# Exercise and Matrix Metalloproteases in Health and Disease: A Brief Overview

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**Abstract** Systematic exercise plays a great deal with health for people to improve and/or prevent many diseases such as hypertension, coronary heart disease and diabetes. However, strenuous exercise markedly increases expression and activation of matrix metalloproteases and thereby causes changes in the regulation of skeletal muscle and tendon functions, immune response, aging and angiogenic processes. This review provides information on some cellular and molecular responses that underlie the prophylactic effects of exercise in some pathophysiological conditions including age related diseases involving matrix metalloproteases.

**Keywords** Exercise • Matrix metalloproteases • Tissue inhibitors of metalloproteases • Aging • Angiotensin • Endostatin • Immunity • Gene expression

## 1 Introduction

Matrix metalloproteases (MMPs) are a family of highly homologous $Zn^{2+}$ endopeptidases that collectively cleaves most, if not all, of the constituents of extracellular matrix (ECM). MMPs in the circulation are thought to modulate the activation of growth factors, cytokines [1] and angiogenesis, thereby facilitating physiological adaptations to exercise training [2–4]. The MMP family of enzymes contribute to both normal and pathological tissue remodeling [5, 6]. Each MMP targets a specific substrate, thus the appropriate MMP is released in a time and location specific manner to orchestrate membrane remodeling and adaptation [7, 8].

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Regular exercise is of great importance for public health. It has been shown to be effective in the prevention and therapy of many wide spread diseases such as hypertension, coronary heart disease and diabetes [9, 10]. However, exhaustive exercise causing inflammatory responses lead to significant change in the activity of MMPs such as MMP-9 and MMP-2. The heavy activities and deleterious effects that activate MMP-9 and MMP-2 are indicators of inflammatory conditions, which eventually cause degradation of extracellular matrix leading to the incidence of diseases, for instance, arthritis [11].

Many aspects of how the prophylactic effects of exercise on chronic diseases are mediated remain unclear [12, 13]. One important way to improve our understanding of these beneficial effects is to gain insight into the cellular and molecular responses to exercise.

## 2 Skeletal Muscle and Exercise

Certain stimuli, particularly those that induce high levels of mechanical stress by high impact exercise activate the local production of MMPs in skeletal muscle [14]. Serum concentrations of MMPs are reported to peak within a relatively short time period following a single bout of exercise. MMPs in the circulation are thought to modulate the activation of growth factors and cytokines through degradation of their precursors, binding proteins and inhibitors [15, 16]. Strenuous exercise, especially fast speed running, is known to cause intra- and extra-myofibrils damage [15, 16]. High intensity exercise increased both mRNA and protein levels of MMPs [3, 17]. It is generally accepted that MMPs function in skeletal muscle to process extracellular matrix (ECM) proteins, thereby regulating matrix degradation and repair, while those released into the circulation facilitate angiogenesis [18, 19].

Skeletal muscle fibre possesses a high degree of functional and structural plasticity and is capable of responding rapidly to changes in contractile activity [20]. The diaphragm is a unique skeletal muscle that is considered to be two muscles in one. This fact is based on anatomical and functional differences between the coastal and crural regions [21] that contain different composition in muscle fibre types. The crural diaphragm is dominated by type IIb fast twitch muscle fibres, whereas the coastal diaphragm contains equally type I (slow twitch) and type IIb (fast twitch) fibres [22]. Type IIb muscle fibres are more susceptible to ECM degradation than type I muscle fibres during exercise [12]. Moreover, a degree of muscle tissue change is fibre type specific and appears to be more pronounced in type IIb fibres following exhaustive exercise, which suggests a higher protein degradation in fast twitch (type IIb) than in slow twitch muscle fibres (type I) [12]. Thus, type II muscle fibres are more susceptible to exercise overuse than type I muscle fibres, and fast fibres are more responsive to exercise induced changes in MMP expression [12].

Superoxide dismutase (SOD) level significantly decreased in the crural diaphragm muscle of rat about a month of fast speed running; whereas it remained unchanged in the coastal diaphragm muscle during the period of running [12].

The expression of MMP-2 was found in both fast and slow running groups; however, it was particularly prominent in fast twitch muscle [12, 15]. High intensity endurance exercise increases MMPs such as MMP-2 and MMP-9 expression, whereas low intensity endurance exercise did not alter MMP-9 and MMP-2 activities in the skeletal muscles such as gastrocnemius (back part of lower leg), quadriceps (large muscle group on the front of the thigh) and soleus muscles (closely connected to gastrocnemious) [12, 13, 15]. In contrast, high intensity exercise increases both mRNA and protein levels of MMP-2 in skeletal muscle containing a high percentage of fast type IIb fibres [19]. Thus, high intensity exercise is required to promote the expression of MMP-2 in skeletal muscles and that the influence of exercise on MMP-2 expression has been found to be dominant in the muscle containing a high percentage of fast fibres [12, 15]. Thus, based on the concept that high intensity exercise in untrained animals' results in significant muscle remodeling [23], Carmeli *et al.* [12] hypothesized that high intensity exercise would promote markedly the expression of both MMP-2 and MMP-9 in skeletal muscle, whereas low intensity results in limited changes in muscle levels of MMP-2 and MMP-9 [19, 23].

