

EXAMINING THE ROLE OF THE CYCLOOXYGENASES AND PROSTAGLANDINS IN THE BIOLOGICAL PROCESSES OF MUSCLE HEALING

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ABSTRACT

Constant adjustments in gene expression and protein stability allow skeletal muscle to readjust its physiological function and bulk in response to shifts in its mechanical environment. Acute damage occurs when mechanical stressors go beyond the limitations that generate adaptations. When muscles are damaged, the immune system responds by orchestrating effective regeneration. Here, we show that muscle stem cells (MuSCs), the fundamental components of muscle regeneration, rely on Prostaglandin E2 (PGE2) as an essential inflammatory mediator. Precursor cell activation, myoblast proliferation, myoblast fusion, and muscle protein synthesis are all biological processes involved in muscle repair that have been studied in vitro and in vivo to determine the function of the cyclooxygenases and prostaglandins. We may be able to learn more about inflammation's function in the recovery of damaged muscles if we utilize more selective cyclooxygenase inhibitors.

Keywords: Muscle Injury, Myofibers, Tissue, Healing, Myoblast

I. INTRODUCTION

Muscle damage from exercise, trauma, or lack of blood flow can be extremely debilitating and have far-reaching effects on many aspects of life. Understanding the healing process in depth will allow for more effective therapy development. In response to various stimuli, satellite cells (myoblasts) proliferate, differentiate, and fuse with injured myofibers throughout the process of muscle regeneration. At the same time, the wounded tissue experiences an inflammatory reaction, and effective repair requires interaction between leukocytes and a wide range of differentiated and undifferentiated muscle cells. Dissecting the function of these signaling molecules—which include cytokines, growth hormones, and prostaglandins—could one day lead to effective manipulation of muscle regeneration. In this article, we'll look at the research on prostaglandins (PGs) and the costs of taking NSAIDs, which are commonly used to treat muscular injuries.

Leukocytes, which trigger an inflammatory response, immediately penetrate the injured muscle tissue after an injury, which can have both helpful and harmful effects on the healing process. Neutrophils initially cause more harm to the injured area by releasing oxygen radicals and proteases, which they employ to breakdown cell debris formed following injury. IGF, TGF- β , LIF, IL-6, and CSF-1 are secreted by macrophages, which then eliminate dead cells by phagocytosis and influence myoblast proliferation and differentiation. At the same time, satellite cells commit to differentiation and merge with the injured myofibers by secreting signaling molecules and become active myoblasts when the inflammation subsides. Thus, the interaction between myocytes and leukocytes affects both the rate and the efficacy of repair.

In order to reduce the severity of muscle injuries, the 'RICE' concept (Rest, Ice, Compression, and Elevation) is typically applied right away. In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to reduce swelling and discomfort. Inhibiting the COX enzymes prevents prostaglandin formation, which is how NSAIDs achieve their anti-inflammatory benefits. Phospholipase A2 (PLA2) moves from the cytoplasm to the perinuclear membranes in response to stimuli (such as cytokines, growth hormones, or mechanical damage) and catalyzes the release of arachidonic acid (AA) from phospholipids. Then, COXs catalyze the two-step process that turns AA

into PGH₂, the PGs' unstable precursor. At last, terminal synthases transform PGH₂ into one of the five major PGs: PGD₂, PGE₂, PGF_{2a}, PGI₂, or TXA₂.

The two types of COX have different roles in the body. The homeostatic levels of PG are the result of the constant expression of COX-1, which is why it is frequently called a "house-keeping gene." While PG synthesis is increased in pathological processes including inflammation and pain, COX-2 expression is normally inhibited but may be activated by a wide range of external stimuli. Although conventional NSAIDs like aspirin, ibuprofen, and indomethacin inhibit both COX-1 and COX-2, isoform-specific NSAIDs are available and can be used to better understand the role of each enzyme. Understanding the function of COXs in muscle recovery is crucial in light of the current clinical practice for muscular injuries.

II. PROSTAGLANDINS AND MUSCLE REPAIR BIOLOGY

Prostaglandins are known to have a part in a variety of biological processes crucial to the healing of damaged muscle, and we will be focusing on these activities for the remainder of this work. Prostaglandins have a function not just in the inflammatory phase following muscle damage, but also in the regenerative and fibrosis phases of healing. As seen in Fig. 1, the precursor cells undergo activation, proliferation, fusion, and differentiation into mature myofibers throughout the regenerative phase of muscle regeneration. The paradoxical early functional improvement and subsequent functional deterioration occasionally found with NSAID therapy may be better understood with deeper analysis of previous data.

