding facilitated spinal level, by respectively

releasing mechanical stress in tissues and diminishing the release of substance-P. This, it is proposed, leads to reflex-based modulating effecting muscle tone and sympathetic influences on blood and lymphatic flow, bringing tissue oxygenation and palpatory features back to normal (Van Buskirk, 2006). An alternative neurobiological model has proposed that therapeutic touch may produce stimulation of pressure-sensitive mechanoreceptors in the fascia (Ruffini's and interstitial receptors), followed by a parasympathetic response (Schleip, 2003). This in turn may induce a change in local vasodilatation and tissue viscosity, together with a lowered tonus of intrafascial smooth muscle cells, accounting for some of the tissue changes produced by manual intervention. This model still remains neurologically-based in nature, however, as discussed in this paper, various non-neurological processes may underlie the establishment and the treatment of somatic dysfunction. Most of these processes take place in the connective tissue and are surely interacting with, but not limited to, neural activity.

A unifying model that re-interprets dysfunctional processes and manual therapeutic effects by integrating neurological influences in a multidimensional perspective is needed, and this paper suggests that a neurofasciagenic model meets that need.

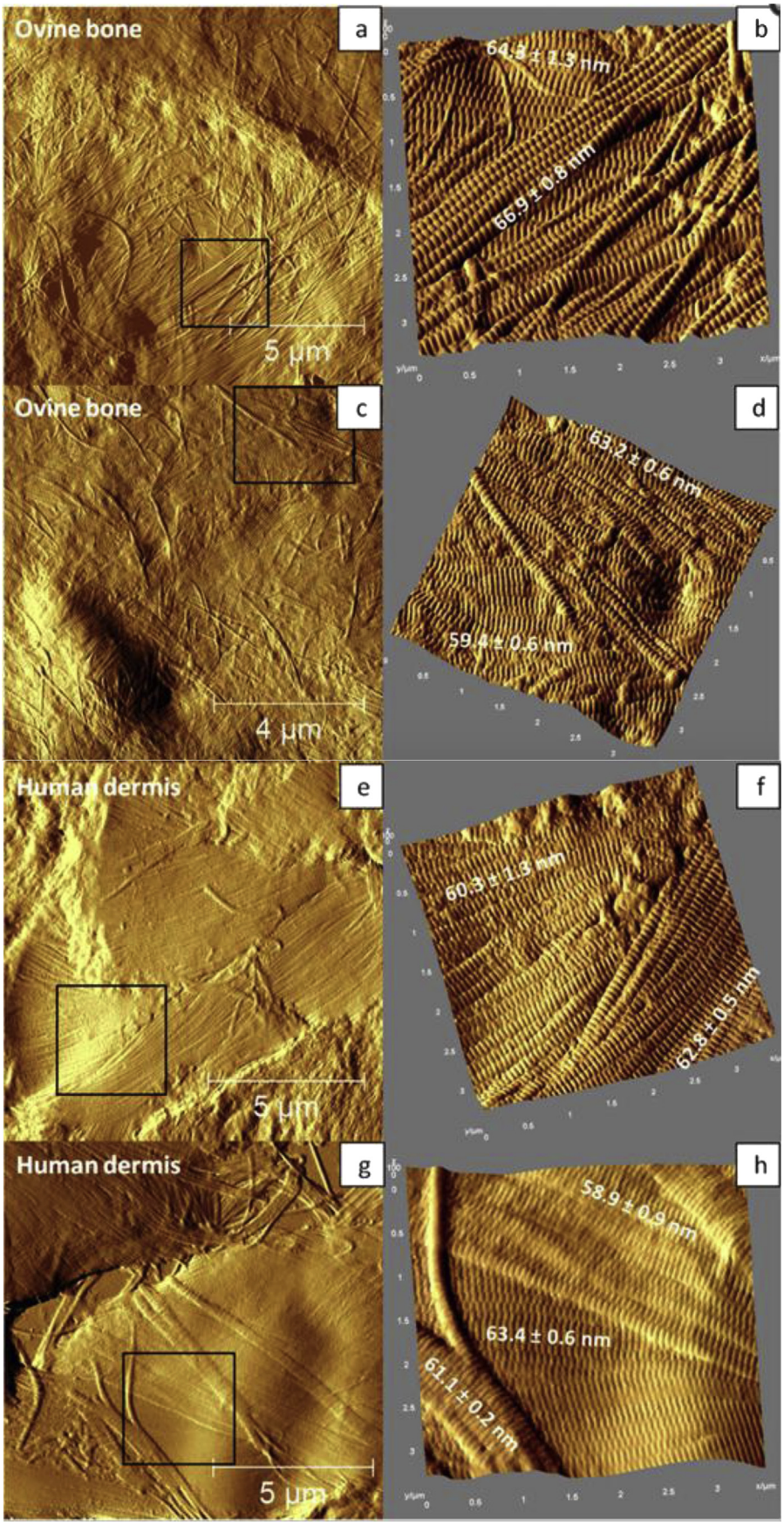
Fascia-related mechanisms associated to somatic dysfunction

In addition to the well-known neurogenic influences of the nociceptive model, various fascia-related mechanisms underlie somatic dysfunction.

Fascial architecture

Fibroblasts display cytoskeletal remodeling as part of normal function and, in particular, under changes in mechanical tension, resulting in actin redistribution and actomyosin contractility within minutes (Langevin et al., 2006). This also changes the architecture of the surrounding tissue by inducing an increase in the number of stress fibers and coupling to focal adhesions. Any deregulation of the mechanisms by which cells sense mechanical signals and convert them into chemical response may thus lead to dysregulation of cell metabolic processes and degradation of connective tissue components (Ingber, 2003). This may result in increased or decreased ECM deposition, altered tissue architecture, impaired function and, in some cases, significant morbidity (McAnulty, 2007).