Treadmill exercise can serve a model to demonstrate different damage pattern in the two separated part of diaphragm muscle during exhaustive exercise. The integrity and the composition of ECM were affected considerably through expression of MMPs, for example, MMP-2 and thereby cause change in the collagen synthesis particularly in type IIb muscle fibres [19]. There are potentially three explanations for the differences in MMP-2 expression between the muscle fibre types. First, in rat skeletal muscles, type IIb fibres are at least twice as big as type I fibres, which probably explains a higher volume of collagen; therefore, white fibres (type IIb, fast twitch) requires more MMP-2 to maintain its integrity than red fibres (type I, slow twitch). Secondly, white fibres elicit better muscle plasticity than red fibres and show faster adaptation to exercise training. Under intensified training, fast fibre may undergo transition to intermediate muscle fibres (type Ia) with corresponding changes in ECM compositions [12]. Following the fast and prolong running, the type II muscle fibres are thought to be more susceptible to oxidative stress in order to produce a greater aerobic energy [13]. And, thirdly, the diaphragm differs from locomotor skeletal muscle in adaptation to exercise [24].

The recruitment of coastal fibres increases from rest to low intensity of exercise. During intense exercise, the coastal region reaches a plateau in motor unit recruitment before meeting the ventilatory demand. This suggests that type IIb fibres are not recruited during normal ventilatory behavior. Therefore, in contrast to type I, high intensity performance of type IIa provides a trigger for type IIb intra-and extracellular adaptations [12, 13, 24].

Currently limited information exists regarding the effects of exercise training on MMPs in skeletal muscle. Studies have been made to compare the ways of activity of two types of proteinases: MMP-2 and MMP-9 during a patho-physiological process in the trained subjects (with long term adaptation to exercise) and untrained or non athlete persons (without adaptation to exercise). MMP-2 and MMP-9 activities in athletes have been found to be significantly increased immediately after exhaustive exercise and significantly decreased in the next day; while in non-athletes,

MMP-2 and MMP-9 activities were also increased immediately after exhaustive exercise and that was similar to athletes, but did not show any discernible decrease in the activities of the enzymes in the next day after exercise [1].

## 3 Angiotensin Blockers and Exercise

Exercise training is emerging as an important complementary intervention in heart failure [25, 26]. Exercise has been shown to enhance aerobic capacity, attenuates left ventricle (LV) dilation, regress cellular hypertrophy and improves cardiomyocyte contractility and myofilament function [27, 28]. These beneficial effects could be due to attenuation of renin-angiotensin system (RAs), which is known to improve cardiac remodeling [29, 30]. Indeed, exercise training normalized circulating RA system in patients with heart failure [31].

The impact of exercise training on factors contributing to myocardial fibrosis is not clearly known. It has been suggested that exercise training induced improvement of cardiac function may be due to marked decrease of myocardial fibrosis and remodeling [30]. So, combination of AngII blockade and exercise training on myocardial remodeling and function after myocardial infarction was assessed by many investigators. Studies on both gene and protein levels of MMP-2, MMP-9 and TIMP-1, angiotensin converting enzyme (ACE) and angiotensin receptor-1 (AT-1) after myocardial infarction (MI) suggest that exercise training improves factors involving post-MI fibres, reduce collagen content and thereby attenuates deleterious cardiac remodeling and preserve cardiac function. Such beneficial effects have been found to be further accentuated by angiotensin II type I (AT1) receptor blockers e.g., losartan [30].

MMPs and TIMPs are the key elements involved in matrix degradation and contribute to myocardial remodeling after MI. Increased MMPs expression or decreased TIMPs expression could result in enhanced proteolytic activity and degradation of ECM molecules [32]. Webb *et al.* [33] demonstrated that TIMP-1 level was high at day 1 post-MI and remain substantially elevated through 6 months in patients with MI. The elevated TIMP-1 level may contribute to the accumulation of collagen content in the infarcted heart, leading to myocardial fibrosis [34]. Interestingly, TIMP-1 has been shown to be increased significantly about 2 months of post MI. Both exercise training and losartan attenuates TIMP-1 expression at both gene and protein levels. Exercise training and losartan treatment in combination after MI has been shown to reduce the TIMP-1 expression, improves the balance between MMPs and TIMPs and enhance the proteolytic activity of post MI, which subsequently decreases collagen accumulation. This leads to decrease in cardiac stiffness, preserve left ventricular systolic pressure and ventricular performance, and reduce left ventricular end diastolic pressure significantly in the late phase of post MI [30]. Although the exact mechanisms of post MI exercise training induced beneficial effects on myocardial remodeling are not fully elucidated, several studies have suggested that the effect of exercise training may be due to increased baroreflex

sensitivity, reduced sympathetic activity and enhanced vagal tone [30, 35, 36]. In addition, a reduction in circulating AngII by exercise training may act favorably on baroreflex control of sympathetic activity [30, 37, 38]. Interestingly, early decrease of TIMP-1 in the infracted heart coincides with collagen degradation in the necrotic myocardium, whereas the subsequent increase of TIMP-1 in the infarct heart contributes to collagen accumulation at the late phase of post MI remodeling [39].

Recent research suggest that a decrease in the expression of TIMP-1 and ACE levels, and also a decrease in AT1 receptor numbers are associated with the mechanism by which losartan and exercise could attenuate fibrosis and preserve cardiac function [29]. Exercise training and/or AngII receptor blockage after MI has been suggested to play an important role in cardiac remodeling by attenuating TIMP-1 expression, improving the balance between MMPs and TIMPs, attenuating ACE and AT1 receptor expression, and thereby decreasing collagen content [30]. These improvements, in turn, attenuate myocardial fibrosis and cardiac stiffness and preserve post MI cardiac function [40, 41].

