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Molecular Effects of Exercise in Rheumatoid Arthritis

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1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder that affects approximately 1% of adults in the United States (Alamanos and Drosos 2005). Clinically, RA is manifested by pain and swelling of joints, disability, and diminished overall patient well-being (Scott et al. 2010). The etiology of RA remains enigmatic, but a range of genetic and environmental factors closely associated with RA have been identified over the past two decades. It is now known that the pathogenic process of RA involves the initiation and establishment of autoimmunity, followed by an inflammatory response, angiogenesis to maintain the chronic inflammatory state, and tissue degradation of the joint (Scott et al. 2010).

Despite the advances in the pharmacological therapies of RA over the past years, most patients (85-90%) do not achieve full remission, with up to 15% showing little clinical improvement in outcomes (Geborek et al. 2002; van der Woude et al. 2009). Accumulating studies have demonstrated the effectiveness of non-drug treatment modalities, e.g. exercise and physical activity, as an adjunct to drug therapy in patients with RA (Stenstrom and Minor 2003; Lundberg and Nader 2008). As a result, physical training is now a standard part of treatment for RA patients.

This chapter will first review results from randomized clinical trials which investigated the effects of exercise on RA disease activity. In RA patients, exercise was demonstrated to improve physical performance, cardiorespiratory fitness and muscle strength without worsening joint inflammation (Ekblom et al. 1975). Subsequent clinical studies have not only shown that exercise leads to meaningful effects on physical performance and fitness, but exercise can also reduce RA disease activity, measured by the number of swollen or tender joints (Stenstrom and Minor 2003). At the systemic level, there are several reports indicating a reduction in circulating levels of inflammatory biomarkers following long-term physical exercise (Dekker et al. 2007; Olson et al. 2007). These beneficial effects of exercise have been observed following different types of physical activity, after short-term and long-term (>2 years) exercise programs, at different phases of the disease course, and even in patients with high disease activity (van den Ende et al. 2000; Stenstrom and Minor 2003).

Next, by focusing on the effects of exercise, delivered in the form of physiologically relevant mechanical loading, this review will provide updated insights into exercise at both the systemic and local (e.g. cartilage and synovium) levels. Studies indicate that exercise

activates an anti-rheumatologic response which includes an inhibition of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) in healthy and diabetic patients (Lundberg and Nader 2008). There is also evidence regarding the potential beneficial effects of exercise in preventing or suppressing the destructive consequences of inflammation in joint tissues (Ferretti et al. 2005; Ferretti et al. 2006). Clearly, the mechanical loading component of the exercise stimulus might be one of the mechanisms by which exercise exerts a protective anti-inflammatory effect at the local tissue level by preventing the expression of pro-inflammatory molecules. For example, studies have shown that moderate mechanical loading *in vitro* and *in vivo* upregulate production of anti-inflammatory cytokines interleukin (IL)-4 and IL-10, and suppress expression of IL-1 β (Millward-Sadler and Salter 2004; Ferretti et al. 2005).

This will be followed by a discussion of how anti-inflammatory cytokines may work in concert with the anti-catabolic nature of physiologic biomechanical signals to mediate the protective effects of exercise. Elevated levels of pro-inflammatory cytokines such as IL-1 β and TNF- α stimulate production of proteolytic enzymes matrix metalloproteinases (MMPs) and A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS) which mediate the cartilage destruction process in RA (Sun 2010). Studies have demonstrated physiological loading suppresses MMP and ADAMTS expression in both inflamed and non-inflamed joints to exert protective effects on the synovium and articular cartilage (Ferretti et al. 2005; Ferretti et al. 2006; Leong et al. 2010). The most recent progress on these mechanotransduction pathways which regulate the loading-induced anti-inflammatory and anti-catabolic responses will be presented, as well as possible crosstalk between these two pathways.

The chapter will conclude with perspectives on how identification of the signaling pathways activated by exercise will lead to the discovery of new treatment targets and development of novel treatment strategies which may have significant clinical potential in treating rheumatoid arthritis.