Furthermore, mechanical forces imposed upon or expressed in the connective tissue modulate and regulate collagen deposition along specific lines of tension at both molecular (Vesentini et al., 2013) and macroscopic (Vleeming et al., 1995) levels. For instance, physical activity stimulates procollagen expression and collagen synthesis in tendons independently from the type of muscle contraction (Kjaer et al., 2009), whereas during immobilization a decrease in synthesis and degradation of collagen occurs (Binkley and Peat, 1986). Also the micro-architecture of the collagenic network is crucial for determining its mechanical properties. It is known that cross-linkages between collagen molecules are reported to stabilize muscular fascial tissue (Purslow and Delage, 2012), whereas fibril diameter has been shown to influence mechanical tissue properties through self-assembled fibrillar subunits that laterally and linearly fuse, resulting in fibrillar growth (Christiansen et al., 2000). Lateral fusion appears better resistant to low strain deformation, while linear fusion resists high strain. Interestingly, a D-periodic spacing of collagen structures (Fig. 1) has been found in various tissues, from higher to lower hierarchical organization, generally ranging from 60 to 70 nm, although within a single collagen fibril bundle the variation can be of only ± 1 nm, suggesting uniform axial packing of collagen monomers within a bundle (Fang et al., 2012). The study has shown that fibril D-spacing differences arise primarily at the bundle level ($\sim$76%), independently from species or tissue types. Such structural organization can decrease in order and density — as in the case of decreased functional loading — with a consequent reduction in mechanical properties (Thomopoulos et al., 2010), or it can become altered or disrupted in pathological conditions (Fang and Holl, 2013), following a series of fibroblast-mediated mechanisms such as mechano—chemical transduction, modulation of gene expression, inflammatory and collagenous remodeling processes (Wang et al., 2007). It has been noted that in chronic musculoskeletal conditions, a change in thickness of the related deep fascia is correlated with an increase in the quantity of loose connective tissue that lies between dense collagen fiber layers, with no increase of the collagen fiber layers themselves (Stecco et al., 2014). This process of thickening and densification of the fascia may explain the reduction of sliding potential between involved fascial layers and adjacent structures, as observed in patients with non-specific neck and low back pain (Tozzi et al., 2011; Langevin et al., 2011). Chronic conditions may ultimately result in fibrosis and tissue adhesions (Wynn, 2008). The latter have been shown to potentially initiate pain in distant structures, such as myofascial pain in adjacent tissues (Lewit and Olsanska, 2004). Adhesions are described as 'active' when at least one of their layers does not move freely and resistance to passive movement in at least one direction can be palpated (Lewit and Olsanska, 2004). In this case, adhesions can be associated with local asymmetrical muscle activity (Valouchová and Lewit, 2009), involving altered muscle activation and revealing a potential source of dysfunction that occurs locally or at a distance. Adhesions can also impair the normal sliding motion between involved tissue layers during physiological functions such as respiration and peristalsis (Chapelle and Bove, 2013). This cascade of events that affects both micro and macro architecture within fascia may account for some features of somatic dysfunction such as tissue texture change and asymmetry. Also due to fascial tensegritive behavior (Ingber, 2008), any fascial dysfunction may easily cause body-wide repercussions from a gross macroscopic anatomy to a molecular level, potentially creating stress on any structure enveloped by fascia, hence requiring progressive body adaptation at a local and global level (Levin and Martin, 2012).


Ovine bone
a
5 µm
b
64.3 ± 1.3 nm
66.9 ± 0.8 nm
Ovine bone
c
4 µm
d
63.2 ± 0.6 nm
59.4 ± 0.6 nm
Human dermis
e
5 µm
f
60.3 ± 1.3 nm
62.8 ± 0.5 nm
Human dermis
g
5 µm
h
58.9 ± 0.9 nm
63.4 ± 0.6 nm
61.1 ± 0.2 nm

Fascial contractility

It has been proposed that fascia may contract in a smooth muscle-like manner (Schleip et al., 2005), independently of skeletal muscle activity. This is possibly related to the presence of smooth muscle cells found in fascial tissue (Staubesand et al., 1997) and the capacity of myofibroblast to contract via intracellular alpha smooth-muscle actin (α-SMA) (Hinz and Gabbiani, 2003b). The ability to express such contractile protein appears to be common amongst various connective tissue cells such as osteoblasts and chondrocytes (Spector, 2001). Although, most myofibroblasts derive from regular fibroblasts modified under mechanical tensions and the influence of specific cytokines (Desmoulière et al., 2005), they can also originate from other tissues that include epithelial, endothelial and bone marrow-derived cells (Hinz et al., 2007). Myofibroblast behavior and contraction are highly responsive to oxygen levels, vasoactive peptides, autonomic activity, proinflammatory cytokines and surrounding mechanical tension (Porter and Turner, 2009). Regardless of their origin, myofibroblasts are able to produce long lasting isometric contractions (Hinz and Gabbiani, 2003b), transmitted to the matrix through focal adhesions and connected stress fibers. It has been suggested that the force generated by fascial contraction may extend to intramuscular connective tissues in order to adapt muscle stiffness to changes in tensional demands (Schleip et al., 2006). In turn, this is likely to influence overall resting muscle tone and musculoskeletal dynamics (Schleip et al., 2005) through both a local redistribution of mechanical force and a segmental neurological influence on somatic motor neurons. Dysfunction of this apparatus may also lead to altered myofascial tonus, diminished neuromuscular coordination, musculoskeletal pathologies and pain syndromes (Klingler et al., 2014). Furthermore, disregulated myofibroblastic activity may result in fibrosis formation and the development of chronic systemic diseases (Hinz et al., 2012). These conditions are commonly associated with restriction of motion and pain in the myofascia that has been attributed to the formation of firm collagenous tissue within the fascial layers involved in force transmission (Klingler, 2012). Such changes may take place locally, or may become widespread, causing postural distortions associated with altered force transmissions, particularly in the traditionally defined 'postural' fasciae such as that in the thoracolumbar region, iliotibial band and cervical fascia (Cathie, 1974). The whole series of these events — disregulated myofascial contraction, altered myofascial tonus and force transmission, impaired neuromuscular coordination, fibrosis formation — may lead to an abnormal fascial contractility and texture that underlies restriction of motion, functional and positional asymmetry, as found in somatic dysfunction.