## 4 Immunity and Exercise

TNF-α level increases within an hour after exhaustive exercise and that has been shown to stimulate activities of MMPs. Cytokines such as TNF-α and interleukins, for example, IL-8 levels in blood of mononuclear cells have been shown to be increased in response to strenuous exercise, which remain elevated, respectively, at 2 h for IL-6 and up to 24 h for IL-1β and TNF-α after exercise [42]. MMP-1, for instance, has been demonstrated to be involved in lymphocyte trafficking [42].

Exercise has been shown to be an important regulator of immune cells and their functions, therefore, white blood cells (WBCs) have been chosen as target cells [43]. In circulating WBC's, exercise induces upregulation of MMP-9, which breaks down native collagen as well as other extracellular matrix molecules [44]. There are a number of reports on an increase in collagen degrading activity as well as release of MMP-9 in muscle, interstitial fluid and serum especially after strenuous exercise [23]. The role of MMPs in haematopoietic system during exercise involves the mobilization of progenitor cells [45]. Studies in rhesus monkeys suggest involvement of MMP-9 in IL-8 induced mobilization of hematopoietic progenitor cells (HPCs) via cleavage of matrix molecules to which the stem cells adhere [46]. Recently, it has been suggested that activation of MMPs, for instance, MMP-1 in peripheral blood mononuclear cells (PBMCs) during exercise may be involved in lymphocyte trafficking and in the recruitment of progenitor cells from bone marrow [11, 47]. Given that exercise regulates function of immune cells, role of PBMCs in the physiological changes associated with strenuous exercise has been suggested to be an important aspect of exercise physiology [48]. Changes in the expression of a group of genes within the leukocytes may serve as surrogate markers for systemic or local modifications induced by exercise [49, 50]. The response of leukocytes to

exercise on the expression of genes is known to some extent [51, 52]; however, complete lists of genes that are differentially expressed have not yet been fully explored. The regulatory mechanisms associated with the expression of the genes are also currently unknown.

Inflammatory responses induced increase in cytokines and subsequently MMPs levels have been shown to be redistributed between the lymphoid and non lymphoid organs, which cause mobilization of HPCs from bone marrow. These processes have been related to exercise induced stress [45, 53]. MMPs, for instance, MMP-1 is involved in the enhanced peripheral invasion and migration to tissues of natural killer cells (NKs). An increase in the production of MMPs from stimulated NK cells plays an important role in the facilitation of lymphocyte trafficking and in the accumulation of lymphocytes in tissues during pathophysiological processes [54]. Cytokines stimulate the expression of multiple MMPs in lymphocytes. MMPs, for example, MMP-1 produced by cytokines, for example, IL-8 stimulated NK cells play a role in the degradation of matrix collagens [55, 56].

Recent reports have suggested that redistribution of leukocytes is a fundamental regulatory mechanism of the haematopoietic system that alters lymphocyte counts during exercise [53]. The ability of immune cells to migrate appears to be closely regulated by molecules such as cytokines and MMPs, for instance, MMP-2, which are mediated through receptors of the integrin family members [57]. Although, the exact mechanism by which lymphocytes invade tissues is not completely understood, this migration seems to be regulated by distinct pathways involving mitogen activated protein kinases (MAPKs). Goda *et al.* [54] demonstrated that MMP-1, for instance, is produced by the cytokines, for example, IL-8 stimulated NK cells and that is associated with $\alpha_2\beta_1$ integrin, indicating that integrins could play a role in the immobilization of MMP-1 on the cell surface. The binding of MMPs to integrins could be the crucial step for promoting lymphocyte migration given the fact that disruption of their association decreases the migratory activity of cells [58]. Integrins are also known to be involved in signaling pathway(s) of the Rho family of GTPase that has been shown to be associated recently with modulation of the expression of IL-8 and MMP-1, which are induced upon inhibition of the MAPKs pathway [57].

Inflammation and the resulting inflammatory response for athletes indicated that MMP-2 and MMP-9 were not return to normal levels even 24 h after exhaustive activity; while for non athletes, the response was even much weaker [11]. There is evidence that exercise stress works an inflammation like reaction on the immune system with the activation of both pro-inflammatory and anti-inflammatory pathways, which is dependent on exercise intensity and duration [59]. Therefore, acute exhaustive exercise is expected to transiently decrease the individual's immune competence, while moderate exercise has an anti-inflammatory effect with improved anti-infections capability [60]. There is growing evidence that the immune system may serve as an important physiological indicator for a person's individual activity to recover from workload stresses [11, 60]. However, the overtraining syndrome, a condition of long term decrement in performance capacity due to continuous training loads, is based on derangement of cellular immune regulation [11, 60].

## 5 Tendon and Exercise

Tendon has been considered as a model to explore sex differences in mechanical and metabolic properties of connective tissue [23, 61–63]. Tendon is a metabolically active structure that transmits force from muscle to bone for mechanical movement. ECM of tendon mainly consists of collagen and elastin fibres and is surrounded by an aqueous matrix of proteoglycans, glycosaminoglycans and glycoproteins [61, 62]. Mechanical properties and metabolism in tendon have been shown to be different in men and women [63, 64]. The elastic modulus is significantly decreased in women compared with men possibly leading to an inefficient matrix for force transfer between muscle and bone [62, 65]. In addition, cross-sectional structure revealed that tendons of habitually trained women have the same size as those of untrained women, whereas men's tendon assumed hypertrophy with exhaustive exercise training [65, 66]. Tendons collagen synthesis at rest and after an acute bout of exercise is significantly lower in women than in men [65, 66]. The increased risk for connective tissue injury in women compared with men may be related to structural and regulatory expression differences in tendon [61, 63].

