MMP inhibition as a potential method to augment the healing of skeletal muscle and tendon extracellular matrix

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Davis ME, Gumucio JP, Sugg KB, Bedi A, Mendias CL. MMP inhibition as a potential method to augment the healing of skeletal muscle and tendon extracellular matrix. J Appl Physiol 115: 884–891, 2013. First published May 2, 2013; doi:10.1152/japplphysiol.00137.2013.—The extracellular matrix (ECM) of skeletal muscle and tendon is composed of different types of collagen molecules that play important roles in the transmission of forces throughout the body, and in the repair and regeneration of injured tissues. Fibroblasts are the primary cells in muscle and tendon that maintain, repair, and modify the ECM in response to mechanical loading, injury, and inactivity. Matrix metalloproteinases (MMPs) are enzymes that digest collagen and other structural molecules, which are synthesized and excreted by fibroblasts. MMPs are required for baseline ECM homeostasis, but disruption of MMP regulation due to injury or disease can alter the normal ECM architecture and prevent proper force transmission. Chronic injuries and diseases of muscles and tendons can be severely debilitating, and current therapeutic modalities to enhance healing are quite limited. This review will discuss the mechanobiology of MMPs, and the potential use of MMP inhibitors to improve the treatment of injured and diseased skeletal muscle and tendon tissue.

MMP; TIMP; collagen; tendinopathy; muscle injury; extracellular matrix

THE EXTRACELLULAR MATRIX (ECM) of the musculoskeletal system is a dynamic tissue that plays an important role in force transmission, protection of other tissues from injury, and regeneration of tissues if they become injured. The ECM is composed of many different molecular components, consisting mostly of collagens, proteoglycans, and glycosaminoglycans. The specific molecules that constitute the ECM vary, depending on the types of cells that are embedded within that matrix and the mechanical demands of the tissue, and this regional specialization helps to optimize efficient force transmission throughout the kinetic chain (1, 21, 35, 41, 44). While there is tremendous variation in the minor molecular components of ECM, the essential structural and functional building block of musculoskeletal ECM is collagen. The molecular diversity between collagen subtypes is striking, with almost 30 unique members belonging to this protein superfamily (11). Having many types of collagen molecules allows for the ECM to become highly specialized to specific mechanical loading regimes. The ability to break down and synthesize new collagen molecules in a tightly controlled and organized fashion is critical to maintain optimized force transmission and reflects the high degree of adaptability in ECM tissue.

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that digest collagen and other structural molecules. MMPs can be organized into four subgroups, based on their primary substrate: collagenases, gelatinases, membrane-bound MMPs, and stromelysins (16, 59). While MMPs are required for baseline ECM homeostasis, injury or disease can disrupt MMP regulation, leading to alterations in normal ECM architecture and disfunctions in normal force transmission (1, 58). Disruption in the normal architecture of ECM can be clinically very challenging to treat, and the targeted manipulation of MMP activity may have the potential to enhance the healing of injured or diseased musculoskeletal tissue. The objective of this review is to discuss the mechanobiology of ECM and MMP regulation and the potential of targeted inhibition of MMP activity to enhance the healing of diseased and injured skeletal muscle and tendon tissue.
An overview of the ultrastructure of skeletal muscle and tendon is shown in Fig. 1. Skeletal muscle consists of hundreds to thousands, sometimes millions, of long, multinucleated fibers organized and held together by an ECM. There are four general layers of ECM in muscle. The outermost layer is the epimysium, which covers the surface of the muscle and has important roles in force transmission and insulation (40). Processes from the epimysium extend into muscle tissue and form the second layer of connective tissue, the perimysium, which structurally divides muscle fibers into functional groups called fascicles. The variation in the number of fascicles allows muscles to adopt a complex geometry and facilitate complicated movements at joints. The epimysium and perimysium are primarily composed of the fibrillar collagens, types I and III (38). These collagens act as molecular springs and exist in parallel with the muscle fibers (11). The endomysium is composed of two layers of mostly type I and type III collagen that surround individual muscle fibers. These layers fuse with the perimysium to form a sheetlike structure that inserts into the tendon and allows for the longitudinal transmission of force (40). The endomysium is connected to the basement membrane that is attached to the sarcolemma itself. The basement membrane is composed mostly of type IV and type VI collagen and is important in transmitting forces generated within the muscle to the tendon, as well as laterally to other muscle fibers (38, 67). Unlike the fibrillar type I and type III collagens, type IV and type VI collagens form meshlike networks that surround the muscle fiber and allow for the lateral transmission of forces generated within activated muscle fiber sarcomeres to the overall ECM (11).

