Skeletal muscle IL-4, IL-4Rα, IL-13 and IL-13Rα1 expression and response to strength training

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ABSTRACT

Interleukin-4 (IL-4) and interleukin-13 (IL-13) are Th2 cytokines involved in various immune responses and only a few reports examine skeletal muscle and the possible role of Th2 cytokines in myoblast fusion and myotube maturation. We hypothesized that IL-4, IL-13 and their receptors are involved in skeletal muscle adaptations to strength training. We investigated the effects of 6 weeks of strength training with different muscle load on IL-4, IL-13, IL-4Rα and IL-13Rα1 expression in skeletal muscle: training with maximal contractions (Max group, n = 12) and training with lower load combined with ballistic and stretch-shortening contractions (Combi group, n = 12). Muscle samples were taken from triceps brachii before and after the 6 weeks of training. mRNA levels of IL-4, IL-13, IL-4Rα and IL-13Rα1 expression were determined by real-time PCR and IL-4 protein expression by ELISA. We demonstrate for the first time that IL-4, IL-13, IL-4Rα and IL-13Rα1 are expressed in skeletal muscle in vivo and are up-regulated after strength training. Higher training load in Max leads to higher cytokine responses, which was significant for IL-4Rα though IL-4 protein expression did not change significantly. Although the exact mechanisms have yet to be established, and these results may be preliminary, we speculate that IL-4, IL-13, IL-4Rα and IL-13Rα1 are involved in muscle hypertrophy, MHC-transformation and anti-inflammatory damage control that occur during strength training.

Key words: Interleukin-4, Interleukin-13, skeletal muscle, strength training

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INTRODUCTION

Interleukin-4 (IL-4) and interleukin-13 (IL-13) are known to be produced mainly by a subpopulation of activated T-cells, TH2 CD4(+) helper cells and by mast cells and neutrophils (16; 19). Induction of cell signaling by IL-4 and IL-13 involves interaction with the α subunit of the IL-4 receptor (IL-4Rα) and the IL-13R chain α1 (IL-13Rα1). In addition to their expression in immune cells, IL-4, IL-13, IL-4Rα and IL-13Rα1 are widely expressed in a variety of non-haematopoietic cells such as cloned stromal cell lines from the bone marrow, spleen, thymus, and brain, and on brain, melanoma, liver fibroblast, and muscle cells (6; 12; 27), as well on some cancer cell lines (9; 20).

Horsley et al. (5) showed that mouse myoblasts express IL-4 and IL-13. Both myoblasts and myotubes express the IL-4Rα subunit of IL-4R, and IL-4Rα is required for muscle growth (5). IL-4 stimulated cell fusion not only of myoblasts but also of mesenchymal adult stem cells and different preparations of primary fibroblasts (22). It was also demonstrated (6) that IL-13 is responsible for the recruitment of reserve cells during human myotube hypertrophy induced by insulin-like growth factor-1 (IGF-1). In spite of newly established functions of IL-4 and IL-13 in myoblasts and myotubes *in vitro*, the role of these cytokines and their receptors *in vivo* in skeletal muscle has not been yet defined.

Strength training is important for force and velocity development and is accompanied by muscle plasticity which may involve fibre transformation, hypertrophy and biochemical adaptation (11). Training with maximum contractions provides maximal muscular load and leads to stem cell activation (7; 11) and inflammation (4; 21). From acute exercise experiments we know that skeletal muscle IL-4 mRNA was not changed (2; 17). We hypothesized that receptors of IL-4 are regulated in response to acute or chronic exercise like in case of IL-6 and its receptor (8).

Therefore, the expression of IL-4, IL-13, IL-4Rα and IL-13Rα1 was examined in maximal strength training (Max group) compared with training with lower muscle load (Combi group). We chose a training of similar strength type but with different recruitment pattern (11) as a control group which we suppose is better than pure endurance training or “no training”.

METHODS

Subjects. Twenty-four male physical education students with experience in strength training were enrolled in this study. They all had 3 months to 5 years of regular strength training of the arms. They were randomized into two groups: the Max group received the traditional strength training with maximum voluntary contractions, and the Combi group received the strength training combined with ballistic and stretch-shortening contractions. Age, height, and body mass were recorded (11). This study was approved by the Ethics Committee of the Medical Faculty of the University of Ulm (Germany), and written consent was obtained from all participants.