Tendon is mainly composed of collagen and an aqueous matrix of proteoglycans that are regulated by MMPs and TIMPs. It has been demonstrated that collagen type-I, -III and MMP-2 mRNA expressions in patellar tendons were downregulated 24 h after exhaustive exercise. Women had higher mRNA expression of MMP-2 than men after 24 h of exercise [67]. This suggests that sex plays a role on the structural and regulatory mRNA expression of tendon. However, details of the mechanisms by which sex influence tendon metabolism and its mechanical properties is currently unknown.

## 6 Aging and Exercise

Regular exercise effectively improves heart function in both young and older populations [68, 69]. Exercise training improves maximal cardiovascular work capacity by increasing stroke volume and cardiac output [65, 68, 69]. Conceivably, exercise training in the aging population may reduce accumulation of connective tissue. It has been suggested that exercise training may attenuate collagen content in the aging heart [65, 69]. The ability of exercise training to attenuate diastolic dysfunction and collagen cross-linking has recently been cited [70]. Collagen cross linking (hydroxylysyl pyridinoline) of left ventricle (LV) free wall was demonstrated to be significantly lower in old trained rats compared with their sedentary counterparts [70, 71]. However, potential pathways by which exercise training ameliorates fibrosis in the aging heart are not understood. Collagen fibrosis with aging is progressive and associated with reduced cardiac contractility and risk of heart failure. Elevation of fibrotic connective tissue could lead to decreased cardiac compliance and impaired diastolic function, thereby increasing the risk of heart failure observed with aging [65, 72].

Collagen of the basement membrane is a typical substrate for MMP-2; though fibronectin, a structural component of the sarcolemma, can also be cleaved by MMP-2 and other MMPs that are inhibited by TIMP-1 [73, 74]. Cleavage of the ECM components may cause structural change that allows for adaptive processes such as satellite cell migration and fusion to the myofibre, or it may play a bioactive role in regulating cell proliferation and differentiation [73–75]. The MMPs, for instance, MMP-2; the MMP inhibitor, TIMP-1; and the ECM proteins, for example, fibronectin have been identified as factors whose expressions are altered by aging and exercise [73–75]. The relationship between expression of these factors and strength gain suggests that cleavage of muscle ECM or altered production thereof is an important process during training adaptation [73, 76].

Exercise training reduced fibrosis when visualized with collagen type I positive staining and novel imaging in the hearts of old rats [77]. Exercise training has also alleviated age-related downregulation of active MMPs, which cleaves fibronectin in sarcolemma and connective tissues [74, 75]. Age is known to up regulate TIMP-1 expression [78]. The inhibitory effect of TIMP-1 on MMP activation in aging has been found to be virtually abolished by exercise training [77, 79]. Recent reports have suggested that habitual exercise training attenuates age associated collagen accumulation and fibrosis through signaling pathway(s) that reduces MMP deregulation through TIMP-1 [69, 74, 77, 80].

Lubos *et al.* [34] reported that human heart failure is associated with a large up regulation of TIMP-1. However, ischemia reperfusion acutely activates MMPs [77, 79]. These observations can be explained by differential regulation between aging and hypertension, where MMP activity decreases with aging and increases with hypertension [77, 79]. Apparently, impaired turnover of ECM proteins could be an important contributory mechanism for accumulation of fibrotic tissue in the hearts due to aging [77].

Exercise training upregulates MMPs such as MMP-1, MMP-2, MMP-3 and MMP-14, thereby mitigating age related reduction in the expressions of MMPs. There are highly novel findings that are consistent with signaling pathways involving MMP regulation eliciting the protective effects of exercise training against remodelling, collagen accumulation and fibrosis. MMP-1, MMP-2, MMP-3 and MMP-14 serve as collagenases and degrade a host of ECM proteins including aggracan (MMP-1, -12 and -3), fibronectin (MMP-2, -3, -14), laminin (MMP-2, -3, -14) and gelatin (MMP-1, -2, -3, -14) [72, 81, 82]. Elevation of TIMP-1 observed with aging appeared to be consistent with upstream suppression of active MMPs such as MMP-1, -2, -3, and -14 [65, 72, 81, 82]. Additionally, exercise training in aged person substantially reduced TIMP-1 along with upregulation of MMP-1, -2, -3 and -14 levels [65]. Given that TIMP-2, TIMP-3 and TIMP-4 are not responsive to exercise training, the TIMP-1/MMP pathway has been suggested to be crucial for exercise-mediated protection against age related fibrosis [78]. Currently, TIMP-1 is considered as a target candidate for the beneficial effects of exercise [65, 78].

## 7 Endostatin and Exercise

Several members of the MMP family have been shown to be associated with ECM remodeling and these proteases mediate the proteolytic release of the angiostatic factor, endostatin from collagen [83]. Endostatin is a ~20 kDa –COOH terminal fragment of collagens [84]. In a recent study, plasma endostatin concentration has been shown to be increased in response to a single bout of exercise [85]. Regardless of the organ, time and/or the mechanisms responsible for the changed plasma level of endostatin, exercise regulates circulating levels of angiogenesis regulatory factors that could influence angiogenesis-dependent processes in the vascular system, for example, atherosclerosis [86].