Tendon tissue is arranged in a hierarchical order, similar to skeletal muscle. Tendons are linked to muscle tissue by myotendinous junctions located at the ends of the tendon (84). Many muscles have an aponeurosis, or internal tendon, that is an extension of the tendon into the muscle tissue. At the other end, tendons are connected to bone by strong fibrous structures called entheses (8). The fundamental anatomical structure in tendons is the tendon fiber (28, 84). The tendon fiber is composed of mostly type I and type III collagen. Individual tendon fibers coalesce to form tendon fascicles that are organized by the endotenon, which is a basement membrane enriched in network type IV and type VI collagens. Superficial to the endotenon is the epitenon, which is a looser layer of connective tissue that covers the tendon along its entire length. The epitenon provides a smooth gliding surface for tendon fascicles and is also the source of vascular nervous and lymphatic supply for the tendon. The paratenon or a synovial sheath surrounds the epitenon to provide lubrication that helps
to cushion the tendon and reduce friction from adjacent tissues as the tendon is stretched and relaxed. The epitenon and paratenon together compose the peritenon.

Fibroblasts are the major cellular component of muscle and tendon ECM and consequently are responsible for the maintenance, repair, and modification of the matrix (34). While muscle and tendon fibroblasts are thought to perform similar functions, they appear to arise from different populations of progenitor cells during development and are regulated by different sets of transcription factors. The transcription factor \( \text{T} \) cell factor-4 is required for the proper formation of muscle ECM during development, while the basic helix-loop-helix transcription factor scleraxis is required for limb tendon formation during development (30, 55). Both transcription factors are required for the initial development of limb tissue and also appear to play important roles in the adaptation of muscles and tendons of adult animals to mechanical loading and regeneration following injury (42, 48, 49, 57, 74).

Satellite cells, which are the main myogenic stem cell population responsible for the repair and replacement of injured muscle fibers, are found within the basement membrane surrounding muscle fibers (23). In response to injury, satellite cells awaken from quiescence, migrate to the site of injury, and fuse with damaged muscle fibers to promote fiber regeneration (23). The interaction between satellite cells and fibroblasts has also been shown to be critical to promote the regeneration of injured muscles (57). While progenitor cells in tendon have been identified in cell culture from segments of tendon digested in vitro, the exact location of tendon progenitor cells in vivo remains unknown, although the epitenon and paratenon are attractive candidates (9, 48, 50). The migration of both fibroblasts and satellite cells through the ECM requires the activity of various MMPs, and although the expression of various MMPs has been evaluated during cell proliferation in vitro, the contribution of the major MMPs to cell migration in muscles and tendons remains unknown (2, 54, 61, 81, 87).

REGULATION OF COLLAGEN AND MMP EXPRESSION AND ACTIVITY

Type I collagen is the most abundant collagen found in the ECM of muscle and tendon (34, 35, 43, 44). Type I collagen is synthesized as procollagen in the lumen of the rough endoplasmic reticulum and secreted for final assembly outside of the cell (11). In tendon, type I collagen is deposited into the ECM by long, thin plasma membrane projections called fibripositors (13). Mature type I collagen is produced from two different genes, \( \text{Col1a1} \) and \( \text{Col1a2} \). Three peptides, typically two \( \alpha_1 \) and one \( \alpha_2 \), coalesce into a triple-helix procollagen molecule. Procollagen is then transported outside of the cell via the Golgi apparatus, and a final extracellular step cleaves extension peptides at the amino- and carboxyterminal ends, resulting in the formation of mature type I collagen (11, 34). The process is similar for type III collagen, except there is only one gene, \( \text{Col3a1} \), and three \( \alpha_1 \) peptides are used to make the mature protein (11). There are several signal transduction pathways that regulate fibrillar collagen expression, but the transforming growth factor (TGF)-\( \beta \) pathway appears to be central to regulating the expression of type I and type III collagen. TGF-\( \beta \) binds to both type I and type II TGF-\( \beta \) transmembrane receptors, which then activate intracellular Smad2/3 and TGF-\( \beta \)-activated kinase 1 pathways (82). Myostatin, a cytokine that is a closely related member of the TGF-\( \beta \) superfamily, activates similar signaling pathways to increase type I collagen gene expression (47).

