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Invited Review Article

Effects of resistance training on the inflammatory response

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Abstract

Resistance training (RT) is associated with reduced risk of low grade inflammation related diseases, such as cardiovascular disease and type 2 diabetes. The majority of the data studying cytokines and exercise comes from endurance exercise. In contrast, evidence establishing a relationship between RT and inflammation is more limited. This review focuses on the cytokine responses both following an acute bout, and after chronic RT. In addition, the effect of RT on low grade systemic inflammation such as individuals at risk for type 2 diabetes is reviewed. Cytokines are secreted proteins that influence the survival, proliferation, and differentiation of immune cells and other organ systems. Cytokines function as intracellular signals and almost all cells in the body either secrete them or have cytokine receptors. Thus, understanding cytokine role in a specific physiological situation such as a bout of RT can be exceedingly complex. The overall effect of long term RT appears to ameliorate inflammation, but the specific effects on the inflammatory cytokine, tumor necrosis factor alpha are not clear, requiring further research. Furthermore, it is critical to differentiate between chronically and acute Interleukin-6 levels and its sources. The intensity of the RT and the characteristics of the training protocol may exert singular cytokine responses and as a result different adaptations to exercise. More research is needed in the area of RT in healthy populations, specifically sorting out gender and age RT acute responses. More importantly, studies are needed in obese individuals who are at high risk of developing low grade systemic inflammatory related diseases. Assuring adherence to the RT program is essential to get the benefits after overcoming the first acute RT responses. Hence RT could be an effective way to prevent, and delay low grade systemic inflammatory related diseases.

Key Words: Cytokines, IL-6, inflammatory markers, acute resistance exercise, resistance training

Introduction

It is well established that long term resistance training (RT) results in health benefits. RT improves the metabolic profile in type 2 diabetes (T2DM) [1], slows the progression of age-related sarcopenia [2], and prevents osteoporosis [3]. Resistance exercise is also associated with reduced risk of low grade inflammation related diseases [4]. Indeed, RT training can prevent T2DM and cardiovascular diseases. Lately, there has been increased interest in the effects of exercise on inflammation [5-7]. This interest was generated after Pedersen *et al*. [8] reported that muscle tissue could release cytokines, such as interleukin 6 (IL-6).

Cytokines play a central role initiating the inflammatory response [9].The majority of the data reporting effects of cytokines on exercise are derived from studies involving endurance exercise training [10-13]. In contrast, the evidence regarding the relationship between RT and inflammation is more limited [14]. Endurance exercise physiology as well as cytokine responses differ from RT [15]. RT is defined as performance of static or dynamic muscle contractions against external resistance of varying intensities [16].

A single bout of RT increases plasma cytokines, paradoxically, the long term effects due to adaptation to training result in lower plasma pro-inflammatory cytokines both at rest and as a response to exercise. This is evident when comparing plasma cytokines levels of trained versus untrained individuals, or pre- versus post-training in the same person.

This review will focus on the cytokine responses after an acute bout of resistance training and after long term RT. In addition, we will address the effect of resistance training on low grade systemic inflammation in people at risk of T2DM.

Inflammatory markers (cytokines) and resistance exercise

Cytokines are secreted proteins that influence the survival, proliferation, differentiation and function of immune cells and other organ systems [17]. Cytokines can be secreted by a variety of cells including neutrophils, activated macrophages, fibroblasts, endothelial cells and damaged muscle cells [18]. Indeed, the muscle itself can also release cytokines as a result of motor unit contractions. For example it has been a consistent finding that interleukin 6 (IL-6) increases by several folds in response to endurance exercise [19]. These increases in IL-6 could be in part related to the decrease in glycogen levels that occur during endurance exercise. There is also a lower magnitude of IL-6

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Table 1. Description of cytokines characteristics and actions

Cytokines	Producer cells [9]	Immune specific actions [9]	Overall effect [18,19,25,28,68,71,78]
IL-1β	Macrophages, epithelial cells	Fever, T cells and macrophages activation	Pro-inflammatory
IL-1ra	Monocytes, macrophages, neutrophils,hepatocytes	Antagonise IL-1 function	Anti-inflammatory
IL-2	T cells	T cell proliferation	Pro-inflammatory
IL-4	T cells, mast cells	B cell activation	Anti-inflammatory
IL-5	T cells, mast cells	Eosinophils growth differenciation	Anti-inflammatory
IL-6	Myocytes T cells, macrophages, endothelial cells	Fever T and B cell growth and differentiation, acute phase protein production	Anti-inflammatory (from muscle) Otherwise Pro-Inflammatory
IL-8 (or newly named chemokine CXCL8)	Myocytes Monocytes, macrophages, fibroblasts, keratinocytes, neutrophils endothelials cells	Mobilizes, activates and degranulates neutrophils. Angiogenesis	Pro-inflammatory Angiogenic
IL-10	Monocytes	Potent suppresant of macrophages functions	Anti-inflammatory
IL-12	Macrophages, dendritic cells	Activates NK cells, T cells differentiation	Pro or Anti-inflammatory Anti-angiogenic
IL-13	T cells	Inhibits macrophages inflammatory cytokine production, B-cells growth, induces allergy	Anti-inflammatory
IL-15	Myocytes	T cells and NK proliferation	Pro or Anti-inflammatory. Anabolic
TNF-α	Macrophages, NK cells, T cells	Promotes inflammation, endothelial activation	Pro-inflammatory. Promotes insulin resistance
sTNF-αR1	Expressed in effector T cells	Cell progammed dead signal and promotes pro-inflammatory genes	Pro-inflammatory

NK : natural killer

response to RT than to endurance exercise. For further details, Hirose *et al*. [20] gave a clear explanation about the differences in RE and endurance regarding cytokine responses.