Endostatin has been suggested to act as an anti-angiogenic factor by inhibiting vascular endothelial growth factor (VEGF) induced endothelial cell migration and proliferation [87, 88] and by the induction of endothelial cell apoptosis [86, 89]. However, Schmidt *et al.* [90] demonstrated that both pro-angiogenic and anti-angiogenic effects of endostatin could occur in a dose dependent manner. Interestingly, a recent study demonstrated that endostatin evokes vascular relaxation by increasing the cytosolic NO production [91], which suggests that endostatin regulates the local blood supply during strenuous physical activity.

In the angiogenic process, MMPs play critical roles in regulating endothelial cell adhesion, proliferation and migration and can, therefore, affect neovascularization [83, 92]. MMPs seem to have bilateral functions in angiogenesis. Firstly, in their active form, these enzymes facilitate the degradation of ECM components and neovascularization; and secondly they indirectly inhibit the angiogenic process of endothelial growth by generating anti-angiogenic growth factors and endostatin [87, 93]. In skeletal muscle, angiogenesis occurs as an adaptation to increased work requirements [87]. Exercise studies have focused on stimulatory (angiogenic) and inhibitory (angiostatic) factors in skeletal muscles [86, 94]. Role of angiostatic factors in human skeletal muscle and their change during exercise is an interesting aspect of exercise physiology.

## 8 Conclusion and Future Direction

Members of the MMP family are present in the skeletal muscles of healthy humans. MMP-9 is induced by a single bout of exercise, presumably by post translational activation and also by an increase in mRNA expression. In contrast, MMP-2 and MMP-14 levels increase after exhaustive exercise training [14]. Further studies are needed to better understand the mechanisms responsible for transcriptional upregulation and activation of the MMP family and to determine the biological significance of MMPs for the adaptation of the skeletal muscle to exercise.

It is currently unknown whether different exercise training programs, to include one that incorporate machine based resistance exercise and one composed of aerobic and body weight exercise such as pull-ups and sit-ups, promote different MMP

responses [95–97]. Such information would be valuable in understanding whether the type of exercise and the specific MMP response plays a role in mediating physiological adaptations to exercise training.

mRNA expression of heat shock proteins in muscle has been shown to occur depending on type and intensity of exercise [49]. Mahoney *et al.* [98] demonstrated that exercise differentially affected the expression of the genes involved in metabolism, cell growth and transcriptional activation as well as apoptosis. Genes that show identical regulatory patterns in leukocytes after exercise are (1) those associated with cell stress management e.g., HSP 90; (2) those associated with proteolysis e.g., MMPs; and (3) those associated with apoptosis e.g., Bcl-2 related anti-apoptotic proteins [11].

Although it is known that vigorous exercise and sex influences tendon metabolism and mechanical properties, it is unknown about the structural and regulatory components that contribute to the responses. It is also currently unknown how sex regulates mRNA expression of collagens, MMPs and TIMPs genes in tendons. Understanding the above will have important implications on why women have differential mRNA expression of MMPs and TIMPs than men.

Microarray technology in exercise physiology is an important tool being used currently for monitoring athletes training process. This is based on the intension of identifying exercise induced gene expression profiles or fingerprints that can be related to exercise intensity(ies) or type(s) [99]. Conceivably, an impact of exercise may be ascertained in the gene expression profiles in blood cells, for example, leukocytes and also exercising muscles and tendons.

The time course of increase in endostatin level may provide evidence of its possible vasoregulatory effect [85] i.e., endostatin could regulate blood supply during physical exercise in addition to its angiogenic effects [90]. MMPs such as MMP-2 and MMP-9 are also elevated after physical performance. Thus, intensified research on endostatin with respect to special physiological and mechanical stimuli that cause an increase in MMPs may lead to better understanding of vascular signaling during exercise in the prevention of a variety of diseases such as coronary heart diseases and diabetes.

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## References

1. Ramin A, Abbas M, Ali GA et al (2011) Effects of exhaustive aerobic exercise on matrix metalloproteases activity in athletes and non-athletes. World J Sport Sci 4:185–191
2. Prior BM, Yang HT, Terjung RL (2004) What makes vessels grow with exercise training? J Appl Physiol 97(3):1119–1128
3. Carmeli E, Haimovitch TG (2006) The expression of MMP, following immobilization and high intensity running in plantaris muscle fibre rats. Sci World J 5:542–550
4. Carmeli E, Moas M, Lennon S et al (2005) High intensity exercise increases expression of matrix metalloproteases in fast skeletal muscle fibres. Exp Physiol 90:613–619