Fascial viscoelasticity

Fascia exhibits the potential for both elastic and plastic deformation in a non-linear fashion, depending on the amount, duration and speed of the load (Yahia et al., 1993; Kirilova, 2012). This viscoelastic property relies on the interdependence between the architecture and composition of connective tissue and water content (Woo et al., 1997; Guilak, 2000). It has been demonstrated that fibrils and the interfibrillar matrix may act as coupled viscoelastic systems, with a qualitatively different response to mechanical deformation, depending on the cross-links in between collagen molecular packing (Puxkandl et al., 2002). At the same time, when tension changes in connective tissue, an immediate reorganization of the fibroblasts cytoskeleton occurs, with a consequent change in tissue stiffness and viscosity (Langevin et al., 2005), through changes in cell signaling, gene expression, matrix adhesions and consequent modification in connective tissue tension and biochemistry.

Interestingly, an intrinsic and independent viscoelastic property of the myofascia has recently been found, independent of nervous system activity, as shown by corresponding silent EMG patterns (Masi and Hannon, 2008). Such intrinsic myofascial tone — defined as *human resting myofascial tone* (HRMT) - is determined by molecular interactions of the actomyosin filaments in myofibroblast cells and miosarcomeric units. It may offer a substantial contribution to maintenance of postural stability with minimal energetic expenditure, differently from neuromotor activation which requires, instead, higher levels of tone to provide stabilization. This is consistent with recent findings in pathological conditions; persistent static load leads to viscoelastic creep of connective tissue, resulting in a transient alteration of neuromuscular activity (muscle spasm and hyperexcitability), with an intensity directly related to the load magnitude (Sbriccoli et al., 2004). Similarly, prolonged repetitive cycling loading may alter viscoelastic properties of connective tissue by causing micro-damage of collagen fibers and necessitate increased muscular activation to maintain joint stability (Solomonow, 2012). Changes in normal levels of HRMT would therefore affect the tension on surrounding fascial structures and have an influence on joint mobility, movement control, posture stability related to different musculoskeletal conditions and dysfunctions (Masi et al., 2010). The combination of these events may also be associated with a change in the colloidal consistency of the ground substance to a more solid state and lead to altered myofascial activation, increased risk of tissue damage/injury, and finally account for the tissue texture change, restriction of motion and asymmetry found in somatic dysfunction.

Figure 1 Different D-spacings at bundle interfaces Atomic Force Microscopy (AFM) images show the domains of fibril bundles and different D-spacings associated with them. Panel a—d are exemplary images of ovine bone. Panel c—f are exemplary images of human dermis. Panel b, d, f and h are the 3D topography plots of a 3.5 μm area marked by the black box in panel a, c, e and g, respectively. Panel b shows two bundles with 64.3 and 66.9 nm mean D-spacings; panle d shows two bundles with 63.2 and 59.4 nm D-spacing; panel f shows two bundles with 60.3 and 62.8 nm mean D-spacings; panel h shows three bundles with 58.9, 63.4 and 61.1 nm mean D-spacings. Image and caption taken from ACS Nano (Fang et al. 2012) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3508361/.

Fascial fluid content and dynamics

Fascia also plays an important role in fluid balance and physiology. Water content is dependent on changes in interstitial fluid pressure resulting from a dynamic interaction between the osmotic pull exerted by negatively charged, normally under-hydrated glycosaminoglycans that are abundant in fascia, and the mechanical stiffness and tension of collagen fibers that resist water extrusion and thus tissue swelling (Mow and Ratcliffe, 1997). It appears that any decrease in collagen tension leads to a reduction in interstitial hydrostatic pressure and causes fluids to be taken up by the constituents of the ECM. The role of fibroblasts is also crucial in determining collagen tension through cell-matrix contacts, acting as modulators of fluid dynamics by adjusting their size and matrix tension in response to changes in osmotic pressure (Langevin et al., 2013). In turn, hydrostatic pressure has been shown to act as a mechanical stimulus inducing cell-matrix processes of mechanotranduction that directs cell behavior in a variety of tissues, including cell movement within the ECM (Polacheck et al., 2014), cytoskeletal polymerization and cellular tuning of sensitivity to fluid pressure, and to accommodate variable levels of stress (Myers et al., 2007). In particular, intermittent cyclic hydrostatic pressure applied to bone-derived cells induces alterations in mRNA levels for a specific subset of genes involved in connective tissue remodeling and differentiation (Tasevski et al., 2005). However, during inflammation, changes in physical properties of the connective tissue, involving hyaluronic complexes, may influence transcapillary exchange resulting in as much as a hundred-fold increase in fluid flow (Reed et al., 2010). This is caused by an integrin-mediated lowering in interstitial fluid pressure following a release of cellular tension exerted on the collagen network that allows glycosaminoglycans to expand and take up fluids. Therefore, a reciprocal influence exists between mechanical force, cell response and interstitial fluid dynamics. A sustained static stretch applied to fascia may produce an extrusion of water in the tissue followed by a compensatory increase in matrix hydration (Schleip et al., 2012a), resembling a sponge-like effect that may be significant for fascial function. Stecco et al. (2011) have shown that in normal physiological conditions, a layer of lubricating hyaluronan is found between the deep fascia and muscle as well as within the loose connective tissue, dividing different fibrous sublayers of the deep fascia. These hyaluronan layers promote normal fascial function and sliding motion. If compromised, as following injury or chronic inflammation, they may underlie various types of myofascial dysfunctions and pain by impairing tissue sliding potential and fluid dynamics, hence tissue chemistry and structure. For instance, an ultrasound (US) study of the superficial and deep thoracolumbar fascia in patients with low back pain has shown a 25% greater perimuscular connective tissue thickness associated with a reduced fascial gliding motion (Langevin et al., 2009).