Training protocol and biomechanical measurements. The training protocol used in this study has been described previously (11). The training was performed

Table 1. Primers used in real-time PCR

Primer	Sense	Antisense	$MgCl_2$, mM	Annealing temperature, °C	Melting temperature of specific PCR product	Amplicon length, bp	Accession No.
IL-4 human	BioZol (Maxim Biotech) Kit	BioZol (Maxim Biotech) Kit	4	58	81	81 bp	NM_000589
IL-4Rα human	CgTCTCCgACTACATgAgCATCT	CCACAggTCCAgTgTATAgTTATCC	4	65	86	211 bp	X52425
IL-13 human	gTCAggCTgCAgTgCCATCg BioZol (Maxim Biotech)	TTgAACCgTCCCTCgCgAAA BioZol (Maxim Biotech)	3	58	87	178 bp	XM_054533
IL-13Rα1 human	gCCAAgAAATATAggTAAgAAgC	TgTCgTACTTCTTCCAgTgCAgA	3	58	85	196 bp	NM_001560
HPRT human	LightCycler-Primer Set for human HPRT	LightCycler-Primer Set for human HPRT	3	68	81	not reported by manufacturer	NM_000194

on Monday, Wednesday, and Friday each week for 6 weeks. In the Max group, the same training was carried out on the 3 training days: bench press with maximum contractions [3-repetitions maximum (RM) load, determined by 1 RM] and five series with three repetitions in each series. In the Combi group, the training was the same as that in the Max group on Monday, 10 ballistic movements (concentric-only bench-press throw) with a workload of 30% of 1 RM on Wednesday, and 10 stretch-shortening-type push-ups on Friday. The interval between repetitions and between series was 3–4 s and 6 min, respectively. Biomechanical measurements were performed as previously described (11).

Muscle biopsy. Muscle biopsy was carried out at rest on a no training day, 3 days before and 7 days after the training protocols as previously described (11). Briefly, muscle samples were taken from the long head of *m. triceps brachii* of the dominant side of the subjects by using the fine-needle biopsy technique. After routine desinfection of the skin, a 13-gauge biopsy needle (Peter Pflugbeil Medizinische Instrumente, Zorneding, Germany) was punctured 1 cm into the muscle belly, and the biopsy gauge was shot three times to attain 3 mg of muscle tissue. The sample was immediately frozen in liquid nitrogen and then stored at -80°C.

IL-4 measurement at protein level. The muscle sample (about 5 mg) was homogenized in 50 µl extraction buffer containing 100 mmol/l Na_4P_2O7 $10H_2O$, 5 mmol/l EGTA, 5 mmol/l $MgCl_2 \cdot 6H2O$, 0.3 mmol/l KCl, and 1 mmol/l dithiothreitol with an ultrasonic homoge-

nizer (Bandelin Sonoplus Homogenisator HD2070, Berlin, Germany). The muscle homogenates were stirred on ice for 20 min and then centrifuged at 4°C and 16,000 g for 10 min. The supernatant was collected and mixed with an equal volume of glycerol. The total protein concentration was determined according to the Lowry method (13).

100 µl aliquots (20 µg protein) were used for the IL-4 human sandwich ultra sensitive ELISA (BioSource International. Inc., Camarillo, CA, USA) carried out according to the manufacturer's protocol. Briefly, a monoclonal antibody specific for hIL-4 has been coated onto the wells of the microtitre strips provided. Samples, including standards of known hIL-4 content (10, 8, 6, 4 and 2 pg/mL) were pipetted into the wells followed by the addition of a second biotinylated monoclonal antibody. After removal of excess second antibody, Streptavidin-Peroxidase (100 µL streptavidin-HRP working solution) was added. This binds to the biotinylated antibody to complete the four-member sandwich. After a second incubation and washing to remove all the unbound enzymes, a substrate solution (100 µL of Stabilized Chromogen) was added to produce colour at 650 nm.