5. Cooksle S, Hsojiss JB, Tickle SP et al (1990) Immunoassays for detection of human collagenases, stromelysins, TIMPs and enzyme inhibitor complexes. Matrix 10:285–291
6. Duffy MJ, McCarthy K (1998) Matrix metalloproteinases in cancer prognostic markers and targets for therapy. Int J Oncol 12:1343–1348
7. Ferlito S (2000) Physiological, metabolic, neuroendocrine and pharmacological regulation of nitric oxide in humans. Minerva Cardioangiol 48:169–176
8. Foda HD, Zucker S (2001) Matrix metalloproteinases in cancer invasion, metastasis and angiogenesis. Drug Discov Today 6:478–482
9. Barengo NC, Hu G, Lakka TA et al (2004) Low physical activity as a predictor for total and cardiovascular disease mortality in middle aged men and women in Finland. Eur Heart J 25:2204–2211
10. Roberts CK, Barnard RJ (2005) Effects of exercise and diet on chronic diseases. J Appl Physiol 98:3–30
11. Buttner P, Mosig S, Lechtermann A et al (2007) Exercise affects the gene expression profiles of human white blood cells. J Appl Physiol 102:26–36
12. Carmeli E, Maor M, Kodesh E (2009) Expression of superoxide dismutase and matrix metalloprotease type-2 in diaphragm muscles of young rats. J Physiol Pharmacol 60:31–36
13. Howald H, Hoppeler H, Claassen H et al (1985) Influence of endurance training on the ultrastructural composition of the different muscle fibre types in humans. Pflugers Arch 403:369–376
14. Rullman E, Norrbom J, Stromberg A et al (2009) Endurance exercise activates matrix metalloproteinases in human skeletal muscle. J Appl Physiol 106:804–812
15. Koskinen SO, Wang W, Ahtikoski AM et al (2001) Acute exercise induced changes in rat skeletal muscle mRNAs and proteins regulating type IV collagen content. Am J Physiol 280:R1292–R1300
16. Zimmerman SD, McCormick RJ, Vadlamudi RK et al (1993) Age and training alter collagen characteristics in fast and slow twitch rat limb muscle. J Appl Physiol 75:1670–1674
17. Langberg H, Rosendal L, Kjaer M (2001) Training induced changes in peritendinous type I collagen turn overdetermined by microdialysis in humans. J Physiol 534:297–302
18. Muhs BE, Gagne P, Plitas G et al (2004) Experimental hindlimb ischemia leads to neutrophil-mediated increases in gastrocnemius MMP-2 and -9 activity: a potential mechanism for ischemia induced MMP activation. J Surg Res 117:249–254
19. Haas TL, Milkiewicz M, Davis SJ et al (2000) Matrix metalloproteinase activity is required for activity-induced angiogenesis in rat skeletal muscle. Am J Physiol 279:H1540–H1547
20. Reznick AZ, Menashe O, Shai MB et al (2003) Expression of matrix metalloproteases, inhibitors and acid phosphatase in muscle of immobilized hindlimbs of rats. Muscle Nerve 27:51–59
21. Powers SK, Shanely RA (2002) Exercise induced changes in diaphragmatic bioenergetics and anti-oxidant capacity. Exerc Sport Sci Rev 30:69–74
22. Sieck GC, Prakash YS (1997) Morphological adaptations of neuromuscular junctions depend on fibre type. Can J Appl Physiol 22:197–230
23. Kjaer M (2004) Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. Physiol Rev 84:649–698
24. Powers SK, Demirel HA, Coombes JS et al (1997) Myosin phenotype and bioenergetic characteristics of rat respiratory muscles. Med Sci Sports Exerc 29:1573–1579
25. Kavanagh T, Mertens DJ, Hamm LF et al (2002) Prediction of long-term prognosis in 12169 men referred for cardiac rehabilitation. Circulation 106:666–671
26. Lee IM, Sesso HD, Oguma Y et al (2003) Relative intensity of physical activity and risk of coronary heart disease. Circulation 107:1110–1116
27. de Waard MC, van der Velden J, Bito V et al (2007) Early exercise training normalizes myofilament function and attenuates left ventricular pump dysfunction in mice with a large myocardial infarction. Circ Res 100:1079–1088
28. Kemi OJ, Høydal MA, Haram PM et al (2007) Exercise training restores aerobic capacity and energy transfer systems in heart failure treated with losartan. Cardiovasc Res 76:91–99

