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Components of the fascia – cells and extracellular matrix

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Abstract

Fascia continues to be a significant topic in numerous studies due to its unique functions that contribute to maintaining various bodily functions. The current article focuses on the crucial aspects of fascia and provides an essential collection of basics to understand the phenomenon of fascia. It describes the anatomical structure, with emphasis on the division into layers. Furthermore, the article explains how fascia affects muscle movement and transduction signals. In addition to the significant role of fascia, the article discusses its components, both cellular and non-cellular. Regarding cellular factors, various types of cells are distinguished and their role in mechanotransduction is explained. Non-cellular components maintain the structure of the fascia and provide scaffolding for the cells of the fascia. The problem of fascia classification is comprehensively considered, including the anatomical, histological, and cellular aspects of fascia. Finally, the article examines aspects of fascia disorders, particularly rheumatoid arthritis, as well as the correlation of structural abnormalities with lymphatic oedema. Not only does it address these abnormalities, but it also discusses the nature of myofascial pain origin and the currently widespread topic of acupuncture.

Running title: Components of the fascia

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Introduction

Definition of the fascia has been changing through the years. It was called "a global connective tissue system" [1] or the soft tissue forming three-dimensional matrix of structural support [2]. The more recent definition, accepted by the Fascia Nomenclature Committee (FNC) in 2016 said that fascia is a layer of connective tissue situated under the skin to attach and separate muscles and other internal organs. The most specific definition developed from the one above is saying that the fascia is a complete system that includes adipose tissue, adventitiae, aponeuroses, membranes, ligaments and meninges, forming functional connective structure. The fascial system surrounds all organs, muscles and nerves and integrates with these components, which allows body systems to function as an integrated totality [3]. Federative Committee on Anatomical Terminology (FCAT) introduced a division of fascia into functional and morphological. The functional perception emphasizes holistic words, including fascial system or fibrous tissue network, which results in seeing aponeuroses, ligaments and tendons as parts of it, whereas they used to be considered as separate structures. The morphological one is focused to follow the conception that fascia is a mass of connective tissue under the skin that attach and separate muscles [4].

The older definitions were generic – fascia was believed to be a membranous part of the body [5]. Today fascia's definition is being emphasized as a holistic – it is thought to be a whole system, which provides support and integration [3].

Summarizing, fascia is a really important multifunctional organ that fills a key role in coordinating muscular activity and acting as a body-wide proprioceptive organ [6]. The aim of this paper was to provide an overview of fascia related topics based on a number of scientific reports and to make it easier for researchers as well as those interested in the subject to understand them better.

Anatomical structure and function of facia

Anatomical classification of fascia can be provided in different divisions; starting from proper fascia, superficial fascia, intramuscular fascia and visceral fascia. This perception defines fascia as a soft tissue component of the connective tissue system that permeates the human body [2]. The proper fascia (also known as the deep fascia) contains muscle envelopes and joint capsules. In addition, ligaments and tendons are also a part of the fascial system, representing its dense and organized structures. Loose tissues are included in superficial fascia – which is situated in subcutaneous tissue, and intramuscular fascia – which stands for perimysium and endomysium [7]. fascia surrounds internal organs – the heart, lungs, liver, and intestines [8]. It is composed of thin connective tissue layers that form a network around them [9].

Meaning of fascia is being broadened and it also includes dura mater and the mesentery of the abdomen. The fascia system is seen as one connected network that differs depending on the needs of other surrounding tissues [10].

The fascial system, especially the deep fascia, which surrounds the muscles, enables the muscles to transmit the produced force to the other parts of the musculoskeletal system. Possibly, the muscular fascia is crucial to feel pain, to coordinate and in proprioception. Connective tissue and muscles are called together myofascial system. Short mechanical stimulation of this system results in temporal change of the morphology of the cytoskeleton, persistent stimulation has consequences in chronic change in form and function. This process is supervised by a specific type of fibroblast – fasciacytes [8]. They produce hyaluronic acid, which allows tissue to form different shapes, protects it from tensions and fills the spaces. Cellular components of fascia adapt it to changing conditions and synthesize extracellular matrix (ECM). ECM is made of collagen type I, collagen type III and 15% of elastic fibers – they organize fascia and give proper support. It also contains a water component, which stands for glycosaminoglycans – they transport metabolites and keep turgor of the tissue [9].