Type IV collagen is formed from six distinct genes, \( \text{Col4a1} \) through \( \text{Col4a6} \), that give rise to six corresponding peptides, \( \alpha_1 \) through \( \alpha_6 \). Mature type IV collagen molecules are trimeric proteins formed first into protomers of three collagen IV peptides that are further arranged into larger, mechanically flexible networks that traverse the basement membrane (11). Type VI collagen is composed of three peptides, \( \alpha_1 \) through \( \alpha_3 \), transcribed from three distinct genes, \( \text{Col6a1} \) through \( \text{Col6a3} \). Mature type VI collagen molecules also coalesce into a variety of structural motifs that span the basement membrane (11). These systems of fibrillar and network collagens work in concert to efficiently transmit forces throughout muscle and tendon ECM, with the fibrillar collagens primarily transferring forces longitudinally and the network collagens transmitting forces laterally between cells (68). Type VI collagen also plays an important role in organizing the overall matrix, as mice deficient in \( \text{Col6a1} \) display mechanically weak tendons with disrupted fibrillar collagen organization (26). Fibroblasts are intimately linked to network collagens via several transmembrane receptors that provide an important basis for mechanotransduction within the cell (15, 26, 75). The signaling pathways that regulate network collagen gene expression are not as well understood as fibrillar collagens, but TGF-\( \beta \) appears to induce the expression of both type IV and VI collagen gene transcripts, either directly or by downregulating miR-29 gene expression (33, 73, 83).

Measuring the collagen content of tissue can be difficult. Collagen molecules are largely insoluble and cross-linked into large structures that can be several megadaltons, which limits the ability to quantify these proteins via immunoblot or ELISA (11). Collagen molecules are relatively stable in tendons, which generally demonstrate low levels of protein synthesis throughout most of the core of the tendon (25). The expression levels of collagen genes are commonly reported in the literature, but, due to the long half-life of collagen molecules, this technique is primarily useful to estimate acute changes in collagen production. More commonly, to quantify collagen content, samples are enzymatically or chemically digested into soluble peptides or amino acids, and the specific peptides and amino acids found in collagen molecules can then be analyzed with colorimetric assays, chromatography, or mass spectrometry (11, 17, 85). While the use of aggressive digestion and extraction techniques can be helpful in quantifying the collagen content of tissues, this approach limits the ability to quantify other proteins that may be of interest in the same samples.

MMPs are the main proteinases that break down collagen in the ECM. MMPs are typically synthesized and released as proenzymes and must then be activated by other proteinases, including other MMPs, once they are outside of the cell (59, 65). The regulation of MMP activity in connective tissue biology is an area of intense study, including the control of MMP synthesis and activation by growth factors, chemical agents, and other soluble factors, as well as mechanical loading and cell-cell interactions (1, 44, 59, 86). Inflammation is a common trigger for the induction of MMP expression and activation of MMP enzymes (14). For acute injuries, the elevation in MMP activity that occurs as part of the inflam-
The use of fluorescent detection reagents (78). TIMP activity acrylamide gels containing specific MMP substrates that can be tissue or cell lysates are subjected to electrophoresis in poly-

method to measure MMP activity is zymography, in which other techniques used to quantify MMP and TIMP protein estimating the actual activity of MMPs. Immunoblots or ELISAs are regulating, which limits the strength of gene expression in the literature; however, MMPs are subject to posttranslational regulation, which limits the strength of gene expression in the understanding of how MMP inhibition may change tissue structure and function. Collagenases degrade whole collagen molecules, especially fibrillar collagens, and include MMP-1, -8, and -13 (10, 65). Gelatinases include MMP-2 and -9 and function to degrade smaller network collagens and the pieces of fibrillar collagens left over from collagenase activity (10, 65). Membrane-bound MMPs have variable levels of endogenous collagenase and gelatinase activity and are also critical for activating other MMPs. MMP-14 (MT1-MMP) is one of the most widely expressed membrane-bound MMPs (10, 65). MMP-14 plays a central role in cell autonomous migration of pulmonary fibro-
blasts through type I collagen-rich ECM (71), but the role of MMP-14 in satellite cell and muscle and tendon fibroblast migration is not known. Stromelysins, which include MMP-3 and -10, degrade many different ECM structural proteins, but are incapable of degrading fibrillar collagens (10).

