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Investigating the Mechanisms of Massage Efficacy: The Role of Mechanical Immunomodulation

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Massage has the potential to attenuate the inflammatory process, facilitate early recovery, and provide pain relief from muscular injuries. In this hypothesis-driven paper, we integrate the concept of mechanotransduction with the application of massage to explore beneficial mechanisms. By altering signaling pathways involved with the inflammatory process, massage may decrease secondary injury, nerve sensitization, and collateral sprouting, resulting in increased recovery from damage and reduction or prevention of pain. Our goal is to provide a framework that describes our current understanding of the mechanisms whereby massage therapy activates potentially beneficial immunomodulatory pathways.

Key Words: inflammation, mechanotransduction, neutrophils, macrophages, apoptotic signaling, sensitization, nociception, afferent nerves

Complementary and alternative medicine (CAM), sometimes referred to as complementary integrative medicine (CIM), is steadily gaining popularity. It covers a vast range of treatments from dietary supplementation to practitioner-based chiropractic and massage therapies.[1–3] Individuals seeking CAM/CIM treatments generally pay out-of-pocket costs that are comparable to family medical practitioner costs in a given year.[1,3] In 2007, the estimated costs were reported to be $33.9 billion for CAM/CIM treatment in the United States alone, a third ($11.9 billion) of which stemmed from costs for practitioners, such as massage therapists.[3] Researchers[2] have shown that the most commonly cited reason for seeking CAM/CIM therapy, such as massage, is the treatment or prevention of musculoskeletal conditions or conditions associated with chronic pain. Most individuals use CAM/CIM modalities in conjunction with traditional treatment, with "relief of symptoms" as one of the most common reasons cited.[1]

Previous investigations regarding the efficacy of massage have been highly variable and inconclusive, most likely due to a lack of randomized control trials[4] and inherent challenges associated with investigating the effects of massage, such as inconsistent modes of massage application (ie, effleurage versus petrissage, or a combination of the two), applied forces, and duration of reported massage application. In a systematic review, Best et al[5] concluded that although researchers have attempted to mimic the clinical setting, the variability that exists between and within these investigations makes them difficult to interpret. Additionally, many of the studies reviewed relied exclusively on subjective participant outcomes[5]; therefore, conclusions about cellular and molecular responses were absent.

Considering the large number of individuals receiving CAM/CIM therapies and the purported positive health benefits these modalities provide, the purpose of this communication is to explore how massage affects inflammatory responses and their modulation of pain. Beginning with an overview of the inflammatory response, readers will gain an in-depth understanding of immune-cell function and how endogenous chemicals released in this process affect pain transmission through the sensitization of afferent nerve fibers. We also introduce the concept of mechanotransduction and its importance in stimulating cell-signaling pathways. Finally, we present the immunomodulatory effects of massage, which combine all of these elements, to discuss the physiologic benefits of massage application following injury. A better understanding of the physiologic consequences that massage induces on cellular mechanisms underlying inflammatory pathways and pain modulation will allow clinicians to make informed decisions about treatments associated with musculoskeletal injuries.

THE INFLAMMATORY RESPONSE TO MUSCLE INJURY

Injury to skeletal muscle is associated with sequelae of inflammatory events, and a sound understanding of the temporal nature of the immune response is necessary to provide effective treatment. Immediately after injury, several distinct populations of immune cells (monocytes) rapidly invade skeletal muscle in response to abundant fluctuating signals regulated by the local tissue.[6–16] Increased expression of several proinflammatory chemical cellular signals known as *cytokines* (ie, interleukin 1β, interleukin 6, interleukin 8, and tumor necrosis factor α) stimulate the activation of endothelial-leukocyte adhesion molecules P-selectin and E-selectin.[6,15,17] In combination

with various chemoattractants, cytokines take part in the activation of the CD4/CD8 T helper inflammatory response, promoting the recruitment, adhesion, and infiltration of neutrophils, macrophages, and other effector cells via diapedesis from the vasculature into the surrounding tissue.[18]