Main anatomical function of fascia is to provide movement of the body – fascia allows sliding of the muscles, nerves and vessels between each other. Additionally, the fascia has the ability to react to mechanical stress by changing its structure. What is more, the fascial network is allowed to receive information about tension in other tissues supported by fascia, which allows the whole system to interact properly [11].

Cellular components of fascia

Cells constitute a significantly smaller percentage of the structure of the fascia than non-cellular components (ECM). The fascia contains numerous types of cells of connective tissue(fibroblasts, myofibroblasts, lymphocytes T, mast cells, adipocytes, macrophages) [8]. However, the distribution of the types depends on the layer of the fascia, for instance: the outer layer of the superficial fascia comprises more adipocytes, whereas there are none of them in the deep fascia [12].

Cellular components of fascia are completely solid with the intercellular spaces, where the localization of the cells is the effect of the reticulation composed of the crisscross matrix filaments. The cells are connected to these structures by integrins, which are in charge of mechanotransduction. There exist two major locations of the cellular elements – clusters along the vessels, or they are scattered in small quantities along the vessels too. The quantity of the cells is correlated with the size of the clusters; 2 mm contains approximately 5 million cells (20% are single, among the vessels as well) [13].

When it comes to cellular components, fibroblasts remain the major factors of the structure of fascia [14]. They characterize the cytoplasmic appendices, each one on the opposite end of the cell, and the plane oval vesicular nucleus. These elongated, spindle-shaped cells are involved in modulating the ECM, the production of carbohydrates, and the resynthesis of collagen, induced by the changeable tension [15]. Furthermore, they produce cytokines, which are interleukins involved in immune system activity [16]. The fibroblasts are described as directionally sensitive, which means, to be specific, that there is dependence on the movements of the extracellular matrix placed below. In reference to collagen production, it is undoubtedly interrelated with pressure [17]. The more increased the tension becomes, the more collagen the fibroblast synthesizes. Based on this information, immobilization, for instance after an accident or a prominent reduction of the movement, results in a significantly decreased activity of the fibroblasts, which leads to abnormalities in the composition of the extracellular matrix [15]. The crucial role of the fibroblasts is partaking in the mechanism of transduction. The essence of the above is converting the mechanical signal into a chemical response. After the mechanical impulse, the tension affects the shape of the fibroblasts, which induces metabolic activity [18]. In this kind of metabolic pattern, the direction, character, and even duration of the mechanical signal are coded. Not only are the inflammatory factors excreted by these cells, but there are also numerous vital enzymes: the matrix metalloproteinases (MMPs), growth factors: connective tissue growth factor (CTGF/CCN2), fibroblast growth factor (FGF) [19]. Using the mechanism of expelling the water from the inside to the ECM, the fibroblasts control the pressure of the fluids in the fascia. In some cases, it is possible to turn the fibroblast into a distinct type of cell – myofibroblast [17].

Another type of cells are myofibroblasts, which are the specialized fibroblasts that connect the features of both the fibroblasts and the cells of the muscular tissue. They contain alpha-actin and have an elevated contractility potential due to the consolidated places of adhesion. What stimulates fibroblasts to transition into this type of cell is the altered length of the fascia. Most of them are located in the lumbar fascia [20]. They enable the contraction of the ECM. They are engaged in the pathological fibrotic contractures concerned with the fascia. In case of injury, myofibroblasts concentrate in the wound, excreting the cytokines and participating in the process of regeneration [21].

Nowadays, scientists are aware of another type of cellular component of the fascia: telocytes, which were not discovered until 2016 [22]. One of the characteristic features is the sensitivity to mechanical factors. They play a role in repairing damaged tissues and immune reactions. The communication between the telocytes and the other cells is enabled by the exosomes, the vesicles that convey information and genetic material [15]. However, some of the research points to cell junctions as the main source of transport [9]. In further research this issue has been examined.

Apart from the described cells, the fascia stores: lymphocytes T (responsible for a cellular response during the inflammation [23]), mast cells (production of prostaglandins, PAF [24]), macrophages (phagocytosis [25]), and adipocytes (the cells of the fatty tissue [26]).