Tissue inhibitor of metalloproteinases (TIMPs) are a class of proteins that act as endogenous inhibitors of MMPs by binding to the active site of the MMP catalytic domain. Four TIMPs have been identified, TIMP-1 through -4, and all TIMPs share a highly conserved amino-terminal domain, and all appear to be expressed in skeletal muscle and tendon tissue (1, 10, 86). Similar to MMPs, multiple signaling pathways appear to regulate the expression of TIMPs (56). While in vitro studies have demonstrated that all four TIMPs can inhibit all known MMPs, the ability of specific TIMPs to inhibit specific MMPs in vivo is an area of continued study (56). In addition to regulating the biological activity of MMPs, the carboxy-terminal region of TIMPs can act as signaling molecules (53), and this particular role of TIMPs as signaling molecules warrants further study in musculoskeletal diseases.

There are several ways to measure MMP activity. The expression of MMP and TIMP mRNA is commonly reported in the literature; however, MMPs are subject to posttranslational regulation, which limits the strength of gene expression in estimating the actual activity of MMPs. Immunoblots or ELISAs are other techniques used to quantify MMP and TIMP protein abundance, but these methods have similar limitations as gene expression in interpreting MMP activity. The most common method to measure MMP activity is zymography, in which tissue or cell lysates are subjected to electrophoresis in poly-
acrylamide gels containing specific MMP substrates that can be quantified by staining the gels with specific dyes, or through the use of fluorescent detection reagents (78). TIMP activity can be measured using reverse zymography, which uses a similar approach, but instead measures the activity of MMPs that are incorporated into the gel (78). While there are some limitations in the ability to connect changes in MMP and TIMP gene expression to the in vivo activity of these enzymes, the extraction of proteins from tissues with a dense ECM-like tendon can be difficult, which limits the use of zymography for certain types of tissue.

MMPs AND TIMPs IN SKELETAL MUSCLE AND TENDON INJURIES AND DISEASES

A pathological accumulation of collagen is a common phenotype among many different types of musculoskeletal disease states, in which the balance between collagen production and degradation becomes dysregulated. This failure in ECM homeostasis can be distilled down to one of three proposed mechanisms: overproduction of collagens, failure to breakdown damaged ECM, and improper reorganization of complex supramolecular collagen networks. Many of these conditions are directly attributed to the dysregulation of MMP activity. This section of the review will discuss ECM synthesis and MMP regulation in the context of physiological and pathophysiological processes involving skeletal muscle and tendon, along with the potential for targeted MMP inhibition to enhance the healing of connective tissue.

Skeletal muscle and tendon adaption in response to exercise training requires the precise coordination between muscle fi-
bers and muscle and tendon ECM to optimize athletic perfor-
mance (37). This necessitates a balance between the synthesis and proper alignment of new collagen molecules, and the breakdown of existing collagen molecules by MMPs. Disrup-
tion of this balance between collagen synthesis and the activity of MMPs and TIMPs may result in chronic injuries, which currently have limited treatment options.