Cytokines are released into the environment from multiple tissues, such as the muscle cells, local resident macrophages, and mast cells. The shifting local environment promotes dendritic cells, which are specialized immune cells found in the bloodstream and tissue, to travel to neighboring lymph nodes.[19,20] When there, dendritic cells influence differentiation and mobilization of T helper cells and B cells to the site of injury or infection based on the demands of the environment (Figure).[19–21] The cytokine expression determines the differentiation of reacting macrophages to their respective cytokine lineage: either T helper 1 (Th_1) or T helper 2 (Th_2). These macrophages are categorized as either the "classically activated" (M_1) macrophage or the "alternatively activated" (M_2) macrophage.[15,19–21] Cytokines of the M_1 phenotype stem from the Th_1 differentiated cell line and are considered proinflammatory.[19–21] Those associated with the M_2 phenotype derive from Th_2 differentiated cells and are considered anti-inflammatory.[19–21] Additional T helper cell pathways have been identified, but for this communication, we focus on the well-established Th_1/Th_2 taxonomy.[20]

Neutrophils

Cytokine signaling is an essential and influential factor driving the inflammatory response. Swift infiltration of neutrophils into the area is due to the activation of the Th_1 cytokine pathway that, in turn, is an important process in inflammation.[15] Activation of the Th_1 cytokine pathway is influenced by the release of established neutrophil attractants that have been shown to be upregulated immediately after electrical stimulation in myotubes in vitro.[15,22,23]

Invading neutrophils are the first to arrive at the site of damage after tissue injury[6–16] and produce tissue damage through "respiratory burst." Arachidonic acid is a structural component of cell membranes and is released with tissue disruption.[24] It is not only a chemoattractant for neutrophils but also a stimulatory agent of respiratory burst.[24] Small concentrations (as little as 5 μM) of arachidonic acid can initiate a respiratory burst in which superoxide is released into the environment.[24] Neutrophils exacerbate the breakdown of tissue through lipid peroxidation, leading to free-radical release within the environment.[12,13] Free radicals scavenge electrons, taking them from the lipid membranes of surrounding cells and starting a chain reaction of free-radical release.[12,13] As arachidonic acid concentrations increase, the local environment greatly influences the respiratory burst of neutrophils in a dose-dependent manner, ultimately increasing the initial tissue damage.[24]

Neutrophil production and release of oxidants has detrimental effects on the surrounding tissue, creating myofibrillar damage in muscle. Using antibodies that prevent neutrophil infiltration and respiratory burst in damaged tissue, such as M1/70, reduces myofibril damage.[25] Similarly, Toumi et al[16] reported reductions in cellular damage 24 hours postexercise when they applied an active stretch to the tibialis anterior muscle of a neutropenic rabbit (animal lacking or having severely diminished levels of circulating neutrophils) compared with healthy control rabbits. Together, the results of these studies indicate that a large amount of cellular disruption is due to the inflammatory process and to neutrophils specifically. This is further supported by evidence showing that the mere presence of neutrophils in the extracellular spaces of muscle is not damaging if they do not undergo a respiratory burst.[25]

Whereas the destructive, oxidative nature of neutrophils within the inflammatory process seems obvious, the beneficial functions of a neutrophilic response are less apparent because the benefits are derived from the ability of the neutrophil to contribute substantially to subsequent macrophage activity. For example, Teixeira et al[26] demonstrated neutrophil-macrophage interaction when skeletal muscle injected with snake venom regenerated at a much slower rate in the absence of neutrophils than control muscle. This attenuated regeneration was likely due to altered macrophage function, resulting in an actual delay of their recruitment to the damaged area.[26] This suggests the tissue environment, and principally cellular signaling, as a target for selective manipulation for regulating the immune response in muscle.

Macrophages

After neutrophils, macrophages arrive on site, and their numbers typically peak around 24 hours postinjury and remain elevated for several days.[7–9,12–14] Macrophages have a predominant role in the repair and regeneration process of muscle tissue and are an excellent source of growth factors. They secrete more than 100 different chemical factors, including established chemoattractants for inflammatory cells.[6,11,27–29] Macrophages are divided into 2 subpopulations (M_1 and M_2) that exhibit a disparate specificity of function in the immune response.