There are different types of muscle actions: concentric, eccentric and isometric. The eccentric actions occur during the lowering phase of any weightlifting exercise and are defined as the muscle actions where the muscle lengthens because the contraction force is less than the resistive force [21]. RT, involving eccentric actions induces muscular damage to a higher extent than concentric actions [22]. The physiological response to tissue injury is inflammation, which involves the production of cytokines [19].These soluble molecules will facilitate the arrival of neutrophils, monocytes and lymphocytes to the affected muscle tissue. The reactive oxygen species (ROS) produced by neutrophils to attack degenerated cells might affect surrounded cells, exacerbating muscle damage [23]. The increase in ROS will activate the nuclear translocation of the transcription factor NF-kB, up regulating the synthesis of more cytokines [19]. ROS increase is one of the potential initial events in exercise induced muscle injury. Cytokine production can be affected by other physiological factors present in exercise such as stress hormones, acidosis, oxidative stress, and heat among others [24]. In addition, cytokine response may vary by the type of exercise, intensity, duration, recovery between exercise bouts and training status [25,26].

Furthermore, cytokines have numerous upstream and downstream effects playing a role in both destruction and repair processes [27]. Thus, understanding the role of cytokines in a specific physiological situation such as a bout of RT can be exceedingly complex. The most studied cytokines regarding exercise are: IL-6, IL-1 β, IL-8, IL-1 ra, IL-10, IL-15, tumor necrosis factor alpha (TNF-α) and its soluble receptor (sTNF-αR1). In addition IL-2 IL-4, IL-5, IL-13 and IL-12 have received some attention in relation to RT. Some of the cytokines functions have been better characterized than others. For instance, IL-1β, IL-8 and TNF-α are considered pro-inflammatory. On the other hand, IL-1ra and IL-10 are considered anti-inflammatory and can be induced by IL-6 as a response to exercise [25,28]. A description of the main functions of the cytokines referenced in this review is presented in Table 1.

There is an ongoing debate regarding the anti-or pro-inflammatory effects of IL-6. IL-6 secreted by myocytes appears to be anti-inflammatory, as opposed to IL-6 secreted chronically by adipose tissue [29]. When IL-6 is secreted by muscle, it has been shown that it increases anti-inflammatory cytokines such as IL-10 and IL-1ra [30] and inhibits IL-1β and TNF-α release with exercise [4]. All these studies support the anti-inflammatory role of reads IL-6 secreted by myocytes as a response to exercise [4,25,30].

The IL-1 family is part of the innate immune system that regulates functions of the adaptive immune system [31]. IL-1β is the secreted isoform of IL-1. IL-1β does not generally increase after endurance exercise [29] and might remain unchanged [32] or slightly increased [33] after RT. In contrast, IL-8 acts as an angiogenic factor and is considered a chemokine that attracts primarily neutrophils [28]. A high local IL-8 expression in working muscle has been observed after RT and seems to be related to the inflammatory response to the eccentric actions [34]. Chronic plasma TNF-α elevation plays a role in impaired insulin signaling [35]. TNF-α does not seem to increase significantly after exercise, unless the exercise is very strenuous [25]. Still, TNF-α could be released from macrophages during damaging exercise [36].

The cytokines with anti-inflammatory functions are IL-1ra and IL-10. IL-1ra is a member of the IL-1 family that binds to IL-1β but does not induce an intracellular response, thus it is considered anti-inflammatory [19]. An imbalance between IL-1ra and IL-1β may predispose individuals to metabolic and inflammatory diseases such as rheumatoid arthritis and diabetes [37]. IL-1ra increases after endurance exercise [25] and also after RT [33]. IL-10 inhibits the production of IL-1β, TNF-α and IL-8 in experiments with lipopolysaccharide activated human monocytes [25]. An increase in IL-10 was reported after an eccentric elbow flexor exercise [20].

IL-15 has been recently discovered as an anabolic molecule. The decrease in protein degradation seems to be the main mechanism for IL-15 anabolic effects [38] . IL-15 is expressed in skeletal muscle and seems to be regulated by RT. Riechman *et al*. [39] reported an increase in IL-15 after an acute RT bout. Meanwhile IL-15 did not change after 2.5 h treadmill running [38]. However, the role of muscle contraction on IL-15 regulation is not clearly defined [28].

Benefits of RT on low grade systemic inflammation

Acute inflammation is the local protective response to injury. This short term adaptive response is crucial for tissue repair. However, the long term consequences of prolonged inflammation are often detrimental [35] . Low grade systemic inflammation is characterized by a two- to threefold increase in the systemic concentrations of cytokines such TNF-α, IL-6, and C reactive protein (CRP) [25].