2. Exercise in rheumatoid arthritis treatment

The primary goals of RA treatment are to suppress inflammation and limit or prevent joint damage, while relieving pain and improving the patients' quality of life (Kowh et al. 2002). There is currently no cure for rheumatoid arthritis and treatment strategies involve a combination of drugs as well as non-pharmacologic treatments such as exercise and physical therapy (Smolen et al. 2010). As soon as the diagnosis for RA is established, prescribed medications include disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs, glucocorticoids, and TNF- α inhibitors (Deighton et al. 2009; Bijlsma 2010).

Although drug treatment helps improve disease outcome, exercise is still a vital part of rheumatoid arthritis treatment. For the general adult population, the American College of Sports Medicine and the Heart Association recommends at least 30 minutes of moderate-intensity exercise five days a week (Haskell et al. 2007). The benefits of regular exercise for healthy adults are well accepted, and include reducing the risk of coronary artery disease and improving cardiovascular health (Muller-Riemenschneider et al. 2011), reducing adiposity (Brukner and Brown 2005), and increasing muscle strength (Brentano and Martins Kruel 2011; Peterson and Gordon 2011). Randomized clinical trials have reported that the

health benefits of exercise are also obtained in patients with RA without adverse effects on disease activity (van den Ende et al. 2000; de Jong et al. 2003; Bilberg et al. 2005; Melikoglu et al. 2006; van den Berg et al. 2006; Neuberger et al. 2007; Baillet et al. 2009; Lemmey et al. 2009). Furthermore, exercise at a high intensity, but within a physiologic range, was more effective in increasing physical function when compared to low intensity exercise (van den Ende et al. 2000; Lemmey et al. 2009).

2.1 Description of prescribed exercises

Based on the beneficial effects of physical activity in RA clinical trials, exercise programs for people with RA typically involve a combination of stretching exercises, aerobic training, and strength training (Stenstrom and Minor 2003; Cairns and McVeigh 2009; Forestier et al. 2009; Hurkmans et al. 2009; Baillet et al. 2010; Metsios et al. 2010). Table 1 summarizes commonly prescribed modes of exercise and their recommended doses (Resnick 2001; Medicine et al. 2009). Exercise programs are initially prescribed and supervised by an experienced professional, who tailors the program according to the patient's disease activity and symptoms (de Jong and Vliet Vlieland 2005). Since many RA patients have severe disability and a below average physical capacity, the intensity of training is initially low and gradually increased. If pain or swelling appears during exercise, patients are advised to reduce exercise intensity and/or duration until the pain or swelling subsides.

Daily stretching is recommended to decrease joint stiffness and maintain or increase pain-free range of motion (ROM). Patients with RA should begin their exercise programs with two to three daily repetitions of each stretching and ROM exercise, and eventually progress to 10 repetitions daily (Nieman 2000; Medicine et al. 2009). Range of motion exercises should be performed slowly with appropriate support, and should not be attempted in a rapid manner with bouncing movements (Resnick 2001).

Walking, cycling, rowing, swimming, water aerobics, and dance are examples of aerobic exercises prescribed to RA patients. Regular brisk walking in previously sedentary adults improved aerobic fitness and reduced cardiovascular risk in healthy adults (Murphy et al. 2002). Cycling at 70-80% predicted maximum heart rate significantly improved aerobic capacity, muscle strength, and joint mobility in RA individuals when compared to patients who only performed ROM exercises (van den Ende et al. 1996). Hydrotherapy, which combines elements of warm water immersion and exercise, was reported to improve the physical and emotional states of RA patients. Specifically, there was a reduction in joint tenderness and an improvement in knee range of motion, and emotional and physiological well-being (Hall et al. 1996). Moderately intensive pool exercise therapy in patients with RA did not improve aerobic capacity, but there were significant improvements in the muscle endurance in the lower and upper extremities (Bilberg et al. 2005). Although dance programs are not well-studied in the RA population, one study did report that female participants in a four week dance-based exercise program involving slow body movements exhibited significant improvements in locomotor ability (Moffet et al. 2000).