The M_1 macrophage subpopulation begins as circulating monocytes that become activated as they invade tissue.[6,12] The main role is to phagocytose necrotic tissue.[6,8,9] They have not been shown to directly cause damage to surrounding tissue but may interact with neutrophils to cause cell destruction indirectly.[15] The M_1 macrophages enter the tissue from the vasculature approximately 24 hours postinjury and sharply decline in number around 48 hours postinjury when they are replaced by nonphagocytic M_2 macrophages.[15]

The M_2 macrophages are called *resident macrophages*.[6,9] They exist throughout the muscle tissue and are thought to be potential sensors of damage,[6,12] but they are not thought to "activate" until the process of phagocytosis has ceased. The M_2 macrophages are divided into 3 subpopulations: M_2a, M_2b, and M_2c. Each macrophage subpopulation is activated by a different set of cytokines that, in turn, release specific signals to promote tissue regeneration through (1) wound healing and tissue repair, (2) anti-inflammatory responses, and (3) deactivation of the M_1 macrophages, respectively.[15] Activation of the M_2 macrophage population coincides with the commencement of the regenerative process,[15] contributing to tissue repair through myoblast proliferation and satellite cell activation.[6,9,10,12]

A unique characteristic of macrophages is their high capacity for plasticity. In response to environmental