29. Wan W, Powers AS, Li J et al (2007) Effect of post myocardial infarction exercise training on the rennin-angiotensin-aldosterone system and cardiac function. Am J Med Sci 334:265–273
30. Xu X, Wan W, Ji L et al (2008) Exercise training combined with angiotensin II receptor blockade limits post infarct ventricular remodeling in rats. Cardiovasc Res 78:523–532
31. Braith RW, Welsch MA, Feigenbaum MS et al (1999) Neuroendocrine activation in heart failure is modified by endurance exercise training. J Am Coll Cardiol 34:1170–1175
32. Creemers EE, Cleutjens JP, Smits JF et al (2001) Matrix metalloprotease inhibition after myocardial infarction: a new approach to prevent heart failure. Circ Res 89:201–210
33. Webb CS, Bonnema DD, Ahmed SH et al (2006) Specific temporal profile of matrix metalloproteinase release occurs in patients after myocardial infarction: relation to left ventricular remodeling. Circulation 114:1020–1027
34. Lubos E, Schnabel R, Rupprecht HJ et al (2006) Prognostic value of tissue inhibitor of metalloproteinase-1 for cardiovascular death among patients with cardiovascular disease: results from the AtheroGene study. Eur Heart J 27:150–156
35. Liu JL, Irvine S, Reid IA et al (2000) Chronic exercise reduces sympathetic nerve activity in rabbits with pacing induced heart failure: a role for angiotensin II. Circulation 102:1854–1862
36. Pliquett RU, Cornish KG, Patel KP et al (2003) Amelioration of depressed cardiopulmonary reflex control of sympathetic nerve activity by short-term exercise training in male rabbits with heart failure. J Appl Physiol 95:1883–1888
37. Townend JN, al-Ani M, West JN et al (1995) Modulation of cardiac autonomic control in humans by angiotensin II. Hypertension 25:1270–1275
38. Grassi G, Cattaneo BM, Seravalle G et al (1997) Effects of chronic ACE inhibition on sympathetic nerve traffic and baroreflex control of circulation in heart failure. Circulation 96:1173–1179
39. Sun Y, Zhang JQ, Zhang J et al (2000) Cardiac remodeling by fibrous tissue after infarction in rats. J Lab Clin Med 135:316–323
40. Fraccarollo D, Galuppo P, Schmidt I et al (2005) Additive amelioration of left ventricular remodeling and molecular alterations by combined aldosterone and angiotensin receptor blockade after myocardial infarction. Cardiovasc Res 67:97–105
41. Wollert KC, Studer R, von Bullow B et al (1994) Survival after myocardial infarction in the rat. Role of tissue angiotensin converting enzyme inhibition. Circulation 90:2457–2467
42. Moldoveanu AI, Shephard RJ, Shek PN (2000) Exercise elevates plasma levels, but not gene expression of IL-1β, IL-6 and TNF-α in blood mononuclear cells. J Appl Physiol 89:1499–1504
43. Wu JV, Krouse ME, Rustagi A et al (2004) An inwardly rectifying potassium channel in apical membrane of Calu-3 cells. J Biol Chem 279:46558–46565
44. Koskinen SO, Heinemeir KM, Olesen JL et al (2004) Physical exercise can influence local levels of matrix metalloproteases and their inhibitor in tendon related connective tissue. J Appl Physiol 96:861–864
45. Morici G, Zangla D, Santoro A et al (2005) Supramaximal exercise mobilizes hematopoietic progenitors and reticulocytes in athletes. Am J Physiol Regul Integr Comp Physiol 289:R1496–R1503
46. Laterveer L, Lindley IJ, Heemskerk DP et al (1996) Rapid mobilization of hematopoietic progenitor cells in rhesus monkeys by a single intravenous injection of interleukin-8. Blood 87:781–788
47. Velders GA, Fibbe WE (2005) Involvement of proteases in cytokine induced haematopoietic stem cell mobilization. Ann N Y Acad Sci 1044:60–69
48. Connolly PH, Caiozzo VJ, Zaldivar F et al (2004) Effects of exercise on gene expression in human peripheral blood mononuclear cells. J Appl Physiol 97:1461–1469
49. Febbraio MA, Koukoulas I (2000) Hsp 72 gene expression progressively increases in human skeletal muscle during prolonged exhaustive exercise. J Appl Physiol 89:1055–1060
50. Puntschart A, Vogt M, Widmer HR et al (1996) Hsp70 expression in human skeletal muscle after exercise. Acta Physiol Scand 157:411–417
51. Zeibig J, Karlic H, Lohninger A et al (2005) Do blood cells mimic gene expression profile alterations known to occur in muscular adaptations to endurance training? Eur J Appl Physiol 95:96–104

52. Zieker D, Zieker J, Dietzsch J et al (2005) cDNA-microarray analysis as a research tool for expression profiling in human peripheral blood following exercise. Exerc Immunol Rev 11:86–96
53. Kruger K, Mooren FC (2007) T cell homing and exercise. Exerc Immunol Rev 13:37–54
54. Goda S, Inoue H, Umehara H et al (2006) Matrix metalloproteinase-1 produced by human CXCL12-stimulated natural killer cells. Am J Pathol 169:445–458
55. Baggiolini M, Dewald B, Moser B (1994) Interleukin-8 and related chemotactic cytokines – CXC and CC chemokines. Adv Immunol 55:97–179
56. Hoffmann E, Breiholz OD, Holtmann H et al (2002) Multiple control of IL-8 gene expression. J Leukoc Biol 72:847–855
57. Deroanne CF, Hamelryckx D, Ho TT et al (2005) Cdc42 down regulates MMP-1 expression by inhibiting the ERK1/2 pathway. J Cell Sci 118:1173–1183
58. Stefanidakis M, Bjorklund M, Ihanus E et al (2003) Identification of a negatively charged peptide motif within the catalytic domain of progelatinases that mediates binding of leukocyte beta2 integrin. J Biol Chem 278:34674–34684
59. Nieman DC (1997) Exercise immunology: practical applications. Int J Sports Med 18:91–100
60. Smith LL (2003) Over training, excessive exercise and altered immunity: is this a T helper-1 vs T helper-2 lymphocyte response? Sports Med 33:347–364
61. Sullivan BE, Carroll CC, Jemiolo B et al (2009) Effect of acute resistance exercise and sex on human patellar tendon structural and regulatory mRNA expression. J Appl Physiol 106:468–475
62. Kubo K, Kanehisa H, Fukunaga T (2003) Gender differences in the viscoelastic properties of tendon structures. Eur J Appl Physiol 88:520–526
63. Miller BF, Hansen M, Olesan JL et al (2007) Tendon collagen synthesis at rest and after exercise in women. J Appl Physiol 102:541–546
64. Magnusson SP, Hansen M, Langberg H et al (2007) The adaptability of tendon to loading differs in men and women. Int J Exp Pathol 88:237–240
65. Westh E, Kongsgaard M, Bojsen-Moller J et al (2008) Effect of habitual exercise on the structural and mechanical properties of human tendon, in vivo in men and women. Scand J Med Sci Sports 18:23–30
66. Kongsgaard M, Reitelseder S, Pedersen TG et al (2007) Region specific patellar tendon hypertrophy in humans following resistance training. Acta Physiol (Oxf) 191:111–121
67. Miller BF, Olesen JL, Hansen M et al (2005) Coordinated collagen and muscle protein synthesis in human patella tendon and quadriceps muscle after exercise. J Physiol 567:1021–1038
68. Taylor RP, Starnes JW (2003) Age, cell signaling and cardioprotection. Acta Physiol Scand 178:107–116
69. Goldspink DF (2005) Ageing and activity: their effects on the functional reserve capacities of the heart and vascular smooth and skeletal muscle. Ergonomics 48:1334–1351
70. Thomas DP, Cotter TA, Li X et al (2001) Exercise training attenuates ageing associated increases in collagen and collagen cross-linking of the left but not the right ventricle in the rat. Eur J Appl Physiol 85:164–169
71. Thomas DP, Zimmerman SD, Hansen TR et al (2000) Collagen gene expression in rat left ventricle: interactive effect of age and exercise training. J Appl Physiol 89:1462–1468
72. Goldsmith EC, Borg TK (2002) The dynamic interaction of the extracellular matrix in cardiac remodeling. J Card Fail 8:S314–S318
73. Ohtake Y, Tojo H, Seiki M (2006) Multifunctional roles of MT1-MMP in myofiber formation and morphostatic maintenance of skeletal muscle. J Cell Sci 119:3822–3832
74. Dennis RA, Zhu H, Kortebein PM et al (2009) Muscle expression of genes associated with inflammation, growth, and remodeling is strongly correlated in older adults with resistance training outcomes. Physiol Genomics 38:169–175
75. Ingber DE (1990) Fibronectin controls capillary endothelial cell growth by modulating cell shape. Proc Natl Acad Sci U S A 87:3579–3583
76. Dennis RA, Przybyla B, Gurley C et al (2008) Ageing alters gene expression of growth and remodeling factors in human skeletal muscle both at rest and in response to acute resistance exercise. Physiol Genomics 32:393–400