Analysis of IL-4, IL-4Rα1, IL-13, IL-13Rα1 mRNA. Total RNA was extracted from the muscle tissue by phenol extraction (RNA Clean System, AGS, Heidelberg, Germany). The total RNA was dissolved in 10 µl for each 1 mg muscle tissue. Oligo(dT) primed synthesis of cDNA was performed by using murine-leukaemia virus reverse transcriptase, according to the standard protocol (Perkin Elmer, Roche Molecular System, Branchburg, NJ). The primer design of the IL-4Rα and IL-13Rα1 was performed by MolBiol (Berlin, Germany). For precise information about primers see Table 1.

Real-time RT-PCR amplification was performed using the QuantiTect™ SYBR Green PCR Kit (QIAGEN, Germany). Prior to quantitative analysis, several titration experiments, for $MgCl_2$ and efficiency test were performed to determine optimum amplification conditions. Standard curves containing a specific number of cDNA copies were generated for each of the gene transcripts analysed. In brief, the total reaction volume for each sample was 20 µl and contained 2 µl cDNA solution, 10 pmol of each primer, 100 µM of each 2-deoxynucleotide 5'-triphosphate, 3 mM $MgCl_2$ for IL-4R, Il-13 and IL-13R or 4 mM $MgCl_2$ for IL-4, and 1 unit of *Taq* polymerase and Syber Green as indicator. After heat activation at 94°C for 15 minutes, fifty five cycles of 15 s denaturation at 94°C, 30 s annealing at 58°C (for IL-4, for other genes see Table 1) and 16 s synthesis at 72°C were performed. The colour signal (Syber Green, which combines exclusively to the double strand DNA) was measured in real-time model at the end of DNA-synthesis phase, and the crossing point (where the colour signal began to increase exponentially) was calculated. The specificity of DNA amplification for IL-4, IL-13, IL-4Rα and IL-13Rα1 was examined with analysis of the melting curve. Elective amplicons were resolved by electrophoresis on a 1.5% agarose gel and visualized by ethidium bromide staining. mRNA contents were normalized to HPRT mRNA levels (the HPRT gene is used as a constitutively expressed housekeeping gene), and samples were expressed relative to the corresponding control sample, which was set to 1.

Statistical analyses. The statistical analysis was performed using a statistical software package (SPSS version 15.01 for Windows; SPSS, Chicago, IL). We

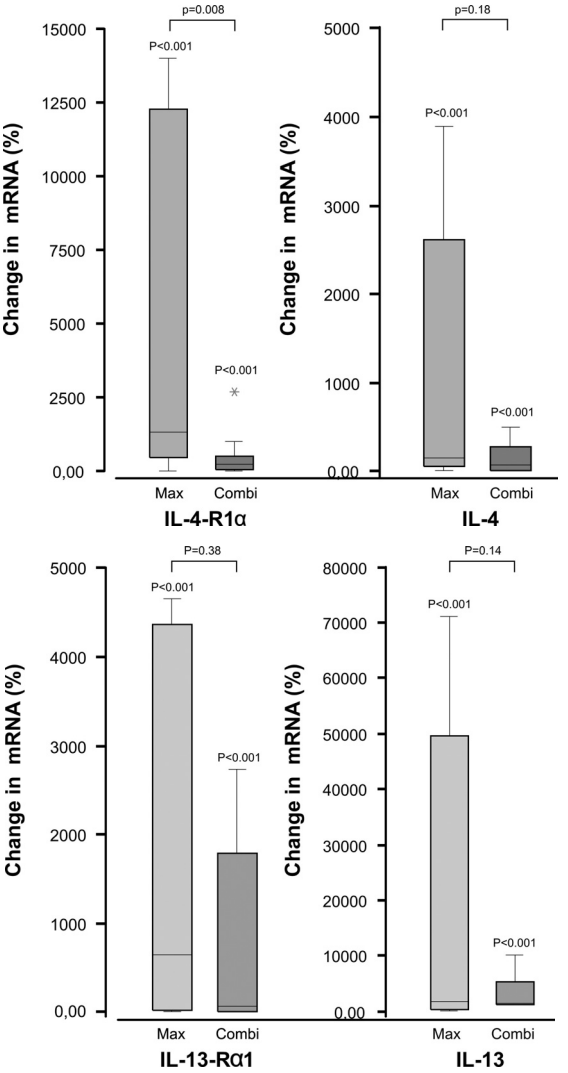

Figure 1A. Identification of IL-4 and IL-4Rα mRNA expression in skeletal muscle determined by real time PCR. Figure 1B. Identification of IL-13 and IL-13Rα1 mRNA expression in skeletal muscle determined by real time PCR.