Cellular components of fascia – fibroblasts maintain the integrity of the structure, provide transmission of force and produce components of ECM [18]. Mentioned before fasciacytes are specialized in synthesis of ground substance – especially hyaluronan, which allows fascial sliding between its layers. Myofibroblasts localized in the fascia have contractile activity, which helps to regulate the tension of the tissue and provides the movement of it. Recently discovered cells called telocytes, are thought to be involved in cell repair and regeneration of fascia [9].

Non-cellular components of fascia

Cellular constituents of the fascia are contained within the ECM, which is a three-dimensional macromolecular network composed of collagens, proteoglycans, glycosaminoglycans, elastin, fibronectin, laminins, and several other glycoproteins [27–29]. ECM provides not only essential physical scaffolding but also initiates crucial biochemical and biomechanical signals that are required for tissue morphogenesis, differentiation and homeostasis [30–33]. Important mechanism whereby these processes can be regulated is ECM remodeling where ECM components are deposited, degraded, or otherwise modified. These constant changes constitute the dynamic structure of ECM [34].

ECM can be divided into protein fibers and ground substance. Collagens are the main fibrous ECM proteins with at least 28 distinctive types [35]. Presence of collagens in fascia with predominant contribution of collagen I determines its mechanical properties, organization, and shape [36]. Aside from their structural role, they interact with cells via several receptor families, including integrins, discoidin domain receptors (DDRs), glycoprotein VI (GPVI), leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1), mannose receptor family, Toll-like receptors (TLRs), and regulate their proliferation, migration, and differentiation [37]. Each type of collagen varies in function and localization with distributional changes implicated in pathophysiology of numerous conditions [38–40].

Elastin is another fibrous agent providing elasticity and high tensile strength of facia [41]. Importantly, elastin stretch is crucially limited by tight as-

sociation with collagen fibrils [42]. Both, abnormal elastin production and decrease in content, is associated with fascia disorders such as inguinal hernia and uterine prolapse [43,44].

Protein fibers of the ECM are immersed in ground substance, which is a highly hydrated, transparent, complex mixture of macromolecules. There are three main classes of macromolecules in ground substance: glycosaminoglycans (GAGs), proteoglycans, and multiadhesive glycoproteins. GAGs are long highly negatively charged heteropolysaccharides that contain repeating disaccharides composed mainly of N-acetylated hexosamines (N-acetyl-D-galactosamine or N-acetyl-D-glucosamine) and D-/L-hexuronic acid (D-glucuronic acid or L-iduronic acid) [27]. Because of their high negative charge, GAGs attract positive cations that exert osmotic influx of water. Together with their relatively stiff character, swelling by great amounts of water makes GAGs ideal space fillers that give volume and can sustain mechanical compression of fascia [45].

GAGs can either exist on their own or bound to a core protein to form proteoglycans (PGs). PGs have a wide variety of functions that reflect their unique buffering, hydration, binding and force-resistance properties [46]. Besides their ability to retain water and provide mechanical support due to their GAG side chains, PGs also play a crucial role in the organization and function of the ECM by assisting in the assembly of its structural components and integrating cell signaling molecules, such as growth factors, into the ECM. For example, certain small leucine-rich proteoglycans such as decorin, biglycan, lumican, and fibromodulin aid in the formation of collagen fibrils in the ECM [47].

ECM remodeling occurs perpetually as an adaptation to environmental stimuli [48]. The mechanism by which this process takes place is the interplay between signaling molecules and their receptors [49]. Signaling molecules may manifest as soluble factors, such as hormones and growth factors, ligands on the surface of other cells, or extracellular matrix itself, like hyaluronan molecules [50]. The type of response induced by a signaling molecule may vary depending on the receptor it is bound to. Ubiquitous and widely known GAG – hyaluronic acid (HA) confers signaling functions by binding to specific cell surface proteins of which toll-like receptors (TLR)-2/4 and CD44 are the best studied [51,52]. By interacting with these receptors, distinct forms of HA can elicit various regulatory responses in the immune system, with some sizes of HA promoting inflammation and others reducing it [53]. There are other noteworthy examples of hyaluronan receptors. One such receptor is RHAMM (receptor for hyaluronan-mediated mobility), which has been shown to promote cell mobility and tissue repair through its interactions with cytoskeletal proteins and gap junctions between cells [54]. Additionally, LYVE-1 (lymphatic vessel endothelial receptor 1) is involved in the transport of hyaluronan from tissues to lymph through lymphatic endothelial cells [55].