77. Kwak HB, Kim JH, Joshi K et al (2011) Exercise training reduces fibrosis and matrix metalloproteinase dysregulation in the aging rat heart. FASEB J 25:1106–1117
78. Bonnema DD, Webb CS, Pennington WR et al (2007) Effects of age on plasma matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs). J Card Fail 13:530–540
79. Booth FW, Gordon SE, Carlson CJ et al (2000) Waging war on modern chronic diseases: primary prevention through exercise biology. J Appl Physiol 88:774–787
80. Greiwe JS, Cheng B, Rubin DC et al (2001) Resistance exercise decreases skeletal muscle tumor necrosis factor alpha in frail elderly humans. FASEB J 15:475–482
81. Jugdutt BI (2003) Remodelling of the myocardium and potential targets in the collagen degradation and synthesis pathways. Curr Drug Targets Cardiovasc Haematol Disord 3:1–30
82. Vincenti MP (2001) The matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP) genes. Transcriptional and posttranscriptional regulation, signal transduction and cell-type-specific expression. Methods Mol Biol 151:21–48
83. Helijasvaara R, Nyberg P, Luostarinen J et al (2005) Generation of biologically active endostatin fragments from human collagen XVIII by distinct matrix metalloproteases. Exp Cell Res 307:292–304
84. Zatterstrom UK, Felbor U, Fukai N et al (2000) Collagen XVIII/endostatin structure and functional role in angiogenesis. Cell Struct Funct 25:97–101
85. Gu JW, Gadonski G, Wang J et al (2004) Exercise increases endostatin in circulation of healthy volunteer. BMC Physiol 4:2
86. Rullman E, Rundqvist H, Wagsater D et al (2007) A single bout of exercise activates matrix metalloprotease in human skeletal muscle. J Appl Physiol 102:2346–2351
87. O'Reilly MS, Boehm T, Shing Y et al (1997) Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. Cell 88:277–285
88. Lamalice L, Le Boeuf F, Huot J (2007) Endothelial cell migration during angiogenesis. Circ Res 100:782–794
89. Shichiri M, Hirata Y (2004) Antiangiogenesis signals by endostatin. FASEB J 15:1044–1053
90. Schmidt A, Addicks K, Bloch W (2004) Opposite effects of endostatin on different endothelial cells. Cancer Biol Ther 3:1162–1166
91. Wenzel D, Schmidt A, Reimann K et al (2006) Endostatin, the proteolytic fragment of collagen XVIII, induces vasorelaxation. Circ Res 98:1203–1211
92. Hiscock N, Fischer CP, Pilegaard H et al (2003) Vascular endothelial growth factor mRNA expression and arteriovenous balance in response to prolonged, submaximal exercise in humans. Am J Physiol 285:H1759–H1763
93. Dong Z, Crawford HC, Lavrovsky V et al (1997) A dominant negative mutant of jun blocking 12-o-tetradecanoylphorbol-13-acetate induced invasion of mouse keratinocytes. Mol Carcinog 19:204–212
94. Suhr F, Brixius K, Marees MD et al (2007) Effects of short-term vibration and hypoxia during high intensity cycling exercise on circulating levels of angiogenic regulators in humans. J Appl Physiol 103:474–483
95. Stellas D, Hamidieh AE, Patsavoudi E (2010) Monoclonal antibody 4C5 prevents activation of MMP-2 and MMP-9 by disrupting their interaction with extracellular Hsp90 and inhibits formation of metastatic breast cancer cell deposits. BMC Cell Biol 11:51
96. Niessner A, Richter B, Penka M et al (2006) Endurance training reduces circulating inflammatory markers in persons at risk of coronary events: impact on plaque stabilization? Atherosclerosis 186:160–165
97. Ra HJ, Parks WC (2007) Control of matrix metalloprotease catalytic activity. Matrix Biol 26:587–596
98. Mahoney DJ, Parise G, Melov S et al (2005) Analysis of global mRNA expression in human skeletal muscle during recovery from endurance exercise. FASEB J 19:1498–1500
99. Fehrenbach E, Zieker D, Niess AM et al (2003) Microarray technology–the future analyses tool in exercise physiology? Exerc Immunol Rev 9:58–69