Total cellular RNA was prepared as described in "Materials and Methods". mRNA change were normalized to HPRT mRNA change, and samples were expressed relative to the corresponding control sample (pre-intervention sample), which was set to 100%. Data are expressed as median, 25% and 75% percentiles (box) and 5%, 95% percentiles (whisker). *: outlier.

analyzed real-time RT-PCR data using the Kolmogorov-Smirnov-Test. Differences between groups were determined by the Mann-Whitney test. A p value < 0.05 was considered to be statistically significant.

RESULTS

The training program was fulfilled totally without adverse events. The effect of both training protocols on biomechanical parameters has been described before (11). Shortly, 1 RM, which represents the highest possible weight that could be successfully lifted, increased significantly with training in both groups, and the increase in maximum velocity was higher in the Combi group.

The expression of IL-4Rα (Figure 1A, Figure 2) was significantly increased after training in both groups ($p < 0.001$) and was significantly higher in the Max group ($p = 0.008$). IL-4 mRNA was expressed at a low level in skeletal muscle, and both training protocols led to IL-4 mRNA up-regulation (Figure 1A). The expression of IL-13 and IL-13Rα1 mRNA is also significantly increased after training in both Max and Combi groups (see Figure 1B).

IL-4 protein was detectable in muscle samples at a low level by ultra sensitive IL-4 ELISA. In the Max group there was a

slight decrease in IL-4 protein expression after training (from 0.38 ± 0.08 to 0.27 ± 0.03 pg/ml, p = 0.263) and in the Combi group there was a slight increase (from 0.26 ± 0.07 to 0.28 ± 0.06 pg/ml, p = 0.47).

DISCUSSION

In the present study we demonstrate for the first time that IL-4, IL-13, IL-4Rα and IL-13Rα1 are expressed in human skeletal muscle *in vivo* and are up-regulated after strength training in athletes. Furthermore, maximal strength training elicits higher responses than training with lower loads.

To our knowledge, there are only two other studies that have attempted to examine exercise effects on IL-4 in human skeletal muscle, which failed to detect IL-4 mRNA and protein before and after training (2; 17). In our study both training regimens led to significant increases in IL-4, IL-13, IL-4Rα and IL-13Rα1 mRNA expression. There was a significant group (training load) difference observed in the case of IL-4Rα expression. The changes in other parameters (IL-4, IL-13 and IL-13Rα1) were also more pronounced in Max group as compared with Combi group (see Figure 1A and 1B). Obviously, the higher training load led to a higher cytokine response, although the training in Combi group contains also some strength elements and eccentric contractions. There is also some indication that satellite cell activation is higher in the group with maximum contraction (11).

Similar dose-response effects have been found for the skeletal muscle expression of pro- and anti-inflammatory cytokines like IL-1, IL-6 and interferon-γ and their receptors (30). There are some studies that have reported the effects of exercise on plasma IL-4 concentration. IL-4 production did not change during acute continuous incremental exercise and plasma IL-4 remained unaffected immediately after marathon races (15). However, plasma and urine IL-4 concentrations were significantly elevated 2 h after short-duration intensive exercise, suggesting that IL-4 is produced by *de novo* synthesis (26). PHA-stimulated IL-4 production in elderly runners was higher compared with an elderly sedentary group (23; 28). In our study we observed no significant change in IL-4 protein during training; the discrepancy between IL-4 protein and IL-4 mRNA level may be mainly attributed to their different kinetics or there may be some mechanisms like in T-cells (29) that inhibit IL-4 production at a post-transcriptional level.