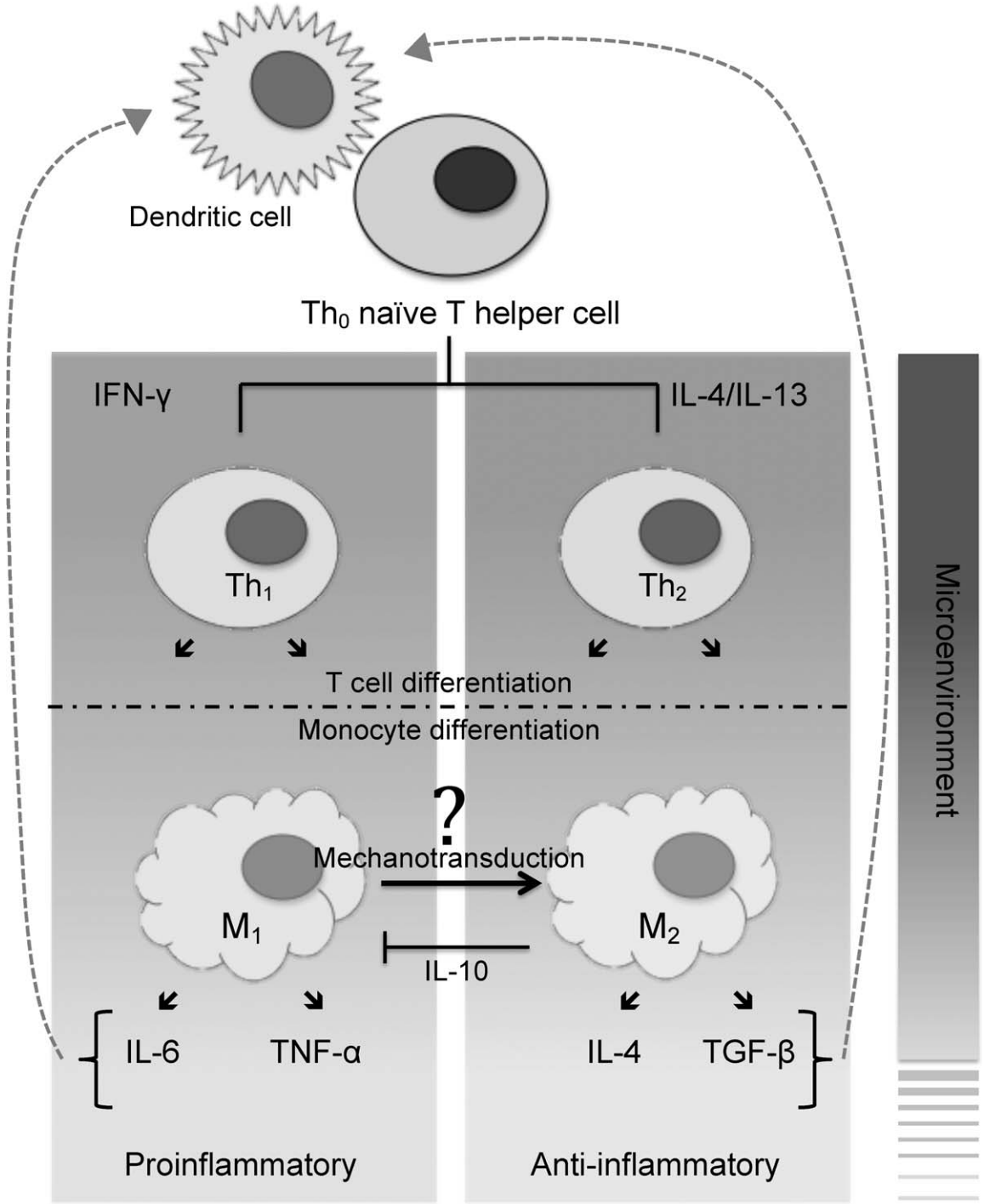

Figure. Simplified depiction of the cytokine lineage of M_1 and M_2 macrophages within their respective pathways. Monocyte polarity is influenced not only by the interaction between dendritic and T helper cells, but largely through the local microenvironment in which they invade. In this figure, the proinflammatory environment consists of cytokines interferon gamma (IFN-γ), interleukin 6 (IL-6), and tumor necrosis α (TNF-α). Input from the dendritic cell, as well as the microenvironment, helps the naïve T helper cell differentiate into a T helper cell of the T helper 1 (Th_1) pathway. This Th_1 cell now will further promote a proinflammatory influence on macrophage differentiation, creating an abundance of M_1 macrophages that, in turn, produce IL-6 and TNF-α in the microenvironment and continuing the cycle. However, this plastic differentiation can allow a phenotype transition based on environmental demands. Manual therapy may allow for beneficial manipulation of this environment through the properties of mechanotransduction. In the event of a phenotypic change from an M_1 to an M_2 macrophage, anti-inflammatory cytokines, interleukin 4 (IL-4), transforming growth factor β (TGF-β), and interleukin 10 (IL-10) will cause a shift in the microenvironment, influencing local dendritic cells to alter the T helper differentiation to the T helper 2 (Th_2) pathway through IL-4 and interleukin 13 (IL-13). Then, the Th_2 cells instead can promote macrophage differentiation, creating an abundance of M_2 anti-inflammatory phenotype and signifying the repair and regeneration phase.

demands, macrophages can undergo a phenotype transition, shifting from an M_1 to an M_2 macrophage (Figure).[15,19] Regarding the inflammatory response, promoting an anti-inflammatory condition with a higher concentration of M_2 macrophages versus a proinflammatory M_1-macrophage–dominated environment may be desirable. Several avenues are available to modulate the inflammatory response: releasing arachidonic acid, recruiting neutrophils, limiting

the respiratory burst, or promoting an early macrophage-phenotype transition.

Macrophages are considered malleable due to their abilities to adapt to their local surroundings and become biased by well-orchestrated intracellular and extracellular signaling mechanisms. Given their malleability, inflammatory-signaling cascades present a logical avenue for manipulation. Clinicians can modulate damage after injury and restrict uninhibited secondary injury through the use of modalities, such as massage. Because M_1 macrophages depend on neutrophil action, an attenuation of neutrophilic response will reduce both lipid peroxidation and M_1 macrophage recruitment.[6,9,12,14] Theoretically, this could lead to early tissue repair and regeneration via the M_2 macrophage subpopulation, or perhaps massage may promote prompt macrophage-phenotype transition of M_1 to M_2 macrophages through tissue manipulation. As with other immunomodulatory interventions that are more common and empirically tested (pharmacologic, thermal modalities), manual therapy holds great potential for its ability to modulate the immune response (Figure).