Loss of muscle mass and strength is a common characteristic in RA patients (Pedersen and Saltin 2006), and therefore muscle strengthening exercises are often recommended. These high-intensity training exercises include the leg press, chest press, leg extension, seated rowing, leg curl, triceps extension, standing calf raises, and bicep curl (Lemmey et al. 2009). Progressive resistance training (PRT) programs involving the large muscle groups as well as

hand exercises have demonstrated improvements in physical function, increase in muscle mass, and reduction in fat mass (Hakkinen et al. 2005; Marcora et al. 2005; Lemmey et al. 2009). Early RA patients who enrolled in a two year strength training program exhibited significant improvements not only in muscle strength, but also showed reductions in systemic inflammation, pain, and disease activity (Hakkinen et al. 2001). With continued training, these gains in muscle strength can be maintained (de Jong et al. 2009).

Class of Exercise	Type of exercise	Recommended intensity/frequency/ duration
Flexibility	Stretching	Daily, before and after aerobic exercise. Hold stretch for 10-30 seconds, 3-5 repetitions
	Range of motion	Full range of motion for all joints daily
Aerobic	Walking Cycling Rowing Swimming Water aerobics Dance	60-80% maximum heartrate Up to 30 minutes/session 3-5 days/week
Strength	Free weights Weight machines Elastic bands	At least 1 set of 2-3 reps (up to 3 sets of 10 reps) at 80% of the 1-repetition maximum (the maximum load lifted for each of the prescribed exercises) 2-3 days/week

Table 1. Exercise management guidelines for the treatment of RA (Resnick 2001; Lemmey et al. 2009; Medicine et al. 2009)

2.2 Beneficial effects of exercise in RA

Many RA patients suffer from cachexia, which is characterized by a decrease in muscle mass along with an increase in fat mass. This is unlike the cachexia associated with conditions such as HIV-AIDS, cancers, chronic obstructive pulmonary disease (COPD), and old age, which is defined by significant muscle wasting alone, and is usually characterized by weight loss (Roubenoff et al. 1992). These changes in body composition may increase the risk of developing diabetes and cardiovascular disease (Roubenoff et al. 1992; Lavie et al. 2009), as well as lead to muscle weakness, decreased physical activity, pain, and fatigue, which together further adversely affect skeletal health (Hakkinen 2004). Muscle strengthening is important not only to regain normal physical function, but it is also necessary for joint stability, which may protect against the development of osteoarthritis (Sun 2010). Exercise has been demonstrated to significantly improve many of the symptoms of rheumatoid arthritis, including disability, pain, joint stiffness and fatigue (Hakkinen 2004; Marcora et al. 2005; Neill et al. 2006; Brorsson et al. 2009; Lemmey et al. 2009). Progressive resistance training was reported to increase muscle mass, improve physical function, and reduce disabilities associated with RA (Marcora et al. 2005; Lemmey et al. 2009). High intensity

resistance exercise also has been reported to reverse RA cachexia by restoring muscle mass (Marcora et al. 2005).

Because of RA cachexia, it was hypothesized that patients with RA were resistant to the anabolic effects of exercise (Rall et al. 1996). However, no differences in the physiological properties of muscle that determine force, including contractile properties, voluntary activation capacity, and contraction velocity, were found between cachectic RA patients and healthy controls (Matschke et al. 2010). Recent clinical trials have found that the muscle of RA patients respond in similar manner to that of muscle in healthy individuals. The strengthening effects of PRT in RA patients (Lemmey et al. 2009) are similar to those observed in healthy middle-aged subjects (Morse et al. 2007). Studies which directly compared RA patients with age-matched healthy patients reported similar findings. Following resistance and aerobic exercise training, comparable increases in strength and thigh muscle cross-section, and decreases in thigh fat thickness were found in both RA and healthy female patients (Hakkinen et al. 2005). Together, these studies demonstrate that exercise training increases muscle mass, strength, and improves physical function in a similar manner in patients with RA and in healthy individuals. In fact, the inclusion of high-intensity PRT is recommended in RA treatment strategies to counteract the effects of rheumatoid cachexia (Pedersen and Saltin 2006; Lemmey et al. 2009).