In skeletal muscle, MMP-2, -9, and -14 are key enzymatic factors involved in the ECM adaption to mechanical loading. Chronic endurance training in human subjects resulted in increases in the expression of MMP-2, -9, and -14 and TIMP-1, although changes in collagen expression were not examined (72). In a study of isometric, concentric, and eccentric training in rats, for all three types of training increases in type I and III collagen, MMP-2 and TIMP-1 and -2 were observed (24). In a mouse model of plantaris muscle hypertrophy caused by ablation of the synergist gastrocnemius and soleus muscles, 2 days after induction of hypertrophy, MMP-2 and TIMP-2 were down-regulated, while elevations in MMP-9 and -14 and TIMP-1 were observed. By 7 and 14 days after overload, MMP-2 and -14 and TIMP-1 and TIMP-2 were upregulated, while MMP-9 was downregulated at these time points (12). MMPs also play a role in muscle regeneration and injury-induced fibrosis. Following cardio
toxin injury, MMP-2 and -9 levels are upregulated and return to baseline by 7 days after injury (32). There is also differential expression of MMPs by fast- and slow-fibered muscles during regeneration, with fast-fibered muscles displaying increased levels of MMP-2 and decreased MMP-9 during regeneration, while slow-fibered muscles displayed increased MMP-9 during regeneration (88). While these studies have provided important descriptive information regarding changes in MMP expression or activity during mechanical loading and regeneration, there are a limited number of studies evaluating...
MMP inhibition as a method to improve muscle repair after injury. In a rat ischemia reperfusion injury model, nonspecific inhibition of MMPs using doxycycline protected the muscle from reperfusion injury (70). Using a crush injury model in rats, the use of doxycycline or an MMP-9-specific inhibitor reduced fibrosis and promoted regeneration, while specific inhibition of MMP-2 did not impact regeneration (89). While these studies have been informative, the use of targeted, temporally controlled, genetically modified mouse models would also allow for further insight into the molecular mechanisms of MMP-mediated muscle ECM adaptation and regeneration.

Adaptation of tendon ECM to mechanical loading follows a similar pattern seen in muscle ECM. While there are similarities between muscle and tendon in the biological mechanisms of ECM adaptation, muscle injuries are often responsive to rehabilitation and other conservative treatments, whereas chronic tendon injuries generally have slower rates of healing and appear to have poorer clinical outcomes than muscle (3, 27). Regional differences in collagen, MMP, and TIMP expression occur throughout the length of the tendon, likely due to different mechanical demands placed on the tendon (45). In response to a single bout of uphill treadmill training, increases in MMP-2 and -9 and TIMP-1 and -2 were observed in Achilles tendon dialysate (35). Similar to what was observed in muscles, the tendons of rats that underwent isometric, concentric, and eccentric training had increases in type I and III collagen, MMP-2, and TIMP-1 and -2 expression for all training types (24). In various studies of cultured tendon fibroblasts, mechanical stretching increased type I collagen and MMP-1 and -3 expression, with no change in MMP-2 or -9 (4, 22, 87). With recent developments in identifying promoters that are generally specific to tendon fibroblasts like scleraxis (66), the use of targeted, temporally controlled, genetically modified mouse models would also provide much greater information about the basic molecular mechanisms that control tendon growth and remodeling.

Tendinopathy is one of the more common chronic musculoskeletal conditions that can result in severe disability, pain, and tendon rupture. Tendinopathies often arise due to the failure of tendons to properly adapt to mechanical loading (43, 44, 86). Tendinopathy typically manifests with the overexpression of fibrillar collagens, disorganization of collagen fibril orientation, a reduction in network collagen content, and grossly altered fibroblast morphology (43, 44, 69, 86). This increase in fibrillar collagens is accompanied by an increase in the expression of MMP-1, -2, -8, -9, and -13 (62, 69). The elevation of MMP-1, -8, and -13 may contribute to the development of tears, as these MMPs digest the primary load-bearing collagen fibers within the tendon. Since fibroblast activity is required to maintain and remodel the ECM, and fibroblasts are surrounded by network collagens that eventually interact with load-bearing fibrillar collagens, increased levels of MMP-2 and -9, which degrade network collagens, may be responsible for the altered fibroblast morphology and inhibition of tendon regeneration that is the hallmark of tendinopathies.

While the use of MMP inhibitors has some potential promise in the treatment of chronic tendinopathies, with the exception of the rotator cuff overuse tendinopathy model (5), the general lack of physiologically relevant small-animal models of chronic tendinopathy has prevented preclinical studies in the area. In a case series of patients receiving injections of the broad spectrum MMP inhibitor aprotinin for the treatment of Achilles or patellar tendinopathies, most patients reported subjective improvements in pain and function and believed that aprotinin therapy assisted in their recovery (62). While the local inhibition of MMP activity has some early but encouraging results, systemic MMP inhibition may be detrimental to normal tendon function. In a clinical trial evaluating the effi-

![Diagram](image-url)
cacy of the broad spectrum MMP inhibitor marimastat to prevent metastasis in cancer patients, 30% of subjects reported tendon inflammation and pain that subsided within 2 wk of discontinuing marimastat treatment (18). Combined, these results suggest a potential role for local and specific MMP inhibition in the treatment of chronic tendinopathies, and that there is a clear need for randomized, double-blind, placebo-controlled studies in this area.