THE AFFERENT NERVE RESPONSE TO MUSCLE INJURY

Given that CAM/CIM modalities, such as massage, often are sought as treatments for chronic pain, the afferent nerve response to inflammation deserves mention. The actual concept of pain is one that involves numerous factors that are processed at several higher centers of the brain, including the linkage of an emotional response. At the tissue level, perceived pain in humans is related to the increased firing rate of nociceptors.[30–32] We focus here on the acute aspects of musculoskeletal injury regarding nociceptive activation.

Muscle fibers contain no afferent nerve endings within the confines of their cell membranes. Instead, afferent nerves are located in the perimysium surrounding muscle fascicles adjacent to the vasculature that serves as the entry point for various immune cells.[33] These nerves are sensitive to noxious (tissue-threatening) stimuli that, when strong enough, will elicit an action potential with an intensity interpreted by firing rate.[32] These nociceptors have varying activation thresholds and, therefore, are not activated during typical functional movement.[30–32] Afferent nerve fibers are classified as either low-threshold or high-threshold mechanosensitive.[34] In the event of an injury, these thresholds can be altered, making them increasingly sensitive and more likely to depolarize.

Afferent fibers also consist of numerous receptors that are sensitive to endogenous chemicals released during injury via the disrupted muscle or inflammatory cells.[32,34] Nerve fibers have receptor sites that are sensitive to bradykinin, serotonin or 5-hydroxytryptamine, prostaglandin E_2, adenosine triphosphate, and histamine.[30–32,34] These have been established as nociceptive stimulants and have been identified as being released from muscles when cell membranes are disrupted in response to injury. These substances can have long-lasting effects, often potentiating one another.[34]

Neuropeptides are released from the nerve itself during the inflammatory response and include substance P and calcitonin gene-related peptide. These vasodilators actively influence the surrounding environment through the introduction of circulatory materials (eg, blood, various inflammatory cells) and eventually lead to the formation of edema.[31,32,34,35] All of these factors have a sensitizing effect on nociceptors, causing a decrease in the excitatory threshold to mechanical stimuli.[34] The decrease in the threshold allows the nerve to become increasingly sensitive to stimuli that normally are classified as non-noxious. However, prolonged activation of nociceptors and nociceptive input eventually can lead to neuroplastic changes in the peripheral and central nervous systems and the development of various chronic pain syndromes.[30–32,36]

The unrestricted production of neurotrophic growth factors after the sensitization of afferent fibers eventually can lead to collateral sprouting of the afferents in the periphery and fibers within the lamina of the spinal cord.[34,36,37] Sprouting of afferents amplifies their input to various pathways within the spinal cord, potentially affecting sympathetic reflex pathways and peripheral skeletal muscle spasticity.[36,38] A potent neurotrophic growth factor, termed *nerve growth factor*, is classified as a neuronal sensitizing agent.[33,34] Nerve growth factor is released by the muscle during injury and, when uncontrolled, can lead to debilitating chronic pain syndromes.[34,36,37] At 12 days, Reinert et al[33] showed an increase in free nerve-ending fiber density in the perimysium after persistent inflammation in skeletal muscle. The mechanism proposed suggested nerve growth factor as the contributing factor to the increase in substance P production in the dorsal root ganglion.[33] This illustrates the rapidity with which the peripheral nervous system can become "efficient" at pain transmission and illustrates the importance of timely modulation of the early immune response.

THE PHYSIOLOGIC EFFECTS OF MECHANOTRANSDUCTION

The cytotoxic environment created via tissue damage and the immune response propagates and induces hypoxia. The less-than-favorable environment that is created includes not only the musculature but also the vascular and nervous tissues. Furthermore, afferent nerve endings in the local area are similarly sensitive to the cytotoxic buildup, which promotes depolarization of afferent nerves and signal propagation associated with pain. Whereas nerve and muscle are anatomically separate structures, clinicians should regard them equally when developing treatment strategies rather than considering them independently. Muscle and nerve not only are dependent on each other for processes such as growth, development, and maintenance, but they are both mechanosensitive structures that respond to a variety of applied mechanical stimuli. Understanding the properties of mechanotransduction will help clinicians better use manual modalities, such as massage.

