HIGHLIGHTED TOPIC | Role of Inflammation in Skeletal Muscle, Connective Tissue, and Exertional Injuries: To Block or Not to Block?

Inflammation: sustaining the balance to optimize recovery of skeletal muscle, connective tissue, and exertional injuries

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INFLAMMATION HAS BEEN DESCRIBED as part of the healing process since Hippocrates in ancient Greece (5). Inflammatory responses are initiated immediately after tissue damage to protect the organism, but a hyperactive inflammatory response may attack healthy tissues. In such situations, anti-inflammatory therapies are warranted, and physically active populations (e.g., athletes and soldiers) often take anti-inflammatory therapies while continuing to be active. The inflammatory response is controlled by a complex communication network. Therefore, although an ideal therapeutic approach would be one that keeps inflammation focused on the area of local trauma, thus preventing the destruction of healthy tissue, the complexity of the inflammatory response has made this approach difficult.

Anti-inflammatory therapies have been used for centuries, and their pharmacological sophistication is rapidly advancing. Over 3000 years ago, the serendipitous discovery that certain plants and their extracts were effective in the relief of pain, fever, and inflammation served as the foundation for the advanced development of anti-inflammatory treatment interventions. In the early 19th century, salicylates were determined to be the component of these plants that promoted anti-inflammatory outcomes. By 1899, salicylate compounds were synthesized in the laboratory to form acetyl-salicylic acid, or aspirin (4). Advanced techniques in chemical discovery and synthesis led to the discovery of nonsteroidal anti-inflammatory drugs (NSAIDs), which is now deemed to be one of the major therapeutic developments of this century. In fact, the use of NSAIDs has become so prevalent, an estimated 30 billion purchases are made annually for NSAIDs (2). Although the application of NSAIDs to treat acute inflammatory conditions has become commonplace, new anti-inflammatory drugs are being developed. Undoubtedly, this therapeutic approach has significant implications in reducing functional and pathological consequences of inflammation. However, obstacles remain particularly in regard to the timing of administration, mechanism of action, and the affected tissue.

This Highlighted Topic “Role of Inflammation in Skeletal Muscle, Connective Tissue, and Exertional Injuries: To Block or Not to Block?” provides an integrative and accessible approach to the topic to expand the target audience in the hopes of fostering discussion and collaboration among disciplines. We also solicited original research articles that are intended to represent the cutting edge of knowledge in this field. The result is a Highlighted Topic series that is a comprehensive overview of inflammation and current therapeutic approaches.

In the first mini-review, Drs. Trappe and Liu (8) review how the cyclooxygenase (COX) pathway regulates skeletal muscle responses and adaptations to exercise training. The authors include an objective review of original research studies that have employed COX inhibition, while elegantly refuting the controversial issue that use of COX inhibitors may have a negative effect on skeletal muscle adaptation. The three main points summarized in this paper are the effects of chronic consumption of COX inhibitors during exercise training, the amount of drug that is needed to influence skeletal muscle adaptation, and the important differences between acute and chronic effects of COX inhibition between younger and older individuals.

The second mini-review by Dr. Mackey (6) focuses on the satellite cell, the stem cell responsible for repair and maintenance of skeletal muscle, as a cell that is particularly sensitive to the inhibitory effects of NSAIDs. Through a careful review of the literature and evidence from her own laboratory, Dr. Mackey presents a compelling argument that the observed effects of NSAIDs on satellite cell activity may have negative long-term consequences, particularly in athletes who engage in chronic NSAID use. This topic is further expanded in the third mini-review by Dr. Urso (9) on the role of various anti-inflammatory approaches in skeletal muscle in exercise-induced and traumatic injury, as also disease. Urso provides an overview of the more recent original research articles in each of these conditions, providing a timely analysis of the therapeutic promise of anti-inflammatory approaches. Overall, the paper implies that the effect and mode of action of anti-inflammatory interventions varies significantly across conditions in how they promote muscle healing and functional recovery. It is this information that indicates an urgent need for scientists to pursue combinatorial and injury-specific treatment approaches.

The next two mini-reviews focus on the role of anti-inflammatory treatment interventions in connective tissue. In the fourth mini-review, Kjaer et al. (3) reviews the effects of inflammation, mechanical stretch, and mechanical overload on tendon injury, healing, and regeneration. An important concept...
introduced in this paper is how inflammation impacts the critical interplay between mechanical signaling and biochemical changes in the tendon matrix. Although mechanical loading stimulates an increase in inflammatory markers and collagen turnover in peritendinous tissue, it is not known whether elimination of this inflammatory response prevents proper healing. Evidence is provided to indicate that complete removal of the inflammatory response is detrimental for the collagen response, possibly impacting tendon adaptation with mechanical loading. The authors subsequently point out that inflammation can be lowered if mechanical loading is introduced during the regenerative phase. These data have important implications for rehabilitation after tendon injury. The fifth mini-review by Su and O’Connor (7) expands upon this research area by delineating the mechanisms by which bone, tendon, and tendon-to-bone healing occurs, while describing the effects of NSAID therapy on each of these processes. The authors contend that NSAID therapy appears to inhibit tendon-to-bone healing, but NSAID therapy may be beneficial in some instances in tendon or bone healing. For example, in tendon, in addition to restoration of mechanical strength, successful healing is dependent on the ability for the tendon to glide freely. During the healing process, any formation of adhesions between the tendon and surrounding soft tissue can severely reduce range of motion. Therefore, the use of NSAIDs to decrease adhesion formation may be a beneficial treatment approach. The controversy over this treatment regimen is summarized nicely in the article, specifically in regards to the evidence that NSAID therapy may also decrease the breaking strength of repaired tendons.

The sixth mini-review examines the effects of manipulating inflammation through inhibition of the matrix metalloproteinases (MMPs), which are enzymes that respond to injury and inflammation to regulate extracellular matrix turnover. Davis et al. (1), explore the evidence regarding how targeted inhibition of MMP activity may enhance the healing of diseased and injured skeletal muscle and tendon tissue. Of note in this paper is the exploration of the author’s hypothesis that, after injury, fibroblasts are unable to detect forces transmitted through the extracellular matrix, impairing their ability to respond to mechanical loading and properly repair the site of injury. In light of this assumption, the authors explore whether targeted, temporal, manipulation of various MMPs may improve treatment of skeletal muscle and tendon.

In totality, these mini reviews provide several intriguing hypotheses addressing the overarching question of this highlighted Topic series, whether it is beneficial or detrimental to block inflammation in skeletal muscle, bone, and connective tissue. The original research papers submitted in response to the call for papers have undergone stringent peer review to ensure that they represent the state of the science in therapeutic approaches to inflammation. It is our hope that this series will provoke scientific debate and exploration into one of the most significant drug discoveries of our time, anti-inflammatory therapeutics. Ideally, continued research in this area and collaboration across laboratories will help the scientific community develop appropriate treatment interventions that may be used when inflammation occurs to promote healing and optimize recovery.

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AUTHOR CONTRIBUTIONS
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REFERENCES