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Connective tissue: A body-wide signaling network? ☆

Helene M. Langevin *

Department of Neurology, University of Vermont, College of Medicine, Given C423, 89 Beaumont Avenue, Burlington, VT 05405, United States

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Summary Unspecialized ''loose'' connective tissue forms an anatomical network throughout the body. This paper presents the hypothesis that, in addition, connective tissue functions as a body-wide mechanosensitive signaling network. Three categories of signals are discussed: electrical, cellular and tissue remodeling, each potentially responsive to mechanical forces over different time scales. It is proposed that these types of signals generate dynamic, evolving patterns that interact with one another. Such connective tissue signaling would be affected by changes in movement and posture, and may be altered in pathological conditions (e.g. local decreased mobility due to injury or pain). Connective tissue thus may function as a previously unrecognized whole body communication system. Since connective tissue is intimately associated with all other tissues (e.g. lung, intestine), connective tissue signaling may coherently influence (and be influenced by) the normal or pathological function of a wide variety of organ systems. Demonstrating the existence of a connective signaling network therefore may profoundly influence our understanding of health and disease.

Going back to the origins of physiological research, the human body has been broken down conceptually into systems (e.g. respiratory, digestive, musculoskeletal) with consequent medical specialization along these lines. As useful as this systemic approach may have been, it also has meant that thinking across existing systems has been, and continues to be, difficult. Efforts therefore must be made to look for bridges across areas that, up to now, may have appeared distinct.

The musculoskeletal system exemplifies a physiological system that has been studied very much in isolation from the rest of the body. This is perhaps because the role of specialized musculoskeletal tissues (e.g. bones, muscles, cartilage, tendons) is so strongly associated with posture and movement. Paradoxically, a more extensive, even global physiological role for connective tissue was suggested over 2000 years ago by the ancient practice of acupuncture. Traditional Chinese medicine is based on the premise that a network of ''meridians'' exists within the ''fat, greasy membranes'' extending throughout the body and that this network functionally ''connects'' all parts of the body with one another [1]. Recent evidence suggests that a

☆ Supported by NIH NCCAM R01-AT01121.
* Tel.: +1 802 656 1001; fax: +1 802 656 8704.
E-mail address: Helene.Langevin@uvm.edu.

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correspondence may exist between the network of meridians and the body-wide network formed by connective tissue [2]. Following this lead, the hypothesis presented in this paper is that the ''connectivity'' provided by connective tissue is not only anatomical, but functional as well. In other words, does connective tissue constitute a previously unrecognized communication network within the body?

Unspecialized ''loose'' connective tissue is part of the musculoskeletal system, and as such participates in movement and posture control. Unlike other musculoskeletal components, however, unspecialized connective tissue not only forms a continuous network surrounding and infiltrating all muscles, but also permeates all other tissues and organs. Within individual organs, the extracellular interstitium and connective tissue matrix play a well-recognized role in integrating the function of diverse cell types existing within each tissue (e.g. lung, intestine) [3]. Moreover, the connective tissue matrix is a key participant in mechanotransduction, or mechanisms allowing cells to perceive and interpret mechanical forces [4]. Rapid progress has been made in the past twenty years in the understanding of mechanotransduction at the molecular, cellular and individual tissue level [5,6]. The continuous interplay between cells, matrix and mechanical forces is also known to control long term sculpting of the connective tissue matrix. Indeed connective tissue proteins have been hypothesized to convey information stability and tissue ''memory'' [7]. No known mechanism, however, explains how mechanical forces might be interpreted and integrated at the level of the whole body. Since connective tissue plays an intimate role in the function of all other tissues, a complex connective tissue network system integrating whole body mechanical forces may coherently influence the function of all other physiological systems. Demonstrating the existence of such a ''metasystem'' would therefore change our core understanding of physiology.

Showing that connective tissue functions as a complex network would require evidence that a signal is generated by some component of connective tissue in response to a specific stimulus, and that the signal can propagate over some distance through the tissue. Overall properties of the network system would be determined by the topography of the anatomical network as well as the dynamics of the response and signal propagation. What type of stimulus, response and signal propagation might take place within connective tissue, allowing it to function as a complex body-wide mechanosensitive system? Three categories of signals responsive to mechanical forces will be considered, each occurring on a different time scale, and each with the potential to influence the other two. First, the possibility that electrical signals generated by mechanical forces may propagate through the extracellular matrix will be examined. The idea that electronic mobility and charge transfer across biological polymeric molecules may be a fundamental mechanism in living organisms was first proposed by Szent-Gyorgyi in 1941 [8]. During the next 30 years, some evidence was accumulated showing that a number of proteins including collagen can display semiconductive, piezoelectric and photoconductive properties in vitro [9]. Whether these types of electronic phenomena occur, and have biological significance, in vivo, however, remains unknown. One of the main obstacles to studying solid state physical properties of proteins in tissues is the necessity to test these properties in a wet, ionically-filled environment. Ionic charge separation occurring locally in response to mechanical stresses (e.g. stretch, compression) is well established in specialized connective tissues and can be measured as stress-induced potentials (or ''streaming potentials'') [10,11]. Ionically derived potentials are known to have important local downstream effects on extracellular matrix biosynthesis [12] but usually decay over short distances. Electronic currents, on the other hand, could potentially flow over larger distances, but would require either a gradient of one type of charge carrier (leading to diffusion current) or a sustained potential difference across some region (leading to drift current). If such electronic currents do occur within connective tissue, the tissue's electrical conductance would be expected to be affected by various external influences (e.g. mechanical stress, illumination, heating). The influence of the localized stimulus may be detectable as a transient change in voltage and/or current at some distance from the excited region, and the time delay between the original pulse and its detection at that distance may be measurable. Thus it may be possible to measure changes in the tissue's electrical properties resulting from physiologically relevant mechanical stresses, as well as the extent and speed of propagation of the influence of these changes.