2.3 Anti-inflammatory effects of exercise

Regular exercise, such as endurance training, can reduce basal levels of many inflammatory mediators/markers (King et al. 2003). Consequently, exercise has been recommended as an anti-inflammatory therapy in chronic inflammatory disorders such as RA (Kowh et al. 2002), and its effects are observed on the systemic and local levels.

2.3.1 Systemic effects

Physical inactivity, a common consequence of RA symptoms, leads to the accumulation of visceral fat and activation of inflammatory pathways (Walsh et al. 2011). Chronic inflammation can also drive the development of insulin resistance and atherosclerosis (Handschin and Spiegelman 2008). Increased physical activity has been reported to reduce inflammation in non-RA patients, as indicated by a downregulation of inflammation markers/mediators (Petersen and Pedersen 2005). In another demonstration of the anti-inflammatory effects of exercise, a model of low grade inflammation was established in healthy volunteers through the administration of a low dose of *E. coli* endotoxin. While circulating levels of TNF- α were increased in resting individuals, this increase was blocked in subjects who exercised prior to the endotoxin administration (Starkie et al. 2003), suggesting exercise may inhibit the production of TNF- α . Together, it is possible the anti-inflammatory effects of exercise are due to a decrease in visceral fat mass as well as the production of anti-inflammatory factors.

With exercise, there is a release of inflammatory-related cytokines from muscle into the circulation. IL-6 is the first cytokine released during exercise. Levels of circulating IL-6 increase exponentially after exercise and then decline post-exercise (Petersen and Pedersen 2006, Walsh et al. 2011). It is unclear whether this acute elevation in IL-6 modulates inflammatory processes during physical activity. Although IL-6 is a pro-inflammatory cytokine in the rheumatic joint, recent studies suggest the transient response of IL-6 may

play a metabolic, rather than an immunological role (Walsh et al. 2011). Following the increase of IL-6 in response to exercise in healthy individuals, IL-10 and IL-1 receptor antagonist (IL-1ra) are released into the circulation (Petersen and Pedersen 2006). Notably, an infusion of IL-6 enhanced plasma levels of IL-1ra and IL-10, (Steensberg et al. 2003). This suggests that the anti-inflammatory effect of exercise can be attributed, at least in part, to the induction of IL-6 and the creation of an anti-inflammatory environment (Table 2). Of note, no changes in serum IL-6 were detected in RA patients after exercise, but this might be attributable to a less strenuous exercise regimen when compared to healthy individuals (Knudsen et al. 2008). It is also possible that the anti-inflammatory effect of exercise is blunted in patients with RA, but this requires further study.

Type of exercise	Beneficial effect on health
Aerobic exercise (humans)	Increase plasma levels of IL-10, IL-1ra (Walsh et al. 2011)
Cycling (humans)	Suppress endotoxin-induced TNF- α (Starkie et al. 2003)
Strength training (humans)	Increase IL-15 (Pedersen and Febbraio 2008)
Continuous passive motion (rabbits)	Suppression of proteoglycan loss Downregulation of MMP-1 Upregulation of IL-10 (Ferretti et al. 2005; Ferretti et al. 2006)
Continuous passive motion (rats)	Suppression of proteoglycan loss Downregulation of MMP-1, -3 (Leong et al. 2010; Leong et al. 2011)

Table 2. Anti-inflammatory and anti-catabolic effects of exercise

2.3.2 Local effects on cartilage

Clinical trials investigating the anti-inflammatory effect of exercise in the articular cartilage of RA patients are lacking, but results from clinical studies of osteoarthritis patients and animal models of RA suggest that moderate exercise has an anti-inflammatory effect on cartilage. Following acute resistance exercise, a significant increase in IL-10 was observed in the intra-articular and synovial spaces of subjects who exercised when compared to a non-exercise group (Helmark et al. 2010). Increases in IL-10 expression were also reported in chondrocytes in antigen-induced arthritis, an animal model of rheumatoid arthritis, after two weeks of continuous passive motion when compared to immobilized joints (Ferretti et al. 2005; Ferretti et al. 2006). Continuous passive motion also suppressed expression of IL-1 β and inflammatory mediator COX-2 (Ferretti et al. 2006). Together, these data suggest that physiologic loading has the potential to generate anti-inflammatory biomechanical signals in cartilage, at least in part, by inducing IL-10.