Fascial pH and factors influencing its levels

Several free nerve endings in the fascia inform the insular cortex of the forebrain about physiological tissue conditions, such as pH changes and warmth (Craig, 2002). Changes in pH, ionic content and temperature may represent key environmental and metabolic factors influencing fascial viscosity (Thomas and Klingler, 2012). For instance, an increase in body temperature, as occurs during physical exercise, may reduce fascial stiffness by reducing tissue viscosity, while breathing exerts a significant influence on pH. In most breathing pattern disorders, a state of hypocapnia can occur, resulting in elevated pH levels due to respiratory alkalosis (Chaitow et al., 2014). In turn, this may lead to smooth muscle cell contraction and even spasm, with profound implications on fascial, visceral and vasal tone (Foster et al., 2001). Such events may be commonly found in a variety of patients, since breathing pattern disorders have traditionally been associated with anxiety, stress (Magarian, 1982) and some chronic connective tissue disorders (Garcia-Campayo et al., 2011). Conversely, a more acidic ECM environment seems to exert a modulating action on the metabolism and protein synthesis of connective tissue cells, such as fibroblasts and chondrocytes (Ohshima and Urban, 1992), ranging from a predisposition to inflammatory reactions and tissue damage during high levels of acidosis (Levick, 1990); impaired remodeling and tissue repair with pH lower than 6.5 (Van den Berg, in preparation); and to beneficial effects on the composition of both gelatinous and fibrous matrix (Mwale et al., 2011). Finally, myofibroblast contractility in vitro has been shown to increase with a lowering of pH (Pipelzadeh and Naylor, 1998), suggesting a potential influence on fascial tone. In conclusion, changes in breathing patterns and temperature, and presumably of physical activities (Shen et al., 2012) and nutrition (Arent et al., 2010) are able to modulate tissue pH levels through environmental and metabolic changes, and oscillations of these may strongly influence fascial function and dysfunction.

Somatic neuro-fascial interaction

A review by Benjamin (2009) describes several studies that showed the presence of primary afferents and nerve fibers within fascia. This innervation is denser in the most superficial layers between the dermis and the deep fascia, and it follows a segmental pattern that resembles the myotome and dermatome distribution (Tesarz et al., 2011), supporting the concept of fascia as a 'sensory organ'. In particular, the presence of mechanoreceptors in fascia suggests a role in dynamic proprioception, force transmission and motor control (Stecco et al., 2007). Research also shows that fascia, rather than muscle tissue, is involved in the delayed onset of muscle soreness following physical exercise, suggesting a role in pain generation in normal physiological conditions (Gibson et al., 2009). However, under abnormal mechanical stimulation, a pathological change in fascial innervation may occur, resulting in dysfunctional ingrowth of nociceptive fibers (Sanchis-Alfonso and Roselló-Sastre, 2000) that generates or maintains inflammation (Herbert and Holzer, 2002). Even the epineurium and perineurium (the connective tissue sheets that surround individual nerve fibers and nerve bundles, respectively) are innervated by *nervi nervorum*, which can in turn cause neurogenic inflammation and consequently

evoke dysesthetic (distal) and nerve trunk (local) pain when a mechanical stimulus is applied along the nerve path (Bove, 2008). In addition, evidence suggests that nociceptive input rising from the thoracolumbar fascia may contribute to pain in non-specific low back pain (although not to localized pressure hyperalgesia) (Schilder et al., 2014). This may also produce changes in the corresponding spinal area. Hoheisel and Mense (2014) noted that following induced inflammation in the thoracolumbar fascia, an expansion of the spinal target region of fascia afferents has been demonstrated, together with the appearance of new receptive fields that could explain the spread of pain in patients with non-specific low back pain. Therefore, irritation of primary afferent fibers in the fascia is capable of initiating the release of neuropeptides, eventually setting up a neurogenic inflammation, with peripheral (Deising et al., 2012) and central sensitization, and altering the texture of surrounding connective tissue via the interaction of fibroblast and immune cells (Mense, 2001). This process may trigger a cascade of either local or global responses: chronic pain and connective tissue remodeling (Langevin and Sherman, 2007), altered mechanoreceptor feedback and muscle control (Panjabi, 2006), followed by further connective tissue alterations, neural adaptation, and eventually cortical reorganization (Flor, 2003). This process may expand to include influences on endocrine and autonomic pathways (Benarroch, 2006), as well as on sensory, cognitive and affective areas of the brain, that may in turn respond to control pain (Peyron et al., 2000). Recent studies have also shown that myofascial pain may alter the activity of related higher centres accounting for a reduction of sensory processing, followed by an altered motor output (Schabrun et al., 2013), together with a reorganization of the motor cortex associated with deficits in postural control (Tsao et al., 2008). Such evidence may explain several local, segmental and global effects of a given fascial dysfunction, proposing fascia as a possible nociceptive source for the establishment of somatic dysfunction and of its features, such as tenderness and tissue texture changes, as well as in supporting at least part of the 'total osteopathic lesion' concept (Parsons and Marcer, 2006) in taking into account the multidimensional aspects of pain. The 'total lesion' has been defined as "'the composite of all the various separate individual lesions or factors, mechanical or otherwise, which cause or predispose to cause disease" (Fryette, 1980).