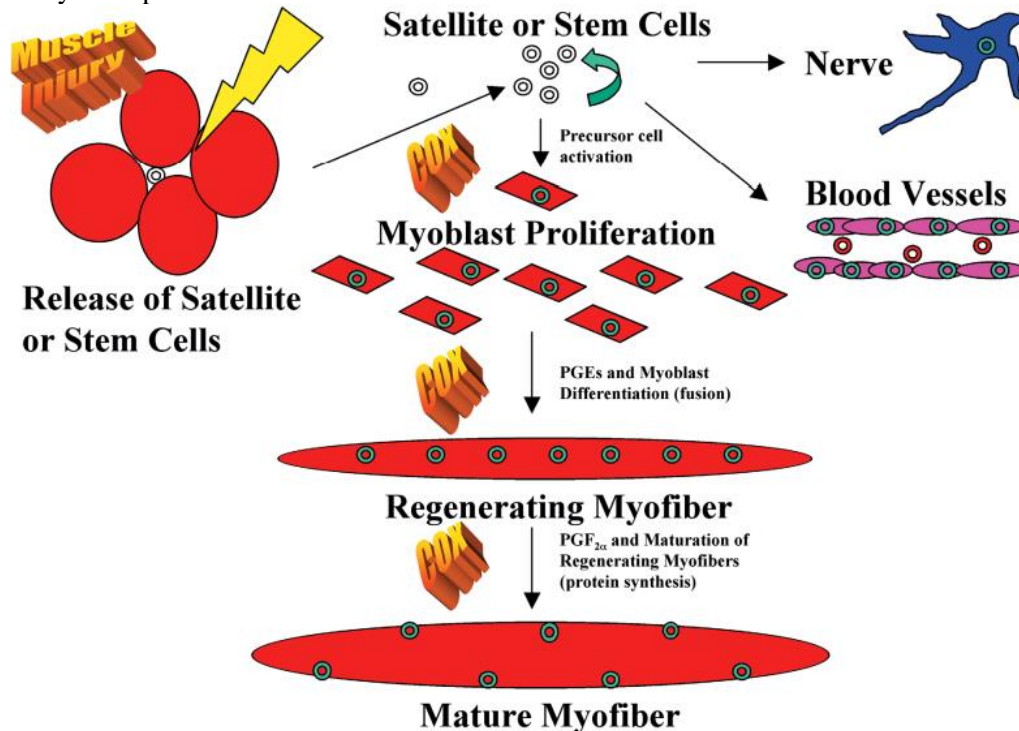


Figure 3: Muscle injuries result in the release and activation of satellite cells and muscle stem cells that proliferate, fuse, and differentiate into mature myofibers.

Prostaglandins in muscle inflammation

PGE₁, PGE₂, PGF₂, and other prostaglandins can be produced in situ and in vitro by skeletal muscle. In instance, there is evidence that PGE₂ levels are elevated in painful or damaged muscle. Furthermore, contractile activity causes an increase in PGE₂ release in both dystrophin-deficient mdx murine muscle and muscle from individuals with Duchenne muscular dystrophy.

PGE₂ appears to have numerous roles in the inflammatory response of muscles, including chemotaxis of inflammatory cells, activation of pro-inflammatory cytokines, production of nitric oxide synthase, vasodilation, and enhanced vascular permeability. PGE₂ synthesis can be stimulated in many different cell types by many different inflammatory mediators (IL1 β , TNF α , and others). When PGE₂ is present, the inflammatory phase is amplified, which might hasten the breakdown of myofibers at the site of injury. Muscle functional ability recovers more slowly in the injured athlete because PGE₂ causes more inflammation, discomfort, disturbance of excitation-contraction coupling, and calcium

homeostasis. As a result, it is possible that the rapid functional improvement associated with NSAIDs is due to the suppression of this mechanism.

Prostaglandins in precursor cell activation and myoblast proliferation

The milieu in which precursor cell activation and proliferation occur coincides with prostaglandin release throughout the regenerative phase of muscle regeneration. Growth factors and prostaglandins appear to have a nuanced relationship in regulating cell proliferation. In previous studies, increasing the proportion of cells that successfully completed the cell cycle was often accomplished by combining a peptide growth factor with a prostaglandin, such as PGF2 α . Although the link between PGF2 α and cell proliferation has been reported for quite some time, its exact nature remains a mystery. Prostaglandins have been shown to have a role in cellular proliferation in vitro, but their precise function in injury-induced in vivo myoblast activation and proliferation and differentiation remains unknown.

Injuries to muscle trigger the release and activation of stem and satellite cells from the basal lamina of myofibers, where they divide and eventually contribute to the regeneration of myofibers. When serum is added to a medium containing numerous kinds of quiescent cells, the cells are stimulated to divide and multiply, leading to elevated COX-2 expression in vitro. One may speculate that COX-2 serves a similar role in launching the proliferation of satellite cells or muscle stem cells, which would be in keeping with the intricate role that COX-2 plays in the cell cycle dynamics of neoplasia. Inhibition of cyclooxygenase-2 (COX-2) by NSAIDs has been hypothesized to reduce the amount of myogenic, vascular, neurologic, and fibrotic tissue-generating stem cells, satellite cells, and myofibroblasts. It is too difficult to tell at this point if this will aid in the quick or slow restoration of muscle function.