To test the direct effect of IL-10 on rheumatic activity, collagen-induced arthritis mice were treated with recombinant IL-10, which resulted in a mild, but significant suppression of arthritic phenotype/symptoms (Johansson et al. 2001). Endogenous IL-10 plays a pivotal role in the regulation of antigen (streptococcal cell wall)-induced arthritis (Lubberts et al. 1998), since the blocking of endogenous IL-10 with anti-IL-10 antibodies resulted in a

sustained arthritis with denser synovial infiltrates as well as enhanced cartilage damage. Adding exogenous IL-10 further enlarged the suppressive effect of endogenous IL-10. However, these findings require further investigation in human clinical trials of RA patients.

2.4 Anti-catabolic effects of exercise on cartilage

Considering cartilage destruction is a hallmark of RA, the role of exercise in maintaining cartilage matrix integrity is of great importance (Table 2) (Maini and Feldmann 2004). Articular cartilage functions as a nearly frictionless bearing surface while uniformly transferring loads on underlying bone and preventing high stress concentrations. Cartilage consists of one cell type, the chondrocyte, embedded in an extracellular matrix of mainly type II collagen and proteoglycans (Milner 2008). Physiologic loading of the cartilage tissue is required to maintain tissue homeostasis, while non-physiologic loading (disuse and overuse) promotes its degradation (Sun 2010). Intensive dynamic and weight-bearing exercises were originally considered detrimental for patients with RA due to concerns of exacerbating disease, (van den Ende et al. 1996), but studies have shown such exercise does not cause an increase in the rate of damage to either large (de Jong et al. 2003) or small joints (de Jong et al. 2004). There were no significant differences in the rate of damage of large joints 18 months following the end of a high-intensity program between RA patients who discontinued exercise and those who were still exercising (de Jong et al. 2009). Furthermore, levels of cartilage oligomeric matrix protein (COMP), a measure of cartilage damage were unchanged after 3 months of exercise in RA patients, suggesting exercise did not cause significant damage to the cartilage matrix (de Jong et al. 2008). Exercise may also enhance joint lubrication, further acting to promote the health of the RA joint. During joint movement, synovial fluid is squeezed out from between the two surfaces of the joint, resulting in fluid film lubrication (Isenberg et al. 2004). Lubricin, a mucinous glycoprotein secreted by synovial fibroblasts, is the factor responsible for lubrication (Jay et al. 2001), and reduced levels of this protein found in RA patients may increase joint friction and promote cartilage degradation (Jay et al. 2004; Elsaid et al. 2007). However, whether exercise increases lubricin expression in patients with RA has not yet been determined. Exercise also promotes adequate strength of the muscles and surrounding joint soft tissues, providing optimal joint stability, alignment and attenuation of impact and compressive forces (Sun 2010).

After vigorous exercise in patients with moderate disease activity, a reduction in the number of diseased joints is observed (Minor et al. 1989; van den Ende et al. 1996). Animal studies have demonstrated physiologic loading of joints exerts beneficial effects by suppressing the activity of proteolytic enzymes in healthy and arthritic rats. Passive joint motion prevented cartilage destruction due to inactivity and downregulated MMPs 1 and 3 (Leong et al. 2010; Leong et al. 2011). In antigen-induced rabbits, passive motion prevented proteoglycan loss and suppressed expression of MMP-1 (Ferretti et al. 2005; Ferretti et al. 2006).

3. Mechanisms of exercise in rheumatoid arthritis treatment

Although the beneficial effects of exercise for rheumatoid arthritis patients are well documented, the mechanisms are still largely unclear. As detailed previously, the effects of

exercise are commonly characterized as anti-inflammatory and anti-catabolic. Each of these components is mediated by distinct signalling pathways and evidence indicates crosstalk between these pathways (see Figure 1 for hypothesized pathways/mechanisms).