Autonomic neuro-fascial interaction

Fascial tension may be regulated via autonomic activity, independent of skeletal muscle tone. This may occur through the interaction of autonomic fibers and smooth muscle cells found in fascia (Staubesand et al., 1997) that may consequently contract in a smooth-muscle like manner (Schleip et al., 2005). However, the adrenergic nerve fibers in fascia have been observed to be distributed mainly around intrafascial blood vessels and to exert a vasoconstriction effect (Tanaka and Ito, 1977). Recent evidence in the field of psychoneuroimmunology have reported that sympathetic activation is an important contributor to the maintenance of peripheral immune response mediators (CD4(+)FoxP3(+) Tregs) to self-antigens, and that this mechanism is mediated by transforming growth factor beta 1 (TGF-β1) (Bhowmick et al., 2009). The latter then forms a bridge between the nervous and the immune system function by relating sympathetic activity with the number of T cells that regulate an immune response. Therefore, because under mechanical tension and through a mechano-transduction process, fibroblasts release TGF-β1 that in turn promotes myofibroblast differentiation and contractility by increasing α-SMA expression (Wipff et al., 2007), it has been suggested that sympathetic activation may induce myofibroblast contraction in fascial tissue via the release of TGF-β1, as well as other cytokines, hence modulating fascial stiffness (Schleip et al., 2012b).

The autonomics have also been shown to strongly interact with the somatic nervous system. Sympathetic nerve fibers, in particular, are able to affect the contractility of muscle tissue through direct adrenergic influence on slow-twitch fibers and modulate the proprioception arising from the muscle spindle receptors, mainly by inhibiting the respective sensory nerve endings (Passatore and Roatta, 2006). In addition, they may play a role in pain modulation by activating sensitized primary afferent fibers, either directly or indirectly (Roberts and Kramis, 1990), and thus contributing to the development of chronic myofascial pain syndromes (Malanga and Cruz Colon, 2010). Therefore, autonomic activity may be involved in the genesis or maintenance of pain and somatic dysfunction in the connective tissue.

Metabolic influences

Different connective tissue cells respond to mechanical stress by inducing collagen expression and remodeling of the matrix under the influence of hormones and growth factors (Kjaer, 2004). Such mechanically induced expression of procollagen and synthesis of collagen appears to be mediated in myofascial tissue by an early upregulation of specific growth factors such as insulin growth factors (IGF), mechano-growth factors (MGF) and IGF binding proteins (IGFBPs) (Olesen et al., 2006). In addition, growth hormone (GH) also seems to promote matrix collagen synthesis in connective tissue (although with no effect upon myofibrillar protein synthesis, hence on muscle cell trophism), thus playing an important role in strengthening the matrix tissue (Doessing et al., 2010). Indeed Zgliczynski et al. (2007) noted that in patients with acromegaly, high blood levels of GH and IGF have been associated with increased collagen content in tissues. Furthermore, cyclic mechanical stretch in vitro increases fibroblast secretion of TGF-β, platelet-derived growth factor (PDGF) and fibroblast growth factors (FGF) (Skutek et al., 2001), that, in turn, exert an influence on matrix remodeling, collagen and proteoglycans synthesis (Robbins et al., 1997). TGF-β also seems to play a crucial role in many progressive fibrotic diseases (Leask

et al., 2002), by stimulating collagen formation within the ECM and causing uncontrolled fibrotic tissue formation.

Fibroblasts also release various cytokines, as interleukins (Van Snick, 1990), under certain physiological and pathological conditions. In turn, interleukins may stimulate fibroblasts to produce collagen and glycosaminoglycans (Duncan and Berman, 1991) as well as induce cell proliferation and expression of matrix metalloproteinases (Unemori et al., 1994), all fundamental for matrix remodeling and wound healing processes.

Sex hormones also seem to influence ECM adaptability to mechanical loading, either directly or indirectly, via the activation of growth factors and cytokines. Estrogen, in particular, exerts an inhibiting effect on collagen synthesis and fibroblast proliferation (Yu et al., 2001), suggesting that the female cyclical hormonal variations (in particular the preovulatory phase of the menstrual cycle) may predispose to injury during physical exercise. Oral administration of estrogens is known to reduce serum IGF and thus lower collagen synthesis in the connective tissue, especially when coupled with physical exercise (Hansen et al., 2009a). However, exogenous estrogen produces a stimulatory action on collagen turnover in the resting state (Hansen et al., 2009b); and a significant increase in muscle collagen and myofibrillar protein synthesis rate was also found after exercise in eumenorrheic women, in one or other of the follicular or luteal phases of the menstrual cycle (Miller et al., 2006). Certainly further research is needed to understand the underlying mechanisms behind such discrepancy in tissue responses to estrogenic influence. Hansen et al. (2009a) suggested that distribution and numbers of estrogen receptors (alpha and beta) might vary in different tissues and produce a different response to the same mechanical loading. A similar mechanism may account for the different connective tissue response to progesterone, that may increase (Yu et al., 2001) or reduce (Hama et al., 1976) collagen synthesis, although the evidence suggests a dominating effect of estradiol over progestogens (Hansen et al., 2009a).