Mechanotransduction is defined as the transformation of a mechanical stimulus into a chemical signal or the resulting cellular signaling cascade after an external mechanical deformation of tissue.[39] Muscle is an extremely elegant structure consisting of a very complex, intricate cellular matrix called the *cytoskeleton*. This structure, in addition to the fibers themselves, is theorized to be sensitive to mechanical changes or perturbations. The cytoskeleton

consists of numerous mechanosensitive structures, such as stretch-activated ion channels and focal adhesion complexes. Activation of these structures can cause depolarization, can change the sensitivity of surface receptors to their substrates, and can serve as a major source of signal transduction within and between cells. This mechanotransduction ultimately can lead to the transmission of signals throughout the cell, altering protein expression.[39] For example, muscle responds specifically to overload by adding sarcomeres in parallel (hypertrophy), which increases the cross-sectional area, and in series when longitudinal stretch is applied.[39–42] These researchers[39–42] have shown that various loads applied to muscle tissue can trigger distinct signaling cascades that lead to adaptive cellular responses.

Hornberger et al[42] suggested that a disparity of responses to a given mechanical stimulus exists within and between cells. The same mechanical signal may recruit a particular immune cell but not control the function of that cell. For instance, passive stretch is an established stimulus that recruits neutrophils but does not necessarily cause a respiratory burst.[10] This demonstrates that neutrophil infiltration does not always lead to tissue damage associated with secondary injury.[10]

Authors[39,41,42] of comprehensive investigations have demonstrated that the response of a muscle to perturbation depends on the type of mechanical stimulus applied, illustrating that these signaling cascades are not random. For example, researchers[39] using muscle cells in culture have revealed that intracellular signaling in response to uniaxial (1 direction) or multiaxial (multiple directions) stretch is strain specific. This observation is noteworthy from a clinical and translational perspective because muscle is isovolumetric and sensitive to distinct perturbations; negative strains induced by axial compression of muscle arguably result in a compensatory positive longitudinal strain in other regions of the tissue. In fact, investigators[43,44] recently have shown that muscle is more stiff when load is applied at an angle (more acute to the fiber orientation) due to the lateral movement of fluid against the plane of fiber orientation, altering shear stress. This illustrates the complexity of the tissue response (eg, sarcolemma deformation, protein distortions, fluid flow) during tissue manipulation. With more than 75 different methods associated with massage alone,[2] the type of manipulation applied should be considered carefully based on the desired outcome. The use of massage versus joint mobilization ultimately will affect the response of the local tissue. Adding a variety of techniques contributes not only to the intricacy of the effect but to the actual application as well. The location, orientation, and application of load that the clinician controls and administers are critical points to be emphasized.

Recent work in the field of mechanotransduction has measured the rapidity of mechanical signal propagation from the plasma membrane to the nucleus, which is essential for cell communication and gene expression.[45] Signals are transduced in skeletal muscle via direct connections between the cell membrane and nucleus at a rate that is 6 orders of magnitude greater than traditional ligand-receptor rates: approximately 5 microseconds and 5 seconds, respectively.[45] Mechanotransduction exists at the sarcomere level as well. Both the Z disc and M line have been regarded as active signal transducers because they transform positive and negative mechanical strain into biochemical responses for protein expression or degradation.[46] Furthermore, the giant protein titin acts as a passive tension sensor within the M line.[46] In response to mechanical stress, a conformational change in this region of the protein exposes adenosine triphosphate binding sites, promoting activation.[46] This process has been linked with downstream phosphorylation and activation of various proteins associated with apoptosis (programmed cell death), autophagy (cell survival), and hypertrophic signaling (cell growth).[46]