III. PROSTAGLANDINS AND MUSCLE PROTEIN SYNTHESIS

There appears to be antagonism between the effects of PGF2 α and PGE2 on skeletal muscle protein turnover. It was shown early on that PGF2 α stimulated muscle protein synthesis and development, particularly in the presence of insulin, whereas PGE2 led to net protein breakdown, probably via activation of the lysosomal system. Muscle protein synthesis was stimulated by a hypertrophy-inducing factor, and this increase was suppressed by the nonsteroidal anti-inflammatory drug (NSAID) fenbufen, suggesting a role for prostaglandins in the control of tension-induced muscle protein turnover rates. Both ibuprofen and acetaminophen, which are available without a prescription, have been shown to reduce the increase in protein synthesis that normally follows eccentric contraction exercise in humans. Their subsequent research showed that ibuprofen and acetaminophen were effective in lowering the raised PGF2 α levels seen in human vastus lateralis biopsies after a high intensity eccentric contraction exercise program.

During a stretch, myofibers, not fibroblasts, are the primary source of prostaglandin synthesis. Mechanical stretch of mature avian myoblast cultures significantly increases cyclooxygenase activity and PGF2 α synthesis within 24 hours. Additionally, when compared to the almost undetectable constitutive COX-1 expression, the COX-2 expression in the stretched skeletal myofibers was much greater. The above information suggests that the inducible COX-2 enzyme and its products play an important role in muscle protein synthesis and that inhibition of this enzyme may lead to a reduction in the accumulation of contractile or bioenergetic proteins necessary for later recovery of full functional capacity; however, there are studies that contradict this.

Prostaglandins and muscle fibrosis

Our research has shown that TGF β 1 plays a crucial role in the development of scar tissue in damaged skeletal muscle. Models of pulmonary fibrosis and wound healing have been used to examine the connection between inflammation and scar tissue development. However, inflammatory prostaglandins' significance in post-injury muscle fibrosis development is unclear. However, the potential interaction between prostaglandins and myofibroblasts following muscle damage may be hypothesized by studying other tissue types.

Multiple studies have shown that scarless repair in fetuses coincides with a lack of inflammation throughout the first trimester of pregnancy. Similarly, several studies have demonstrated that the introduction of pro-inflammatory cytokines like PGE2 and TGF- β 1 changed the scarless wound healing process into a fibrotic scar formation phase. Celecoxib, a selective COX-2 inhibitor, has been shown to lessen the development of scar tissue in skin wounds by decreasing inflammatory cell infiltration and transforming growth factor beta 1 production. However, it is not yet known if blocking

COX-2 and inflammation has the same effect on scar formation following muscle damage as it does on skin wounds.

COX-2 appears to have a role in mitogen-stimulated fibroblast cell proliferation, as was previously reported in relation to satellite cells. PGE₂, a byproduct of the cyclooxygenase 2 enzyme, is the primary prostaglandin produced by fibroblasts and is a strong regulator of TGF- β 1-stimulated fibroblast proliferation and collagen formation. Higher doses of PGE₂ have been demonstrated to have a negative feedback function on stimulators of collagen synthesis in fibroblasts, despite the fact that PGE₂ has been proven to stimulate fibroblast proliferation and collagen production. The synthesis of PGE₂ and the expression of COX-2 are both boosted in fibroblasts by TGF- β 1. Fibroblast proliferation and collagen synthesis may benefit from low levels of PGE₂, whereas PGE₂ inhibits these processes at greater amounts. High amounts of PGE₂ produced by regenerated skeletal muscle make it hard to tell whether targeted inhibition of COX-2 promotes or hinders the fibrotic phase of muscle healing. It is challenging to anticipate the effect of NSAIDs on muscle fibrosis due to the involvement of cyclooxygenases and prostaglandins in TGF- β 1 negative feedback, as well as their roles in fibroblast proliferation and extracellular matrix formation.

IV. CONCLUSION

When muscle is damaged, myoblasts become activated and secrete PGE₂, PGI₂, and PGF_{2a} in a COX-2-dependent manner. PGI₂ and PGF_{2a}'s signaling mechanisms have been thoroughly defined, whereas PGE₂'s remain poorly understood. The roles of PGE₂, PGD₂, and 15d-PGJ₂, all of which can be produced by invading leukocytes, are well-described in inflammation. The effect of PGs produced from leukocytes on myogenesis, however, is poorly known. Studies on isolated primary myoblasts often only consider PGs made by the myoblasts themselves, despite the fact that PG-mediated communication between leukocytes may play an important role. We are now working to elucidate some of the processes behind the contradiction of early functional improvement and late functional impairment found with usage of NSAIDs in muscle injuries and healing by employing selective COX-1 or COX-2 inhibitors, as well as COX-1 and -2 knockout mice.

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