Resistance training is associated with reduced risk of low grade inflammation related diseases [4] such as atherosclerosis, obesity and insulin resistance [40]. Long term RT can decrease basal cytokine levels, this is important because certain cytokines play a role on glucose metabolism [35]. Specifically TNF-α and IL-6 can alter insulin sensitivity by triggering different key steps in the insulin signaling pathway [35]. These cytokines stimulate phosphorylation of insulin receptor substrate 1 (IRS) on its serine residues, instead of the tyrosine phosphorylation which is the regular activation pathway. This phosphorylation in another site prevents the normal insulin activation signaling and results in insulin resistance [41]. This turns into a vicious cycle because hyperglycemia also induces IL-6 production from endothelial cells and macrophages [35].

T2DM is a metabolic disorder characterized by chronic hyperglycemia, due to insulin resistance, inadequate insulin secretion or both. Diabetes is associated with a 2 to 4-fold higher risk of CVD, as well as an increased risk of mortality by up to 3-fold [42]. RT improves insulin sensitivity and glucose uptake by the muscle. This is important because insulin resistance over time leads to T2DM [35]. Furthermore, improving glycemic control may contribute to reduced inflammation [35]. Hence RT can impact IR and T2DM in at least two synergistic manners: first by decreasing low grade systemic inflammation and second by improving glucose uptake by the muscle. These effects may be driven partially by the improvement on body composition (increase in muscle mass), quality of muscle mass and by the metabolic adaptations per se. There is scarce data on the effect of long term RT on reducing inflammation in people at risk of T2DM compared with endurance exercise [30,43]. In contrast, the beneficial effects of RT on glucose metabolism are well established [44,45]. In this review, only the long term effect of RT on improving low grade inflammation will be discussed.

Long term RT and low grade inflammation

In addition to CRP, a well establish marker of inflammation and CVD risk [46], the cytokines more commonly evaluated to test improvement in low grade systemic inflammation are IL-6 and TNF-α. Although CRP does not seem to change after an acute bout of RT [47], long term RT can affect its basal levels [32,48]. Thus CRP is measured at rest in the majority of the studies in individuals with low grade inflammation.

One maximum repetition (1RM) is defined as the maximal amount that can be lifted through the full range motion, for one repetition, with proper form. In RT the intensity is determined by the % of 1RM that a person can lift [49]. A typical RT protocol is described by the number of sets and repetitions, for example 3 sets of 10 repetitions at 70% of what the person can lift in 1 repetition maximum, and is written as follows: *3X10Reps 70%1RM.*

In a recent study men and women (51 ± 6 y combined) were classified into two groups: high (n = 28) vs low metabolic risk factors (n = 27) and then half of the people in each group started a RT protocol for 10 wk (RT sessions 3 d/wk) [50]. The RT protocol consisted of 7 exercises (upper and lower body) of 3 sets with various intensities (from 40-80%1RM) and repetitions (8-20) depending of the training day. IL-1β, IL-6, IL-8, TNF-α and CRP were measured at rest before and after the training period. The results showed that RT as a single intervention did not modify any inflammatory marker at rest for any of the tested groups [50]. A possible limitation of this study was gender bias, since there were different proportions of men and women for each group. Authors suggested that long term RT interventions may be required to see the effect on the tested inflammatory markers [50]. In contrast, a long term RT study (1 year, RT sessions 2 ds/wk) carried out in overweight women (39 ± 5 y) showed a reduction in plasma CRP levels and an increase in muscle mass for the training group [51]. However there were no significant changes in IL-6 at rest after 1 yr training. The training protocol targeted upper and lower body and consisted of 3X8-10Reps free weights (the %1RM was not reported). The physical performance assessment did not show improvement for all the muscle groups tested in this study (eg: there were no statistic differences with the control for the leg press). One of the reasons could be that only the first 16 wk of RT were

supervised, followed by meetings to address adherence two times every 12 wk. To summarize long term RT, unlike short term RT seem to have an impact in CRP but not in IL-6 levels. The reduction of CRP with training could be associated among others with reduction in fat mass or specifically with waist circumference that usually occurs with training.

A review published in 2010 analyzed the effectiveness of RT studies on CRP and TNF-α among others parameters [48]. The studies included in this review had a broad array of populations: men and/or women; young, adult and older individuals; overweight and obese and finally people with multiple sclerosis, healthy or infected with HIV. Thus it is hard to extrapolate conclusions or generalize the effects of RT with this diversity of studies. Particularly when gender, due to the effect of hormones, may result in different cytokine response to exercise [52] or age that is associated with increases in basal CRP and TNF-α levels [52,53]. Additionally in animal studies, the magnitude of the exercise-induced cytokine response decreases with age [54]. Nonetheless, authors conclude that: 1) overall there was no apparent response of TNF-α to RT; 2) the majority of the randomized controlled trials support decreases in CRP with RT [48] Additionally, women, obese individuals and older adults seem to be more responsive regarding CRP improvements with RT. Most of the people included in Salles *et al*. [48] review (except for one study done in healthy young men) could be considered at risk for low grade inflammation and thus probably at risk of IR.

Finally a thorough systematic review of the literature [43] regarding the effects of acute and chronic exercise in adults with systemic chronic inflammation compared to healthy controls emphasized the lack of studies on RT compared to endurance training. In fact there was only one study regarding T2DM in this review and the exercise protocol involved endurance training. Authors concluded that the responses to an acute bout of RT in people with low grade inflammatory disease may differ from those in healthy individuals. Meanwhile there seems to be a benefit on the chronic effect of RT [43]. However, the exercise training response seems to depend on the type and severity of the disease and the exercise protocol engaged. After considering the limitations of this review, the conclusions do not necessary apply to people with IR risk per se, but the available information regarding low grade inflammation and exercise is pertinent. Based on the knowledge that the beginning of any RT program might not unveil all the benefits regarding inflammation, the importance of maintaining adherence to an exercise program, specifically for obese individuals or those at risk for low grade inflammatory disease cannot be emphasized enough.