3.1 Anti-inflammatory signaling

One of the first evidences of anti-inflammatory signalling in chondrocytes was the elucidation of the $\alpha 5\beta 1$ integrin/IL-4 pathway. In this pathway, mechanical stimulation of normal chondrocytes acts through the $\alpha 5\beta 1$ integrin to release IL-4, which acts in an autocrine/paracrine manner. Following IL-4 release, there is a decrease in MMP-3 and an increase in aggrecan mRNA, resulting in a net increase in cartilage extracellular matrix production (Millward-Sadler and Salter 2004). The transcription factor Signal Transducer and Activator of Transcription 6 (STAT6) plays a principal role in IL-4 signaling as demonstrated in mice lacking STAT6 that show a similar phenotype as mice lacking the IL-4 receptor alpha (IL-4R α) (Takeda et al. 1996). IL-4 stimulates intracellular signaling pathways including the recruitment of STAT6 to the IL-4R α . STAT6 binds to specific phosphotyrosine residues within the IL-4R α (Ryan et al. 1998). In this complex, STAT6 is quickly phosphorylated by a JAK-dependent mechanism. After phosphorylation, STAT6 leaves the receptor, dimerizes, and migrates to the nucleus where it binds to specific DNA sequences in the promoter of genes (Darnell 1997). It is believed that STAT6 is tightly regulated, because in the absence of IL-4 stimulation, STAT6 is quickly deactivated (Andrews et al. 2002). Methylation of STAT6 is a regulator of STAT6 activity, necessary for optimal STAT6 phosphorylation, nuclear translocation, and DNA-binding activity (Chen et al. 2004). Accumulating evidence suggests that IL-4 STAT6 is a central anti-rheumatoid signaling pathway because it upregulates three factors known to antagonize the actions of specific pro-inflammatory agents implicated in RA: (1) soluble IL-1 receptor antagonist (sIL-1ra); (2) tristetraprolin (TTP), which antagonizes TNF- α ; and (3) the β_3 integrin, which was shown to antagonize the angiogenic actions of vascular endothelial growth factor (VEGF) (Vannier et al. 1992; McHugh et al. 2001; Suzuki et al. 2003).

While the mechanisms underlying the anti-inflammatory effects of IL-10 are largely unknown in chondrocytes, studies which overexpress IL-10 provide insight on the downstream targets of IL-10. IL-10 treatment in an antigen-induced arthritis animal model resulted in a marked reduction of TNF- α levels (Lubberts et al. 1998). In human chondrocytes treated with TNF- α , IL-10 overexpression suppressed MMP-13 levels and antagonized the TNF- α -mediated suppression of aggrecan (Muller et al. 2008). It has been hypothesized that IL-10 may exert its effects by stimulating the production of endogenous TNF- α inhibitors such as soluble TNF- α receptors (Fernandes et al. 2002).

3.2 Anti-catabolic signaling

In vivo, motion-based therapies have been demonstrated to mitigate joint inflammation in animal models of antigen-induced arthritis. Mechanical signals generated from these passive joint motion therapies were reported to be potent inhibitors of pro-inflammatory gene induction and inhibit expression of catabolic mediators, e.g., IL-1 β , COX-2, and MMP-1 (Ferretti et al. 2005; Ferretti et al. 2006). At low magnitudes *in vitro*, biomechanical signals inhibit IL-1 β - or TNF- α -induced transcriptional activation of COX-2, MMPs, IL-1 β , and

other pro-inflammatory molecules (Chowdhury et al. 2003; Agarwal et al. 2004; Ferretti et al. 2005; Chowdhury et al. 2006; Deschner et al. 2006).