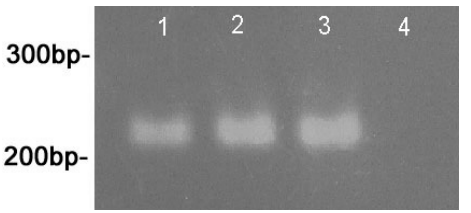

Figure 2. Representative ethidium bromide staining of agarose gel für IL-4Rα mRNA (211bp). 1 – before maximal strength training, 2 – after maximal strength training, 3 – positive control (pancreatic cancer cell line ASPC-1), 4 – negative control (H20)

Interestingly, it was demonstrated already in 1988 (12) that numerous cloned stromal murine lines including muscle expressed significant numbers of IL-4 receptors. For example, the murine skeletal muscle cell line BC3H1 expresses about 1200 receptors for IL-4 per cell. This is a relatively high number as usu-

ally IL-4Rα is expressed at densities of 100-5000 copies/cell (12). No biologic effects of IL-4 on non-haematopoietic cells had been reported at that time. Another related finding may be that IL-4 has a protective function in experimental Myasthenia gravis. B6 mice genetically deficient in IL-4 (IL-4-/-) develop long-lasting muscle weakness after a single immunization with *Torpedo* acetylcholine receptor while wild type mice develop long-lasting muscle weakness after three immunization procedures (18). Horsley and co-workers demonstrated a role for interleukin-4 in regulating the fusion of myoblasts with differentiated myotubes (5), and the group of Schulze revealed that IL-4 stimulated cell fusion of mesenchymal adult stem cells (22). Transcriptor factor NFATc2 (nuclear factor of activated T-cells) regulates IL-4 in a subset of fusing muscle cells and induces muscle growth through the IL-4 receptor (5). It was also demonstrated that human IL-4 can act as a pro-migratory agent for myogenic cells that explains IL-4 activity during differentiation (10). Human IL-4 was not required for fusion between mononucleated myoblasts but for myotube maturation (10). It is known that regulation of myoblast fusion and myotube maturation is important not only during embryonic development but also in maintenance and repair of adult muscle. Thus, we speculate that during and after 6 weeks of strength training, among other adaptation processes, stem cell activation, myoblast fusion and myotube maturation which both contribute to myotube growth and repair occur and it could be regulated and/or induced by IL-4 and IL-4Rα.

In mice IL-4 has been demonstrated to be more potent than IL-13 in inducing myoblast fusion (5). In the human model *in vitro* myotube hypertrophy induced by IGF-1 was IL-13-dependent and IL-4 was not responsible for the recruitment of reserve cells (6). Results from our working group (non-published data) showed that in both groups IGF-1 was up-regulated and this change was more during strength training with maximal contractions. Here, in contrast to Jacquemin and co-workers (6), we found that both IL-4 and IL-13 expression was increased after strength training. The mechanisms involved should be examined further.

It is known that strength training with maximum contractions leads to an increase in MHC_{2a} and a decrease in fast MHC_{2X}, whereas combined strength training produces an increase in MHC_{2a} and a decrease in MHC_{slow} (11). In the present study, there was a significant difference between the two groups in the case of IL-4Rα. Thus, it could be speculated that IL-4Rα could be involved in a shift in MHC isoform expression to MHC_{2a}.

Damaged muscle may be the source and trigger of cytokine release because muscle inflammation occurs following strength exercise and tissue macrophages and other cells should be activated (1; 26). Intensive training leads to local inflammation through production of reactive oxygen species, and it activates proinflammatory pathways such as Nuclear Factor kappa B (14; 21). IL-4 is a main inducer of anti-inflammatory and type-2 cytokines (IL-1ra, IL-5, IL-6, IL-10 and IL-13). The shift toward type 2 T-cell dominance might be beneficial, because it is also suppresses the ability of the immune system to induce tissue damage (3). So, the protective role of IL-4, IL-13, IL-4Rα and IL-13Rα1 up-regulation after strength training could also be important. Additionally, cytokines are likely involved in the regulation of glucose homeostasis (24; 25).

There are some limitation factors in this study. As this is a preliminary investigation examining mostly gene expression of two Th2 cytokines, follow-up

work needs to be performed including immunohistochemistry and western analysis. Additionally, time course experiments should be performed before final conclusions could be drawn.

In conclusion, a possible role of IL-4, IL-13, IL-4Rα and IL-13Rα1 could be postulated for the adaptation of skeletal muscle in response to strength training and training load in humans. The relevance of this finding has to be determined in further studies.

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