Relaxin is another important hormone, mainly produced during pregnancy, with a strong antifibrotic effect and a key role as an inhibitor of collagen turnover in several organs (Samuel, 2005). There is evidence that it may inhibit collagen and fibronectin secretion by both stimulating collagenase expression and down-modulating collagen synthesis, even under the influence of TGF-β and interleukins (Unemori and Amento, 1990). It has also been shown to reduce alpha-smooth muscle actin expression and cell differentiation, while increasing fibrillar collagenase activity (Bennett et al., 2003), with a plausibly strong effect on myofascial tension and matrix remodeling.

Finally, despite the old belief of its acidosis-induced detrimental effects, lactate is nowadays recognized as an important cell-signaling molecule that can upregulate gene and protein expression (Gladden, 2008). This includes stimulation of angiogenesis and collagen deposition in aerobic conditions (Hunt et al., 2007), hence playing a potential role in tissue repair.

In conclusion, various hormonal and metabolic factors may influence myofascial texture and stiffness, playing a possible role in the genesis and maintenance of fascial dysfunction and of its features.

Piezoelectricity

Piezoelectricity is a property associated with a variety of biological structures ranging from bones to proteins and nucleic acids (Fukada, 1982). It is based on an electromechanical coupling by which a mechanical force is converted into an electrical stimulus through a stress-induced polarization and vice versa. In connective tissue, thanks to this electromechanical transduction, collagen may exchange physical information from a macroscopic to a cell scale, either directly or via biochemical process (Stroe et al., 2013). Electric potentials are naturally produced in the ECM under mechanical deformation, possibly accounting for a modulating mechanism of cell behavior along common biochemical and mechanical pathways (Grodzinsky, 1983).

Although collagen generates different piezoelectric charges based on the type and intensity of the stress applied (Ahn and Grodzinsky, 2009), an intrinsic piezoelectric heterogeneity has been shown to exist within a collagen fibril, and is related to periodic variations in its gap and overlap regions (Minary-Jolandan and Yu, 2009a). It seems that the physicochemical properties of collagen critically depend on its hierarchical structure. Tropocollagen molecules, the basic units of collagen, have been shown to be arranged in a crystallographic superlattice with a quasi-hexagonal symmetry (Orgel et al., 2006), while collagen fibers display a D-periodic spacing within fibril bundles and at different levels of hierarchical complexity (Fang et al., 2012). The piezoelectric response seems to be directly proportional to the level of order by which molecules of collagen fibrils are assembled, including the D-periodicity (Denning et al., 2014). With regards to fascia, piezoelectric properties of collagen fibrils have only recently been imaged using piezoresponse force microscopy (Harnagea et al., 2010). The analysis of the signal revealed clear shear piezoelectricity associated with piezoelectric deformation along the fibril axis, with the direction of the displacement being preserved along the whole fiber length, independently of the fiber conformation. The study has also shown that collagen fibrils in muscular fascia display an organization in domains, with groups of fibers with same polar orientations and others in the opposite one. Nevertheless, each single collagen fibril has a unipolar axis polarization throughout its entire length, with a piezoelectric coefficient on the order of 1 pm V(-1) (Minary-Jolandan and Yu, 2009b).

This may help in understanding biological functions of fascia and the processes by which cells assemble collagen fibrils in response to specific directional mechanical forces. In fact, piezoelectric currents generated by mechanical strain on collagen fibers during wound formation have been proposed as driving forces in the first stages of tissue repair, acting in concert with TGF-β to determine collagen fibers deposition and orientation (Farahani and Kloth, 2008). In conclusion, it is plausible that alterations of collagen architecture following injury, surgery or chronic inflammation, may lead to changes in piezoelectric responses of the area involved, with consequent repercussions on fascial function and structure.

Epigenetics

Epigenetics is defined as "the collective heritable changes in phenotype due to processes that arise independent of primary DNA sequence" (Tollefsbol, 2011). Through these events, genes are up or down regulated in a more durable fashion than other transient mechanisms such as transcription factors. Various environmental influences, such as radiation, drugs, infection, diet, lifestyle and metabolic compounds, may produce cell changes at an epigenetic level, hence impacting on the heritable human genome. These changes of accessibility of genes and of their expression are related to germline independent alteration of chromatin architecture, mainly occurring through DNA methylation, histone modification and microRNA processes. The result is the remodeling of chromatin organization that is then preserved during cell division and thus heritable. Epigenetics seems to be implicated in the control of several cellular processes including gene regulation and genomic imprinting; cell differentiation and fate; tissue regeneration and aging.

Although mechanical signals are known to be a crucial regulator of connective tissue cell behavior and differentiation, only recently have they been shown to affect gene regulation at the epigenetic level (Arnsdorf et al., 2010). Epigenetic changes, including DNA and histone methylation, might cause a stable fibroblast activation that is capable of altering immune function, thus producing inflammatory responses up to the development of chronic connective tissue disorders (Ospelt and Gay, 2014). Altered epigenetic patterns may also be responsible for myofibroblast differentiation and extracelluar matrix accumulation in chronic inflammatory conditions (Cho et al., 2012) and fibrotic disorders (Hinz et al., 2012). Epigenetic histone methylation in mesangial cells has been shown to increase TGF-β1-induced expression of ECM genes for connective tissue growth factors (Sun et al., 2010), suggesting a key role of epigenetic changes in the development of fibrotic diseases. Furthermore, epigenetic alterations seem to be cell specific, as in synovial fibroblasts being deregulated in rheumatoid arthritis (Karouzakis et al., 2011), or CD4+ T cells and B cells in case of systemic lupus erythematosus (Renaudineau et al., 2011), or cerebral cells in multiple sclerosis (Küçükali et al., 2014).