Exposure of meniscal or articular chondrocytes to proinflammatory cytokines (e.g. IL-1 β and TNF- α) is reported to result in the expression of cyclo-oxygenase 2, inducible nitric oxide synthase, and genes involved in cartilage catabolism, such as matrix metalloproteinases 9 and 13 (Gassner et al. 1999). By contrast, when cells are subjected to mechanical stimuli in the form of cyclic tensile strain, they display a blunted response to cytokine exposure, thereby antagonizing the proinflammatory and catabolic effects of these cytokines (Ferretti et al. 2006; Madhavan et al. 2006). Interestingly, this anti-catabolic response seems to be mediated by inhibition of nuclear translocation of Nuclear factor-kappa B (NF- κ B) and modulation of upstream signaling events associated with NF- κ B, suggesting that mechanical activity can act at multiple points within the proinflammatory signaling network to counteract cytokine-induced proinflammatory gene expression (Dossumbekova et al. 2007). NF- κ B transcription factors regulate a wide range of pro-inflammatory and anti-apoptotic genes, and are involved in both acute and chronic inflammatory responses. NF- κ B is a rapid response, multiple-stimuli inducible transcription factor that is controlled by sequential signal activation cascades (Seguin and Bernier 2003). In the classical NF- κ B signaling pathway, binding of pro-inflammatory mediators, such as IL-1 β , TNF- α , and/or LPS to their cognate receptors leads to activation of a series of receptor-associated signaling molecules leading to activated NF- κ B, which translocates to the nucleus, where it binds to the consensus sequences of several genes including pro-inflammatory cytokines and mediators (Ghosh and Karin 2002; Hoffmann et al. 2002; Liacini et al. 2003). Mechanical signals of low/physiological magnitudes block the IL-1 β -induced transcriptional activity of NF- κ B by intercepting multiple steps in the NF- κ B signaling cascade. In chondrocytes, cyclic tensile strain of low magnitudes does not appear to inhibit IL-1 β , TNF- α , or LPS receptor-mediated pro-inflammatory gene induction (Agarwal et al. 2004; Dossumbekova et al. 2007; Madhavan et al. 2007). These findings suggest that mechanical signals use specific target sites to trigger NF- κ B signaling.

Another transcriptional regulator which plays a critical role in cartilage homeostasis is CBP/p300-interacting transactivator with ED-rich tail 2 (CITED2). CITED2 expression is increased by moderate flow shear (5 dyn/cm²), intermittent hydrostatic pressure (1-5 MPa), and joint motion (Yokota et al. 2003; Leong et al. 2011). The induction of CITED2 *in vivo* by joint motion loading was correlated with the downregulation of MMP-1 and the maintenance of cartilage matrix integrity (Leong et al. 2011), suggesting it plays a key role in mediating the anti-catabolic effects of moderate loading. The induction of CITED2 by physiologic loading was mediated by mitogen-activated protein kinase (MAPK) p38 δ , and CITED2 regulated the transcription of MMPs (ie. MMP-1) by competing with MMP transactivator ETS-1 for binding to limiting amounts of co-activator p300 (Leong et al. 2011).

3.3 Crosstalk between anti-inflammatory and anti-catabolic responses

There is also evidence of crosstalk between the anti-inflammatory and anti-catabolic pathways. CITED2, induced by p38 δ , has also been demonstrated to be upregulated in response to IL-4 (Sun et al. 1998), raising the possibility these two pathways could work in synergy. Furthermore, treatment strategies involving gene transfer of IL-4 or IL-10

combined with mechanical stimulation may augment the chondroprotective effects of exercise. However, these hypotheses still require further investigation.