Platelet-rich plasma (PRP) is a therapeutic modality that is gaining in popularity in the sports medicine field for the treatment of patients with muscle injuries and tendinopathies (51, 63). A detailed analysis of the results of clinical trials of PRP for the treatment of tendinopathies is reviewed elsewhere (76, 80), but, in general, PRP has shown some promise and improved clinical outcomes with proper use. PRP is readily administered percutaneously, and exposure to the fibrillar collagens induces platelet activation and subsequent degranulation and release of various growth factors, cytokines, and MMPs. Injected locally into the site of injury, PRP is thought to stimulate cell proliferation, migration, and differentiation, as well as collagen synthesis and angiogenesis (19, 52). There is a lack of consensus on the ability of PRP to regulate collagen degradation and the expression and activation of specific MMPs, but PRP contains MMPs, and some of the growth factors concentrated within PRP have roles in regulating MMP expression (29, 46, 64, 77, 79). Both the basic science and clinical literature regarding PRP are complicated by a lack of standardization of PRP preparation, study models, assessment techniques, and subject selection. While there is some encouraging early work, further investigation into regulation of MMPs by PRP and appropriately designed prospective clinical studies is warranted.

Tendon rupture, either from an acute traumatic event or following chronic tendinopathy, is a more severe injury that, in most cases, requires surgical repair. MMPs play a central role in the susceptibility of the tendon to tear, as well as in the recovery of tendons following surgical repair. In ruptured Achilles tendons, there is an increase in the activity of MMP-2 and -9 and TIMP-1 and -2 (31). While Achilles tendon tears occur relatively infrequently, the most common site of tendon tear following chronic tendinopathy is the rotator cuff (6, 7). In ruptured rotator cuff tendons, MMP-1, -9, and -13 expression is elevated and positively correlated with size of the tear, while TIMP-2, -3, and -4 are downregulated (36, 39, 86). Furthermore, MMP-1 expression (25: 617–624, 2007) and TIMPs, and disordered collagen expression. We hypothesize that an MMP-9-mediated degradation of network collagens impairs the ability of fibroblasts to properly sense forces transmitted through the ECM, disrupts their potential to respond to mechanical loading, and leads to the failure of fibroblasts to repair sites of injury (Fig. 2). Targeted, temporal inactivation or overexpression of various MMPs and TIMPs using fibroblast-specific promoters would allow for the testing of this hypothesis. Gaining a greater understanding of MMP biology will help in the design and selection of specific MMP inhibitors that could substantially advance the treatment of skeletal muscle and tendon injuries and diseases.

EVALUATION AND FUTURE DIRECTION OF MMP INHIBITION IN CONNECTIVE TISSUE HEALING

It is clear that MMPs play a central role in the adaptation of skeletal muscle and tendon tissues to mechanical loading, injury, and disease. There is strong potential for the application of MMP biology in the treatment of connective tissue disorders, and also for the use of MMPs as biomarkers of disease progression. While much attention has focused on factors that regulate type I collagen synthesis and degradation, in part due to the overwhelming abundance of type I collagen in the ECM, the role that type IV and type VI collagen play in muscle and tendon injuries and diseases has been overlooked. Even though these network collagens only make up a small fraction of the total mass of muscle and tendon ECM, they serve as a critical link between fibroblasts and their surrounding environment. A frequent observation in many musculoskeletal injury and disease states is an upregulation of MMP-9, a downregulation of TIMPs, and disordered collagen expression. We hypothesize that an MMP-9-mediated degradation of network collagens impairs the ability of fibroblasts to properly sense forces transmitted through the ECM, disrupts their potential to respond to mechanical loading, and leads to the failure of fibroblasts to repair sites of injury (Fig. 2). Targeted, temporal inactivation or overexpression of various MMPs and TIMPs using fibroblast-specific promoters would allow for the testing of this hypothesis. Gaining a greater understanding of MMP biology will help in the design and selection of specific MMP inhibitors that could substantially advance the treatment of skeletal muscle and tendon injuries and diseases.

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