Growth factors determine the rate of growth, proliferation and biochemical activity of fascia cells. Basic fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) were found to be mitogenic for fascia cells, and transforming growth factor beta was a potent stimulator of collagen production [56].

Hormones also play an important role in ECM remodeling. Higher prevalence of myofascial pain in women remained unexplained until recent observation of relaxin receptor 1 (RXFP1) and estrogen receptor-alpha (ERα) in the deep fascia (crural fascia of the leg, rectus sheath of the abdomen, fascia lata of the thigh) [57]. Estrogen and relaxin can stimulate fascial fibroblasts by linking with receptors on the plasma membrane, contributing to collagen and ECM remodeling, regulating fibrosis and inflammation, and consequently defining fascial stiffness. Another hormone family present in myofascial tissue contributing to pain signaling are cannabinoids. Cannabinoid receptor 1 and cannabinoid receptor 2 are expressed in human fascia [58] and their activation can suppress proinflammatory cytokines such as interleukin-1 beta and tumor necrosis factor and increase antiinflammatory cytokines, providing antifibrotic activity [59].

The problem of fascia classification

Fascia is made of sheets of connective tissue which is located beneath the skin. It attaches to, separates, compresses and links muscles, groups of muscles and variant internal organs. Fascia encloses internal organs and helps stabilize the human body. Recently, the definition of fascia has been broadened to include all collagenous based soft tissues in the body, including cells that create and maintain the extracellular matrix. The new definition also includes certain tendons, ligaments, bursae, endomysium, perimysium, and epimysium [60].

Histologically, fascia is made up of soft, loose and dense fibrous connective tissues, which contains collagen. The definition of fascia includes it as a form of connective tissue proper, but on a histological level, the fascial system is made up of several, rather than just one, types of connective tissue [61].

According to anatomical location, fascia is classified as superficial, deep, visceral, or parietal. Superficial fascia is found directly under the skin and superficial adipose layers. Deep fascia surrounds bones, muscles, nerves, and blood vessels. Visceral fascia surrounds organs in cavities like the abdomen, lung (pleura), and heart (pericardium). Parietal fascia is a general term for tissues that line the wall of a body cavity just outside of the parietal layer of serosa. The most commonly known parietal fascia is found in the pelvis [60].

Fascia is not located in one place, it encloses different organs, muscles and groups of muscles. Therefore, fascia's function is very important for all the body. Fascia is involved in linking muscles with other tissues, organs and bones. Many tendons and ligaments flare out at their attachment on the bone and commonly have fascial expansions linking them with neighboring structures [6]. Function of linking is also connected with coordinated work of muscles. In the vast majority of cases the muscles had extensive attachments to ligaments and fascia that effectively link the muscles together to promote their contraction as a coordinated unit [6]. Fascia holds together a number of muscle bundles or fascicles, which are the components of each organized skeletal muscle in the human body. This form of fascia is called the endomysium tissue and it provides pathways for the passage of blood vessels and nerves. Fascia must cope with very large forces during the work of muscles. The spatial orientation of the collagen fibers is different in each layer of fascia and each individual layer of fascia assumes anisotropic characteristics, i.e. the mechanical response of a single layer differs if the layer is loaded along the direction of the collagen fibers or along another direction. All soft biological tissues including fascia when subjected to mechanical forces respond in a way which is described by large displacement theory [2]. It results in very large forces, outside the physiological range, that are required to produce a small amount of compression and shear. Separating fascia divides the body in visible sheets and layers of varying fibers allowing it to take up forces and friction in all directions. While its major function is to allow more efficient sliding of tissues over one another, it may still form adhesions from faulty movement patterns or injury [62].

Fascial disorders and treatment implications

Rheumatoid arthritis

Rheumatoid arthritis is an inflammatory disease characterized by symmetric involvement of joints and tendons, especially those of the hands and wrists [63]. RA can also affect other extra-articular muscular structures, such as ligaments and fascia [64] leading to their stiffness. It has been shown that myofascial release therapy reduces pain and accompanying symptoms and improves range of motion in patients with rheumatoid arthritis [65]. Stretching stiff fascia can also noticeably reduce inflammation and pain sensitivity [66]. Most patients with rheumatoid arthritis experience foot problems such as pain, swelling, and stiffness during the course of the disease [67]. This may suggest that people with rheumatoid arthritis are more susceptible to developing plantar fasciitis [68].