IL-6 controversial aspects

Chronically elevated IL-6 levels have been associated with IR and obesity. Paradoxically, IL-6 increased several fold post-exercise in a period of enhanced insulin action [30]. One proposed relationship of IL-6 on insulin function is that IL-6 activates suppressors of cytokines signaling (SOCS) in the liver which could result in IR by inhibiting IRS [55]. However this SOCS' activation is not as potent with the IL-6 released from muscle tissue. SOCS are a family of proteins capable of inhibiting Janus kinase (JAK) signal transducers and activators of transcription (STAT) signaling in various tissues [56]. JAK and STATS are essential intracellular mediators of immune cytokines action [17]. Supporting the beneficial role of IL-6 on glucose metabolism, Pedersen *et al*. [57] proposed that the increases in AMP-activated protein kinase (AMPK) by muscle derived IL-6 may overrule SOCS activation.

The IL-6 role in IR is controversial because IL-6 levels are elevated in people with IR, however it is TNF-α from adipose tissue that stimulates the release of IL-6 and thus TNF-α is proposed as the main driver of chronic low grade inflammation [30] and for glucose pathogenic metabolism [4]. IL-6 and TNF-α increase lypolisis, but only IL-6 released with exercise seems to induce fat oxidation via AMPK activation [30]. Experiments *in vivo* and *in vitro* suggest that IL-6 influences glucose metabolism in peripheral tissues (muscle and adipose tissue). One of the possible mechanisms is through AMPK activation [58] which in turn stimulate glucose uptake by increasing glucose transporters translocation to the cell membrane [59].

Furthermore, IL-6 activation in muscle is independent of a previous TNF-α response or of NFkB activation [30]. Intramuscular IL-6 is regulated by other pathways such as calcium/ nuclear factor of activated T cells (Ca/NFAT) and glycogen/p38MAPK [30]. Lastly, muscle IL-6 has been recently identified as an essential regulator of satellite cells (muscle stem cells). IL-6 has been shown to mediate hypertrophic muscle growth both *in vitro* and *in vivo* studies [60]. Hence it is necessary to differentiate between the effects of chronically elevated IL-6 (secreted by adipocytes or infiltrated immune cells in the adipose tissue) from the acute several fold IL-6 increased that occurs with muscle contractions (predominantly released from muscle cells) [57].

Effects of acute and long term RT on cytokines

The metabolic adjustment and cellular repair processes that initiate with a single bout of exercise result in the beginning of the training effect. As proposed by Lehman *et al.* [61], acute RT response differs from the response to *chronic/long term* RT. In the acute response, the metabolic needs and the muscular damage play a major role. Meanwhile long term RT training response leads to changes in body composition, metabolism and organs function [61] For example: An acute bout of RT increases the generation of ROS [62]. In contrast, long term RT training results in increasing cells antioxidant capacity [63]. An analysis of the current published research regarding the cytokine responses after an acute bout of RT and after long term RT is presented in the next sections.

Acute effects of RT

The acute effects of RT on inflammation are summarized in Table 2. It is noteworthy that the studies examining the acute effect of RT were all performed in untrained healthy individuals, thus this so called acute effects might differ from the acute cytokine responses in trained healthy individuals, were the RT stimulous is not as novel and strenous as it is for untrained people.

Peake *et al*. [47] investigated cytokine responses to a submaximal and maximal elbow flexor exercise using the right and left arms respectively. There was an increase in IL-6 at 3 h

Table 2. Studies evaluating the acute effect of a RT bout on inflammatory markers