Hypothesis

Water

Water may display coherence oscillations that are able to collect noise energy from the environment and transform it into high-grade coherent energy in the form of electron vortices (Del Giudice and Tedeschi, 2009). Such 'coherence domains' of interfacial water have shown to be highly responsive to various form of electromagnetic field (Foletti et al., 2009), and may activate resonating biomolecules to self-organize (Brizhik et al., 2009), contributing to various tissue functions and structural organization. Sommer et al. (2008) suggest that interfacial water plays a key role in protein folding, cell to cell recognition and behavior. Every collagen fiber in the body is embedded in layers of water molecules that, when associated with proteins, behave in a highly ordered and patterned, or crystalline, manner (Pollack et al., 2006). This water-protein-interaction based system may offer a dynamic framework to understand various biological mechanisms, such as DNA transcription and duplication, that underlie various biophysical processes (Pang, 2013). It may also serve for bioenergy transport, mainly released by hydrolysis of adenosine triphosphate. In addition, the hydrophilic interactions of hydrogen bonds that stabilize this system may

Box 1.2. Psychophysiological and cognitive-behavioral influences.

As originally proposed by the psychophysiological approach, different emotional factors, including memories, may initiate or aggravate musculoskeletal pain and influence motor pattern (Flor and Turk, 1989). In addition, various psychological factors may predispose to the development of chronic musculoskeletal pain and disability (Pincus et al., 2002). In particular, fear of pain, or that of its potential reoccurrence, seems to be more disabling than pain by itself, especially in chronic conditions (Waddell et al., 1993). Even the fear to return to physical, or work activities, may provoke the same type of reactions (Vlaeyen et al., 1995). It appears that a stressful work environment that lacks flexibility and supervisor support can play a role in the genesis and maintenance of persistent musculoskeletal pain (Kaila-Kangas et al., 2004). Even more, catastrophizing (tendency to misinterpret and exaggerate situations, perceived as threatening) may strongly alter the experience and the perception of pain (Turner et al., 2000). The result of these events is the strong tendency to avoid activities, predisposing to the development of connective tissue fibrosis, further risk of injury and inflammation, that in turn reinforces chronic pain patterns, and leads to further decreased mobility (Langevin and Sherman, 2007).
The personality type of a given individual (Radnitz et al., 2000) as well as his/her faith and religion (Koenig, 2004) may influence the perception of pain and disability together with the control or treatment of the condition. As suggested by the cognitive model (Weisenberg, 1984), beliefs, expectations and generally cognitive and affective components of the pain experience are fundamental influences on the development of pain control and coping strategies. In addition, psychosocial and environmental factors may also generate maladaptive pain behaviors that can be analyzed and changed, as traditionally proposed by the behavioral model (Fordyce, 1976). All of these elements may come into play in any patient, influencing their perception, experience and pattern of pain and disability, as well as the awareness and control of the resources available to develop adequate coping strategies.

support non-linear fast transfer of protons through the molecular structure (Pang, 2013), under the influence of temperature and electrical fields. Therefore, mechanical or metabolic forces may generate vibrational deformations of peptide bonds, which will involve polarization waves along the proteins. This will be accompanied by proton conduction in the structured water shell sensitive to electrical, thermal and chemical changes in the surrounding environment (Pang, 2012). Furthermore, proton transfer may be coupled with hydrogen-atom translocation along the water—proteins complex (Cukier, 2004) as well as electron transfer, thanks to an electron donor hydrogen-bonded-interface electron acceptor system (Cukier and Nocera, 1998). This phenomenon, dependent upon the solvent response to electron and proton transfer, may produce a proton-electron vibrational motion through a dielectric continuum and molecular dynamics that may underlie various biological processes (Hammes-Schiffer and Soudackov, 2008; Soudackov et al., 2005). Again, temperature and pH levels seem to influence this phenomenon; accounting for the control of radical proteins, cytochrome oxidases, and DNA photolyase (Sjödin et al., 2005). It is plausible that fascial dysfunction may rise from dysfunctional self-reinforced circuits of proton-electron-hydrogen transfers following structural alteration of the collagen-bound-water network, as may occur in injury, inflammation and scar tissue.

Bioenergy

Procollagen molecules have been shown to undergo liquid crystal-like ordering in solution, prior to fibril assembly (Hulmes, 2002). The structural continuum of the collagenous matrix with the intracellular skeleton may work as a semiconductive system exhibiting coherent vibrations throughout the organism, with a potentially regulatory role (Pienta and Coffey, 1991). This communication system may influence cell metabolism and function (Pienta and Hoover, 1994), leaving metabolic activities as a result of interacting electromagnetic and electromechanical forces (Fröhlich, 1982).

There is evidence that cells and tissues may communicate through various forms of energy, ranging from electromagnetic radiation to phonons and photons. Phonons are collective excitations of atoms or molecules in solids, and in some liquids, with elastic arrangement. They produce modes of vibration though interacting particles that