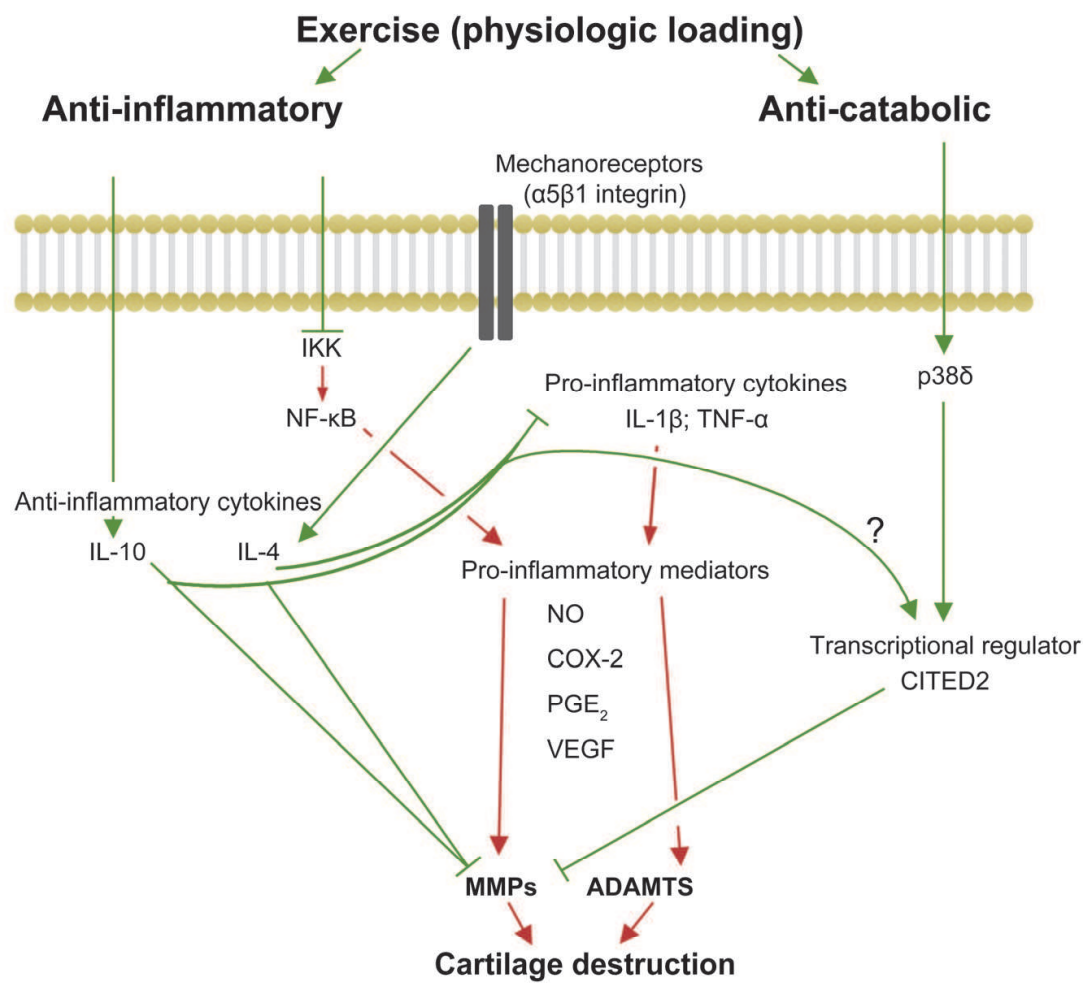


Fig. 1. Hypothesized anti-inflammatory and anti-catabolic mechanisms underlying the effects of exercise in suppressing cartilage destruction in arthritis.

4. Conclusion

Compelling evidence suggests that physiologic exercise exerts beneficial effects in rheumatoid arthritis patients that not only increases quality of life but also suppresses disease activity. The beneficial effects are dependent on the mechanical nature of exercise, including the loading intensity, frequency, and duration. Exercise regimens may have varying effects with age and stage of disease. Furthermore, elucidating mechanisms underlying these beneficial effects of exercise may lead to the development of novel therapeutic strategies to prevent joint destruction in rheumatoid arthritis.

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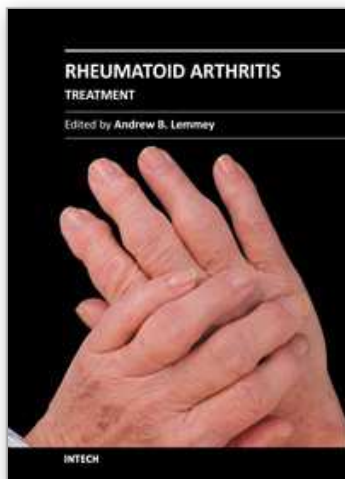
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The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 17 chapters, with contributions from numerous countries (e.g. UK, USA, Canada, Japan, Sweden, Turkey, Bosnia and Herzegovina, Slovakia), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Treatment will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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