Author	Population	Exercise test protocol	Sampling	Cytokines	Results
Phillips *et al*. [64] (2010)	14 recreationally active men (untrained for RT) (22 ± 2 yr) followed 2 different exercise protocols and a rest condition in a randomized order	8 exercises working major muscle groups of upper and lower body. *Low intensity*: 2X12Reps 65%1RM *High intensity:* 2X8Reps 85%1RM and 3rd set until exhaustion for both protocols. 2' rest	Plasma Pre-, Immediately Post- and 6 h after each test exercise session	IL-6	IL-6 increased immediately Post-exercise compared to control for both exercises and went back to baseline levels at 6 h. The *Low* intensity protocol resulted in the highest total volume load and greater circulating IL-6 compared to the *High* intensity protocol at the Inm Post-Ex time point.
Buford *et al*. [67] (2009)	24 recreationally active women (untrained for RT) (54 ± 4 yr)	3 exercises: squat, leg press and leg extention. 3X10Reps 80%1RM for each exercise	Serum and muscle leg biopsies at baseline and 3 h post-exercise to determine cytokines mRNA expression	IL-1β, IL-2, IL-5, IL-6, IL-8, IL-10 and TNF-α	No changes in serum cytokines after the exercise session. But there was mRNA up-regulation for TNF-α, IL-1β, IL-6 and IL-8 Post-exercise.
Uchida *et al*. [65] (2009)	35 male Brazilian soldiers (19 ± 2 yr) physically trained but not involved in RT for at least 1 yr	A control (n = 6) plus 4 groups follow 1 single bench press exercise: 4X20Reps 50%1RM (n = 8) 5X11Reps 75%1RM (n = 7) 3X10Reps 90%1RM (n = 7) 3X10Reps 110%1RM (n = 7) 2' rest Same total load volumen for all groups	Plasma Pre-exercise and 24, 48 and 72 h after the test exercise session	IL-1β, IL-6 and IL-10	No changes in any cytokine compared with pre-exercise. No differences in cytokine responses among the different intensity protocols. Cytokines levels were not even detectable for some of the participants.
Nielsen *et al*. [68] (2007)	8 healthy physically active men (25 ± 1 yr)	20 min 8set rutine of leg press and knee extensor. 2X6-8Reps and 2X10-14Reps for each exercise. Intensity: to reach total exchaustion in each set	Plasma and muscle leg biopsies at baseline and 6, 24 and 48 h post-exercise to determine IL-15 mRNA expression and protein levels	IL-15	IL-15mRNA levels were up-regulated twofold at 24 h of recovery without any changes in muscle IL-15 protein content or plasma at any of the time points.
Peake *et al*. [47] (2006)	10 healthy untrained men (23 ± 5 yr) completed a submaximal followed by a maximal exercise protocol using dominant vs non-dominant arm randomized and counterbalanced	*Submaximal*: 10X60rep10%1RM elbow flexor of one arm *Maximal:* 10X3rep100%1RM elbow flexor of the opposite arm	Serum Pre-, Immediately Post-1, 3 h and 1-4 d after each test exercise session	IL-1ra, IL-6, IL-10, TNF-α, sTNF-αR1 and CRP	IL-6 was elevated 3 h Post-ex after *Submaximal* but not for *Maximal* protocol. sTNF-αR1 increased after exercise (1,3 h and 1 d) for both protocols. The rest of the cytokines and CRP remain unchanged after the exercise protocols, with a trend for an increase in IL-1ra
Hirose *et al*. [20] (2004)	10 healthy untrained men (20 ± 2 yr) performed 2 bouts of eccentric action of the elbow flexor using the same non dominat arm separated by 4 wks	6X5Rep40%1RM 2'rest for each exercise bout	Plasma Pre-, Immediately Post-1, 3 h and 1-4 d after each test exercise session	IL-1β, IL-1ra, IL-4, IL-6, IL-8, IL-10, IL-12p40 and TNF-α	After the 1st bout there was an unexpected decrease in plasma pro-inflammatory IL-8 (6 h and 4 d) and TNF-α (1, 3 h and 1 d) Post-ex. After the 2nd bout there was an increase in the anti-inflammatory IL-10 (1 and 6 h). There were no changes in the rest of the cytokines between bout or Pre-ex
MacIntyre *et al*. [66] (2000)	12 healthy recreationally active men (20-29 yr)	30X10Rep of eccentric actions of the right leg (quadriceps muscles) using the continuous eccentric mode on an exercise machine	Plasma Pre-, Post- 2, 4, 6, 20 h and 1, 2, 3, 6 and 9 d after the exercise session	IL-6	IL-6 increased at 6 Hs compared to Pre-Ex. By 20 h post-exercise IL-6 levels return to baseline values and continued the same for the rest of the time points, except for a higher value at 24 h compared to Pre-Ex
Smith *et al*. [69] (2000)	6 active men (24 ± 3 yr) (untrained for RT)	Bench press and leg curl eccentric actions 4X12Rep100%1RM$_{con}$ 2'rest	Plasma Pre-, Post- 1.5, 6, 12 h and 1-6 d after the exercise session	IL-1β, IL-6, IL-10, and TNF-α	IL-1β was reduced at 6, 24 and 120 h after exercise. IL-6 was elevated at 12, 24, and 72 h after exercise. IL-10 was elevated at 2, 3 4, 5 and 6 d after exercise. No effect on TNF-α

Post-exercise following the submaximal but not the maximal protocol. An increase in sTNF-αR1 after exercise (1, 3 h and 1 d) was observed in both protocols. A similar approach studying different intensities but using a whole body RT protocol was taken by Phillips *et al*. [64] evaluating the effects of a Low and High intensity RT protocol in untrained young men using a cross-over design. The Low intensity group resulted in the highest total volume load and greater circulating IL-6 compared to the High intensity protocol at the Immediately Post-Exercise time point. Uchida *et al*. evaluated IL-1β, IL-6 and IL-10 responses to different intensities of a bench press exercise maintaining the same total work load in RT untrained men [65]. Authors reported no changes in circulating cytokines after 24 h compared with Pre-exercise. Thus, this research group [65] accounted for the differences in work load in their study but the timing of the samples and the type of exercise protocol differs from the studies mentioned previously [47,64]. MacIntyre *et al*. [66] also examined the relationship between delayed onset of muscle soreness with neutrophils and with markers of inflammation such as plasma and muscle tissue IL-6 after eccentric quadriceps actions. They reported an increase in neutrophils in the exercised muscle leg. Unlike the previous protocol [65], in this study there was an increase in plasma IL-6 at 6 h and 24 h Post-exercise [66].

Results from another study suggest that RT can induce mRNA expression of IL-1β, IL-2, IL-5, IL-6, IL-8, IL-10 and TNF-α in muscle tissue without its increment on plasma [67]. However, a limitation of this study was that protein levels were not measured. In contrast, Nielsen *et al*. [68] reported that IL-15mRNA levels in skeletal muscle were not paralelled by similar changes in muscular IL-15 protein suggesting a translationally inactive pool of IL-15.