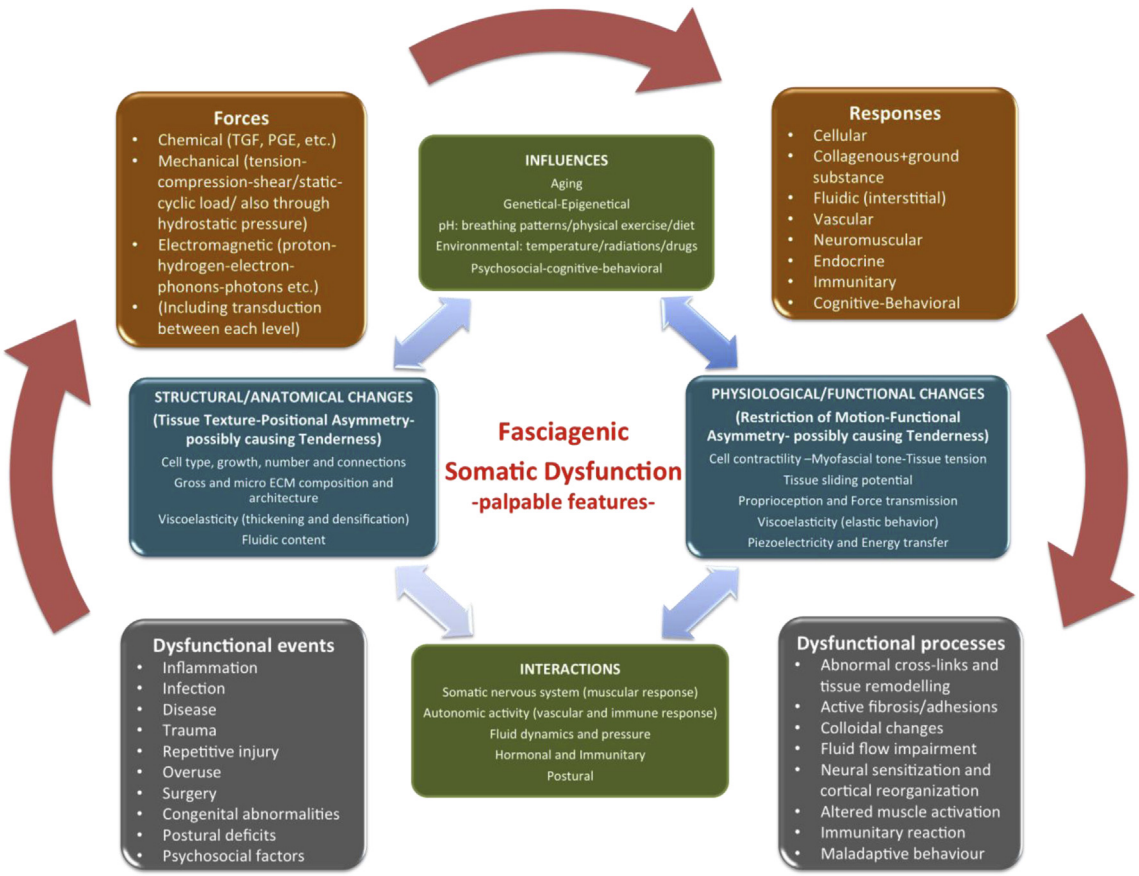


Figure 2 The neuro-fasciagenic model of somatic dysfunction. The diagram illustrates the two main interacting fascial changes — structural and functional — that may underlie somatic dysfunction and account for its palpable features (tissue texture changes, asymmetry, restriction of motion, tenderness). They may occur through various types of interactions and under different kinds of influences. Several dysfunctional events may produce different forms of forces and responses in the fascia with consequent dysfunctional processes.

oscillate at a single frequency (Mehrotra, 2004). They play a role in electrical and thermal conductivity, since phonons at shorter-wavelength and higher-frequency give rise to heat, while long-wavelength phonons give rise to sound. The ability of connective tissue to transfer phonons is related to its elastic property (Harley et al., 1977). Conversely, the viscoelastic properties of connective tissue can be measured from the propagation of sound, using several techniques such as scanning acoustic microscopy and micro-Brillouin scattering (Matsukawa et al., 2014). Sonic velocity in connective tissue decreases with wetness but increases with mineral content and higher crosslinking density between adjacent collagen molecules (Lees et al., 1990). This property therefore seems to be strictly related to the hierarchical collagenic molecular architecture and its viscoelastic properties. Plausibly, any structural disruption or alteration may lead to changes in sonic transmission and scanning acoustic microscopy-like investigations may be one useful way to detect somatic dysfunction.

Conversely, biophotons have systematically been measured in human bodies to reflect various types of information transfer and regulatory energy (Cohen and Popp, 2003), and to display a spectral range from at least 260—800 nm (Popp, 2003). They are considered to be radiations of non-thermal origin (Schwabl and Klima, 2005), emitted from a de-localized and fully coherent biophoton field within the living system (Popp et al., 1992), and play a potential role in cell communication and regulation of cell behavior, including DNA replication and protein synthesis (Chang, 2008). DNA structure seems to be an important source of biophotonic emissions, since induced conformational changes in vivo are clearly reflected by changes of the photon emission of cells (Popp et al., 1984). With regards to fascia, fibroblasts in culture have shown different proliferation patterns under the influence of bone growth factors, which could be correlated with an ultraweak photon emission following irradiation with a moderate dose of ultraviolet A (Niggli et al., 2001). This property may be deregulated or altered in the case of disease, in association with many pathogenetic processes underlying various conditions — including those affecting connective tissue — related to a generally high oxidative status of the organism (Van Wijk et al., 2008; Popp, 2009) (Box 1.2).

Conclusion

In conclusion, all the fasciagenic factors described above may play a role in the genesis and maintenance of somatic dysfunction and of its features that are certainly related to, but not exclusively limited to, neural influences. Such fasciagenic processes might also cause and maintain types of somatic dysfunction that have not yet been classified in terms of plane and quality of impaired motion (Tozzi et al., 2012; Bongiorno, 2013).

These processes can be organized into a unifying model of structural and functional changes in the fascia, under various influences and interactions, leading to the palpable features of somatic dysfunction. The latter may be the result of a series of dysfunctional processes caused by the interplay of various forces and responses following several dysfunctional events (Fig. 2).

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