THE IMMUNOMODULATORY EFFECTS OF MASSAGE

To discern the biochemical and cellular changes occurring with massage, our laboratory has developed a device that serves as a massage mimetic, which allows for tunable and highly reproducible application of force. Under these controlled conditions, Butterfield et al[47] observed a dramatic influence of massage on skeletal muscle inflammation and function. Application of a 30-minute bout of a massage mimetic to an eccentrically damaged rabbit tibialis anterior muscle once each day over 4 consecutive days reduced the amount of cellular infiltration and tissue necrosis compared with a nonmassaged, eccentrically exercised muscle.[47] Treated muscles not only recovered mechanical function at a faster rate than exercised, nonmassaged muscles, but histologically the massaged muscle tissue more closely resembled that of nonexercised healthy control muscles.[47] Massaged muscles exhibited little cellular infiltration and regular intracellular spacing. Butterfield et al[47] were the first to show that massage effectively reduced cellular infiltration and subsequent inflammation and edema, thereby facilitating recovery of function. These findings, in conjunction with our ongoing work on massage and inflammation, lead us to propose massage as an immunomodulatory therapeutic modality.

The inflammatory response to damaging eccentric exercise commences immediately after the activation of muscle and continues long after exercise ceases.[16] Damage has been related to the intensity and duration of the exercise and is likely additive over time as cells repeatedly transduce mechanical signals to chemical responses.[48] The timing of the massage application with respect to exercise cessation appears to influence its immunomodulatory efficacy. Recent pilot work in our laboratory has shown that as the delay in massage application increases, its effectiveness for reducing secondary hypoxic injury decreases. This finding is especially important for clinicians when developing acute treatment plans.

Recently, Waters et al[49] applied massage to healthy undamaged muscle to investigate its action without the confounding elements of exercise-induced damage. They showed that the magnitude of applied load affects resident (M_2) and nonresident (M_1) macrophage numbers in the muscle. An optimal load that increases M_2 macrophage numbers in healthy skeletal muscle, suggesting a better environment for repair and regeneration, appears to exist.[49]

Our ongoing hypothesis is that application of mechanical compressive loading (a massage mimetic) is a potent immunomodulator after damaging exercise. Moreover, a specific combination of timing, force, and technique exists

in which an optimal inflammatory environment that promotes tissue repair is created. This model of massage application and tissue response is based on our current findings and ongoing research. We propose that the magnitude of a single bout of massage modulates the levels or density of 3 physiologic factors: M_1 and M_2 macrophages and afferent nerve fibers. We have not included neutrophils because we demonstrated that massage application immediately after eccentric exercise limited damage through the attenuation of secondary injury (due to respiratory burst) and limiting edema. Therefore, we are most interested in macrophage recruitment, potential phenotype transition, pain modulation, and tissue repair.

In our working model, the optimal range for massage application in the event of an injury, such as a moderate to mild contusion or tear, appears to be a low to moderate magnitude of load sufficient to beneficially influence M_1 and M_2 macrophages. These loads have the potential to modulate, elevate, or promote early activation of M_2 macrophages, suggesting an M_1 macrophage transition into repair and regeneration. We suggest that massage promotes a restorative environment, minimizes respiratory burst and proinflammatory cytokine release from M_1 macrophages, and limits the amount of cytotoxic chemicals in the surrounding area. Potential for afferent nerve sensitization is reduced, leading to an attenuation of nerve-fiber–density adaptations in the periphery, thereby preventing plastic changes at the spinal cord level.

In the event of a substantial, very destructive, untreated inflammatory response, the numbers of M_1 macrophages appear to remain elevated past the 48-hour peak when they typically begin to decline. Crushing injury and grade 3 tear in the musculature are examples of this type of injury. The combination of highly elevated M_1 and M_2 macrophages would indicate an extreme inflammatory condition. Increased density of macrophages in the area also suggests a previous and potentially ongoing neutrophil infiltration, resulting in the excessive breakdown of local tissue and promoting further proinflammatory cytokine signaling. Membrane lesions due to secondary injury result in an increased level of neural sensitization agents, such as nerve growth factor, which propagates the action of substance P and increases afferent nerve fiber density. Changes in afferent density at 1-week postinjury potentially can cause detrimental plastic changes (collateral sprouting) in the dorsal horn of the spinal cord.