Another study used two high intensity RT bouts, one in the upper and another in the lower body in active men [69]. Both acute RT bouts resulted in reductions of IL-1β and increments in IL-6 and IL-10 post-exercise with no effects on TNF-α. In contrast a study following an eccentric action of the elbow flexor in untrained men showed a decrease on TNF-α after exercise [20]. In this particular study, subjects performed two bouts of eccentric action of the elbow flexor using the same non dominant arm separated by 4 wk. Some of the cytokines responses differ between the two bouts. Specifically, there was an increase in the anti-inflammatory IL-10 (1 and 6 h) only after the 2nd exercise bout. Authors suggested that the repeated bout effect could have accounted for the different cytokine response, implying the beginning of an adaptation to exercise.

In summary, only two studies [20,69] demonstrated increases in IL-10. The increases in IL-6 was the more consistent finding after an acute RT in untrained individuals [47,64,66], however the timing for the peaks in IL-6 differ among studies. For example in some protocols IL-6 increased at 3 [47], 6 [20,66], 12 [69] or even 24 h [66,69], while in another study [64] IL-6 returned to baseline levels at 6 h. The increases in IL-6 with RT seem to be of a lesser magnitud than those seen in endurance exercise [28]. Overall, there were no changes in TNF-α levels after the actue RT bout, except for one study [20] which was also the only one to report an unexpected decrease in IL-8. Likewise, only one study [69] showed a decrease in IL-1β, where the rest showed no changes in this cytokine [20,65,67].

The studies presented employed a broad variation of muscles groups, had different intensities and exercise protocols and in general they failed to demonstrate a consistency in the increase or a significant change in most of the circulating cytokines measured after a single RT bout in untrained men and women [20,47,65,67,68]. A possible explanation could be related to the intervals for sampling which were too separate from the exercise bout leading to clearance of cytokines from circulation before being measured. To illustrate this point, results from another study where samples were taken Pre- mid and post-exercise 0, 15 and 45 min after a 5X10 (1RM absolute and relative load) leg press in untrained men, showed changes in some of the cytokines [33], which suggest that to evaluate an acute bout of RT it is better to choose inmediate sampling time points as well as 1, 2, 4 or 6 h to cover a wider espectrum of cytokine kinetics.

Effects of Long term RT

The chronic effects of RT are summarized in Table 3. One of the fundamental adaptations to RT is the increase of muscle mass. This takes place by enlargement of muscle fibers (hypertrophy) not by an increase in their number [70]. RT improves neuromuscular efficiency, muscle mass and enhances muscle metabolism [33]. There are two aspects to consider when analyzing training effects, one is the possible changes to the acute responses to each new exercise bout, and the other is the changes in cytokines at resting. Some of the reviewed studies evaluated plasma cytokines at resting [32,71] meanwhile others [33,72] examined the acute RT response after the training period. In fact, the adaptations to the exercise stimulus might be easier to observe after each acute bout than at resting. Data using endurance strenuous exercise comparing athletes and non athletes showed an attenuated magnitude of the IL-6 and TNF-α responses only in the athletes after the acute exercise bout [73]. In addition the duration of the training protocol in the studies presented in Table 3 was between 6-12 wk. A longer period of training would probably allow further physiological adaptations that might show more robust effects on cytokine responses.

Some studies evaluated acute RT responses after training in which case, the effect of moderate and intense exercise and downhill exercise (eccentric actions) on changes in anti-inflammatory cytokines in trained individuals are compared [72]. Even though the design is not testing directly the differences in Pre- and Post-training, this type of study illustrates the cytokine responses expected for trained individuals. Peake *et al*. [72] reported that exercise intensity has greater effect on IL-10 and IL1ra compared to running downhill. The latter involves

Table 3. Studies evaluating the effect of long term RT on inflammatory markers at resting or after an exercise bout in healthy individuals