Myofascial pain

The cause of myofascial pain generally involves pathological changes of various types affecting the soft tissues of the musculoskeletal system. Contemporary knowledge allows for demonstrating a certain role of the deep fascia in this mechanism. It is important to emphasize the significance of fascial nociceptors, particularly their sensitization to chemical and mechanical stimuli. It has been demonstrated that injection of hypertonic saline solution into the deep tissues of the back, including the thoracolumbar fascia, induces strong lower back pain, which is stronger if the salt is injected directly into the fascial area than into the muscle or subcutaneous fat tissue areas [69]. On the other hand, the introduction of NGF into the fascia of the erector spinae muscle resulted in lasting sensitization of the fascia to mechanical and chemical stimuli for about two weeks, indicating a high susceptibility of nociceptors to such stimuli [70]. Moreover, changes in the structure of the fascia can also lead to chronic pain. It has been shown that in patients with low back pain, compared to those without low back pain, the gliding ability and susceptibility to deformation of the thoracolumbar fascia is reduced by approximately 20% [71].

Lymphatic oedema

The superficial fascia suspends superficial blood vessels, lymphatic vessels, and fat cells. When there is lymphatic stasis and swelling, we can be sure that there are blockages or changes at the level of the superficial fascia. Therefore, any treatment involving the superficial fascia should improve edema symptoms [72]. Marotel et al. [73] using computed tomography, retrospectively examined 11 patients with isolated unilateral lower limb lymphedema, which allowed him to conclude that increased subcutaneous tissue area and thickening of the muscular fascia significantly contribute to lymphatic stasis. To improve the impaired lymphatic drainage, manual lymphatic drainage based on massage can be applied. However, if the thickening of the fascia increases the resistance along the connective tissue fibers where lymphatic drainage is initiated, the drainage will be significantly impeded [74].

Fascia and acupuncture

The impact of acupuncture on pain relief is the subject of many studies, with the main assumption involving chronic modulation of the autonomic nervous system function [75–77]. Potentially, the needle insertion causing deformation of the connective tissue, including the change in the structure of the fascia matrix, through mechanotransductive stimulation, engages the myofascial and neuro-muscular junction, leading to the stimulation of the sensory pathway,

which weakens the pain stimulus [78]. Structural deformation, even through micro-injuries, stimulates the release of myofascial trigger points [79] by engaging the entire intracellular and extracellular matrix, which can last up to 5 days with a single minimal puncture [80]. The signals generated by damaged fascial cells can then propagate through various pathways: neurons, the flow of paracrine signaling molecules, communication through gap junctions using ion potentials, the distribution of mechanical forces, or some combination of these processes [81].

Conclusions

Understanding of the anatomy, histology, and function of fascia is crucial in diagnosing and treating fascia-related disorders. Research in the subject of fascia will provide many new insights and innovative approaches in the aspect of healthcare, due to its significant clinical implications and broad profit potential in various fields of medicine. Fascia-focused treatments, such as myofascial release techniques and fascial manipulation, are gaining recognition in the treatment of musculoskeletal disorders and chronic pain conditions. Strategies targeting fascial remodeling and functional restoration may provide benefits in enhancing athletic performance, optimizing recovery, and preventing injuries. Its regenerative potential and role in tissue repair, have stimulated interest in regenerative medicine and tissue engineering. Understanding the influence of fascial health on skin elasticity, firmness, and overall appearance has led to the development of products and procedures targeting fascial layers, including facial massage techniques, fascia-stimulating devices, and specialized skincare formulations, creating profit opportunities within the beauty sector. Finally, research can improve surgical planning by providing detailed insights into the three-dimensional organization and biomechanics of fascial structures. Surgeons might better understand the relationships between fascial layers, muscles, and other anatomical structures. This knowledge helps in preoperative assessments, surgical approaches, and the prevention of iatrogenic injuries during procedures.

Ethical approval

This conducted study is not related to either human or animal use.

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Conflicts of interest

The authors declare they have no conflict of interest.

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