The second category of signals to be considered is at the cellular level. Fibroblasts in ''loose'' subcutaneous tissue are linked together in a cellular network expressing connexin 43 at points of cell-to-cell contact, but without ultrastructural evidence of gap junctions [13]. These connective tissue fibroblasts exhibit active cytoskeletal responses (spreading, lamellipodia formation)

within minutes of tissue lengthening [14]. Whether these cytoskeletal responses are accompanied by some type of cell-to-cell signaling remains unknown. Cultured fibroblasts from tendon, bone, cartilage and intervertebral disc are known to respond to mechanical loads with a variety of measurable effects including extracellular calcium influx through stretch-activated membrane channels, calcium-induced release of intracellular calcium stores (from stimulation of ryanodine-sensitive endoplasmic reticulum receptors), release of ATP through connexin hemichannels and paracrine activation of purinergic receptors on neighboring cells [15]. In astrocytes, connexin 43 expression has been associated with cell-to-cell propagation of mechanically-induced calcium waves [16]. Analogous cell-to-cell signaling involving calcium and/or ATP may exist within connective tissue and may be accompanied by active tissue contraction or relaxation [17]. If this were the case, one can envisage the whole body web of connective tissue involved in a dynamic, body-wide pattern of cellular activity fluctuating over seconds to minutes reflecting all externally and internally generated mechanical forces acting upon the body. Such complex mechanotransduction signaling patterns could be simulated using artificial neural network computational models.

The third category of signals concerns long term connective tissue responses to changing levels of overall movement patterns. A well recognized property of connective tissue is its plasticity in response to varying levels of mechanical stress. These changes take place over the course of days to weeks following a change in posture or activity (such as beginning a new occupation or sport). Known physiological connective tissue responses involve remodeling of the collagenous matrix, with changes in collagen fiber density and orientation with resultant changes in tissue viscoelastic properties (e.g. changes in stiffness) [18]. Local levels of growth factors such as TGF β-1 and enzymes such as metalloproteinases are well-known regulators of the balance of collagen deposition and breakdown [19]. So far, these effects have been studied as local responses in specialized connective tissues (tendons, ligaments, joint capsules). If such remodeling responses were shown to occur in unspecialized loose connective tissue, this would suggest the existence of a slowly evolving global pattern of connective tissue plasticity reflecting an individual's overall movement patterns.

The three categories of signals mentioned above (extracellular, cellular and tissue remodeling) all have the potential to create dynamic and evolving patterns that could interact with one another. For example, locally increased tissue stiffness (e.g. connective tissue fibrosis following a shoulder injury) may affect both electrical conductivity as well as fibroblast-to-fibroblast communication across the shoulder (i.e. between arm and chest). Such mechanisms may form a basis for understanding the impact of local pathology on connective tissue signaling. Finally, exploring the function of connective tissue as a network also should involve understanding the relationship between direct communication within the network, and possible indirect communication via the nervous system. Exciting new developments in the field of neuroplasticity indicate that a two way ''conversation'' exists between sensory neural pathways and target organs [20]. Although connective tissue is richly innervated with mechanoreceptors and nociceptors, very little is known about connective tissue as a sensory target organ, or how sensory information from connective tissue is integrated spatially in the central nervous system. As a first step to ''dissecting'' the function of connective tissue away from that of the nervous system, and at the same time understanding the interplay between both systems, animal experiments could be performed in combination with general and selective connective tissue sensory denervation (e.g. tetrodotoxin, capsaicin).

Understanding the temporal and spatial dynamics of connective tissue bioelectrical, cellular and tissue plasticity responses, as well as their interactions with other tissues, may be key to understanding how pathological changes in one part of the body may cause a cascade of ''remote'' effects in seemingly unrelated areas and organ systems. For example, a patient presenting with a flareup of ulcerative colitis preceded by a two week exacerbation of knee osteoarthritis would probably be thought to have two distinct problems, one in the gut and one in the knee. Establishing the presence of a connective tissue ''bridge'' between these two medical problems would potentially have important repercussions on both diagnosis and treatment of these conditions. One of the greatest problems of modern medicine is its fragmentation. Connective tissue may be a key missing link needed to improve cross-system integration in both biomedical science and medicine.

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