Author	Population	Exercise protocol	Training period	Sampling	Cytokines measured	Results
Izquierdo *et al*. [33] (2009)	12 physically active men untrained (33 ± 4 yr)	Pre training and Post training test 5X10RM leg press. The Post training test using the same absolute load (kg) or another day using the same relative load (%RM) than pre-training. 2' rest between sets	7 wk (2 d/wk 45-60 m/session) Non linear undulating multi set progresive program.	Plasma baseline and after 7 wk training: Pre-ex, middle-ex, Post ex 0, 15 and 45 min	IL-1β, IL-1ra, IL-6 and IL-10	Post-training: there was a greater released of IL-1β and IL-1ra after both exercise tests (absolute and relative load). However the increases in IL-6 and IL-10 were seen only after the same relative load test. Intensity plays a role in anti-inflammatory cytokine responses
Stewart *et al*. [32] (2007)	Young (25 ± 5 yr) and old (71 ± 4 yr) men and women were divided in YPA(15) or YPI(14) and OPA(14) or OPI(17)	20 min warm up (walking or jogging) and 2 sets x 8 exercises at 70-80%1RM (1st set) and muscular failure (2nd set), stretching and cooling period.	12 wk (3 d/wk) The physically inactive trained for 12 wk and the physically active participants serve as Controls.	Plasma baseline and after 12 wk training at rest	IL-1β, IL-6, TNF-α and CRP	No age or physical activity differences in IL-6 or IL-1β among groups at baseline or after training. TNF-α levels were higher in the young group (PA and PI) compared to the old group. No effects on TNF-α with training There was a decrease in CRP for young and old physically inactive after 12 wk of training.
Prokopchuk *et al*. [71] (2007)	24 men (25 ± 3 yr) with 5 m-3 yr RT experience divided in: Maximal contraction group (Max) and a Combination group with lower muscle load (Combi)	*Max group*: traditional strenght training: bench press 5X3Reps100%1RM; and *Combi-group:* strenght training combined with ballistic and stretch shortening contractions:10 ballistic movement 30%1RM or 10 shortening type push up.	6 wk (3 d/wk) Both groups trained, the *Combi* was considered the *control group*	Muscle tissue (triceps) at baseline and after 6 wk training at rest	IL-4, IL-4rα, IL-13 and IL-13rα mRNA and protein expression	IL-4, IL-4rα, IL-13 and IL-13rα are expressed in human skeletal *in vivo* and are up-regulated after RT in athletes. IL-4rα mRNA was significantly higher in the Max group compared to the Combi group. IL-4 protein was not significantly different among groups
Peake *et al*. [72] (2005)	9 well trained runners (28 ± 3 yr)	-Treadmill run at 60%VO2max 60 min - Treadmill run at 85%VO2max 60 min -Downhill runing at 60%VO2max 45 min	Already trained	Plasma Pre-Ex, Inm Post-Ex and 1 H Post-Ex.	IL-1ra, IL-4, IL-5, IL-10, IL-12p40 andIL-13	High intensity running had a greater effect than moderate or downhill running on plasma IL-1ra and IL-10 (anti-inflammatory)
Nienam *et al*. [74] (2004)	30 strenght trained male athletes (21 ± 1 yr)	10 different exercise of upper and lower body, (lasted 2 h) 1X10Reps 40%1RM +3X10Reps 60%1RM 2' and 3' rest between sets and exercises respectevely	Already strength trained	Muscle tissue (vastus lateralis) and plasma Pre-Ex and Inm. Post-Ex.	Muscle (mRNA): IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-15 and TNF-α Plasma: IL-1ra, IL-6, IL-8 and IL-10	Muscle mRNA was detected Pre-Ex for IL-1β, IL-6, IL-8, IL-15 and TNF-α and of these, IL-1β, IL-6, IL-8 and TNF-α mRNA were increased Post-Ex. Plasma IL-1ra, IL-6, IL-8 and IL-10 were modestly but significantly increased Post-Ex.

YPA: Young Physically Active
YPI: Young Physically Inactive
OPA: Old Physically Active
OPI: Old Physically Inactive

eccentric actions that are seen in RT and as mentioned earlier can induce muscle damage. As an explanation of their findings, the authors suggest that higher intensity could increase stress hormones and IL-6 leading to higher anti-inflammatory cytokine responses [72]. However, they did not measure plasma IL-6 levels. Similarly another study evaluated the impact of intensity on cytokines to an acute RT test after 7 wks of RT in young men. Authors concluded that the differences on cytokine levels after a relative or absolute load test post-training indicates that intensity has an effect on cytokine responses [33]. The increases in IL-6 and IL-10 were seen only after the same relative load test. Thus, intensity plays a role in cytokine responses where higher intensity appears to have a more favorable response. Izquierdo *et al*. [33] stated that even though IL-1β response was higher after 7 wk of training, so was IL-1ra which could have blunted the IL-1β physiological activity. The training protocol in this study was short, corresponding to the early phase of RT, which could explain the absence of an attenuated cytokine response with training.

Other studies evaluated cytokines levels at rest after the RT period such as Stewart *et al*. [32] who evaluated the effect of 12 wk RT on young and old individuals. There were no training effect on any of the cytokines measured but there was a decrease in CRP at rest in the trained group. There seem to be differences between the local (muscle tissue) and the systemic (plasma) cytokine responses to RT. The *mRNA expression* of IL-1β, IL-6,

IL-8 and TNF-α increased immediately Post-Exercise in trained individuals [74]. However, except for IL-8, the increases in *plasma* were mostly of the anti-inflammatory cytokines type (IL-1ra, IL-6, and IL-10). These data suggest that in trained individuals the acute response to a RT bout could exert a more favorable systemic cytokine response probably due to the body adaptation to RT. Still the increase in plasma cytokines was modest. As an explanation for the blunted cytokine responses in this study, Nieman *et al*. [74] suggested that rest intervals during an extended exercise protocol (eg: 2 h) might result in lower plasma cytokine concentrations. Interestingly, authors did not advocate for the adaptation to training as one of the possible reason for the blunted cytokine responses. After 6 wk of RT, IL-4, IL-4rα, IL-13 and IL-13rα mRNA expression but not protein levels were increased in healthy active individuals [71]. Prokopchuk *et al*. [71] proposed that IL-4, IL-4rα, IL-13 and IL-13rα might be involved in muscle hyperthophy. Specifically IL-4 can promote muscle regeneration, which involves de novo myofiber formation [75]. IL-13 has affinity for IL-4 receptor complex 2 thus it can activate similar cellular pathways than IL-4 [76]. Comparable responses were found for IL-15, also considered to have anabolic effects after an acute RT bout in untrained individuals [68]. As presented earlier (Table 2), Nielsen *et al.* [68] reported that the acute RE bout in untrained individuals up regulates mRNA IL-15 but does not change IL-15 protein or plasma levels.