Currently, one contraindication for massage includes acute muscle injuries. However, based on our understanding of the inflammatory response and secondary injury in skeletal muscle, we have proposed that massage can be beneficial when applied immediately postinjury.[47,50] To this end, we have been systematically studying the effects of massage application immediately after damaging eccentric exercise. Given the inherent biologic variability, muscle damage was normalized using exogenous supramaximal stimulation during eccentric exercise.[50–54] Whereas this represents a nonphysiologic force production, it results in a reproducible, controlled degree of muscular damage for our study of massage efficacy.[55] Subsequent application of our massage mimetic was calculated based on allometric scaling laws and a ratio of species-specific muscle mass to lumbar vertebrae cross-sectional area.[47] We propose that the translational capacity for effective loads in our laboratory could be similarly scaled for application to humans. Butterfield et al[47] reported that muscle damage responded very well to an immediate postexercise 30-minute bout of massage, which not only reduced the inflammatory response but also accelerated functional recovery. At this time, we consider all aspects of massage application, including massage technique, type, magnitude, timing and duration of applied load, and even the nature of the injury, to be important variables for optimal cellular response.

The influence of massage on apoptotic signaling may be one explanation for its physiologic benefits. Apoptotic signaling of neutrophils has been shown to influence a phenotype change in the macrophage population.[56] The M_1 macrophages, which are phagocytic, seek and engulf apoptotic cells and lysed fragments. If an M_1 macrophage engulfs an apoptotic cell rather than its lysed parts, it can influence a phenotypic change in which the M_1 macrophage transitions to an M_2 macrophage, secreting anti-inflammatory products.[15,56] Macrophages that engulf apoptotic neutrophils prevent the release of neutrophil cytotoxic chemicals, ceasing respiratory burst and increasing the secretion of transforming growth factor β and interleukin 4.[15,56] The release of transforming growth factor β and interleukin 4 results in decreased release of proinflammatory cytokines (eg, tumor necrosis factor α and interleukin 6) and promotes a transition to the Th_2 cytokine pathway (Figure).[15,56] The anti-inflammatory nature of the Th_2 pathway promotes the repair and regenerative process.[20,45,46]

Using massage to influence phenotype change, prompting the transition into the repair and regeneration phase, may play an important role in the physiologic benefits of massage. Preventing the exacerbation of a toxic environment through the attenuation of neutrophil recruitment, respiratory burst, or the phagocytosis of apoptotic neutrophils also would greatly decrease endogenous chemical availability and the potential of nerve sensitization. In doing so, massage may be able to prevent transient and more detrimental plastic changes in afferent nerve density in the periphery and the spinal cord. Attenuating the inflammatory and subsequent nervous response may allow clinicians to treat, manage, and prevent acute and chronic pain syndromes, as well as inflammatory-related diseases, with massage and without pharmaceutical intervention.

CONCLUSIONS

Currently, massage therapy is tied to numerous indications and contraindications, with a lack of rigorous scientific evidence to reinforce present guidelines. Many critics of CAM/CIM therapy disregard its proposed effects due to the lack of randomized control trials.[4] Recently, investigators[47,49,50] have demonstrated a clear physiologic response to the application of massage. Further mechanistic investigations of massage are critical to establish a better understanding of its beneficial immunomodulatory effects. Researchers should focus on the temporal nature of the various inflammatory cell populations while attempting to limit the confounding effects of multiple bouts of massage. Additionally, with their study designs, investigators should attempt to closely mimic the clinical setting, and contributions to the establishment of goals and appropriate

guidelines for massage application are encouraged. Special attention should be given to the technique of application, because distinct cell-signaling pathways may be activated with different massage strokes. Just as structure dictates function, mechanism should dictate treatment. Identifying specific signaling pathways that massage affects will provide insight into the proper clinical application through the creation of an advantageous inflammatory environment to promote repair.

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