The effects of RT on TNF-α are equivocal, depending of the compartment the TNF-α is measured, either in plasma or muscle (protein or mRNA expression). There are studies showing no effects of RT on plasma TNF-α [32,48,74] while one of the same studies reported increases on mRNA TNF-α [74]. Conversely, mRNA TNF-α reduction in response to RT has been reported as well [77]. Results from our laboratory [78] showed a decrease in plasma TNF-α response to an acute resistance exercise test (6x10 75%1RM squats) after 9m of RT (3 d/wk) in healthy young adults. This TNF-α suppression by exercise is consistent with results from an *in vitro* study [24]. In this study [24], pre- and post-exercise human serum (30 min bout of heavy exercise) from 16 young adults and a T-lymphocyte model (Jurkat cells never exposed to exercise) were used. TNF-α production was significantly suppressed in T-lymphocytes from the exercising participants [24]. As proposed by Radom *et al*., exercise can affect T cells cytokines production by different mechanisms [24]: 1) Alterations of circulating factors (lactate, catecholamine, growth factor); 2) Stimulation of lymph nodes and 3) Mobilization into the circulation of natural killers' cells relative to T cells. These mechanisms explain how the intensity, through the effect on hormones or lactate levels for instance can play a role on cytokines levels. Indeed, epinephrine inhibits cellular TNF-α production [79].

There are differences in the cytokine responses depending on the intervals for taking samples and if the comparisons with pre and post-training are at rest or after the acute bout of RT. To summarize there are studies that reported no changes on some of the plasma cytokine responses with RT [32,71] while other studies showed higher anti-inflammatory cytokines responses after RT [33,72,74]. Interestingly, two studies [33,74] reported both, increases in anti- and in pro-inflammatory cytokines after RT. This implies that a broad array of cytokines increased after an exercise bout, thus evaluating the magnitude of the pro to anti-inflammatory ratio should be considered in future studies.

Concluding remarks

We have addressed the effect of RT at improving low grade inflammation, and as a result helping in the prevention of IR. The prevalence of T2DM in the US is increasing [80], thus actions to prevent it are warranted. RT allows the maintenance of a healthy body weight and increases muscle mass, the main insulin target site. The increase in muscle mass has positive impact in energy expenditure and insulin sensitivity and in turns decreases CRP. The overall effect of long term RT appears to ameliorate inflammation, but the specific effects on TNF-α are not clear, requiring further research. Finally, it is essential to differentiate between chronically and acute IL-6 levels and its sources.

We discussed the cytokine responses after an acute bout of RT and after long term RT in healthy individuals. The majority of the studies [20,64,66,69,72] reported an increase in the response to an acute bout of RT on specifically the anti-inflammatory IL-10 and IL-6. Meanwhile there are studies that reported no changes on the plasma cytokine response after the acute RT bout in untrained individuals [65,67,68].There are differences in cytokine responses to long term RT depending on the time intervals during sampling and if the comparisons with pre and post-training are at rest or after the acute bout of RT. To further understand the effect of RT, it will be necessary to evaluate the magnitude of the pro to anti-inflammatory ratio.

Another key determinant of the effects of RT on the inflammatory response is the number of variables associated with the presented studies. For example, the time intervals for taking samples, the methods utilized to measure the cytokines (ELISA vs flow cytometry), the exercise protocol and training (specifically the intensity), make study comparisons difficult.

The intervals in time for sampling may have a profound effect on the inflammatory response. To measure training effects at rest, samples should be taken previous to the exercise bout or at least 72 h after the last RT bout. To measure the training effect on the acute RT bout, samples should be taken while the exercise is performed or immediately after. Some of the differences in protocols are related to each study specific objective whether it was to measure delayed onset muscle soreness and the inflammatory response to muscle damage or study the most acute inflammatory response related to muscle contraction stimulus, and stress hormones. In addition, studies measuring a systemic

inflammatory response in plasma might differ from the local response in muscle tissue or in specific cells types such as mononuclear cells. It is noteworthy that those training studies reporting improvement on inflammatory responses had higher intensity RT than those who did not.

As summarized by Miles [26] exercise training could be pro-inflammatory depending on the degree to which recovery occurs between exercise bouts. This is an important aspect to consider when designing a protocol or extrapolating results from different studies. The majority of the exercise protocols presented in this review include non consecutive training sessions to assure recovery. Another confounding variable is the effectiveness of the training intervention. If the physical assessment of performance does not show a significant improvement over the control group, it cannot be concluded that RT did not result on improvements of cytokine profile. For instance, in the study by Olson *et al.* [51] there were not significant changes in IL-6 and there were not significant changes between groups (training and control) when the leg press strength progress was evaluated.

The intensity of the RT and the characteristics of the training protocol may exert singular cytokine responses and as a result different adaptations to exercise. Thus more research is needed in the area of RT in healthy populations, specifically sorting out gender and age RT responses and more importantly studies are needed in obese individuals who are at high risk of developing low grade systemic inflammatory related diseases. Finally, assuring adherence to the RT program is essential to get the benefits after overcoming the first acute RT responses. Hence long term RT could be an effective way to prevent, and delay inflammatory chronic diseases.

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