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Macrophage migration inhibitory factor diminishes muscle glucose transport induced by insulin and AICAR in a muscle type-dependent manner

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ABSTRACT

Skeletal muscle is a primary organ that uses blood glucose. Insulin- and 5′AMP-activated protein kinase (AMPK)-regulated intracellular signaling pathways are known as major mechanisms that regulate muscle glucose transport. It has been reported that macrophage migration inhibitory factor (MIF) is secreted from adipose tissue and heart, and affects these two pathways. In this study, we examined whether MIF is a myokine that is secreted from skeletal muscles and affects muscle glucose transport induced by these two pathways. We found that MIF is expressed in several different types of skeletal muscle. Its secretion was also confirmed in C2C12 myotubes, a skeletal muscle cell line. Next, the extensor digitorum longus (EDL) and soleus muscles were isolated from mice and treated with recombinant MIF in an *in vitro* muscle incubation system. MIF itself did not have any effect on glucose transport in both types of muscles. However, glucose transport induced by a submaximal dose of insulin was diminished by co-incubation with MIF in the soleus muscle. MIF also diminished glucose transport induced by a maximal dose of 5-aminoimidazole-4-carboxyamide ribonucleoside (AICAR), an AMPK activator, in the EDL muscle. These results suggest that MIF is a negative regulator of insulin- and AICAR-induced glucose transport in skeletal muscle. Since MIF secretion from C2C12 myotubes to the culture medium decreased during contraction evoked by electrical stimulations, MIF may be involved in the mechanisms underlying exercise-induced sensitization of glucose transport in skeletal muscle.

1. Introduction

Skeletal muscle has recently been recognized as a secretory organ. Pedersen and Febbraio suggested that cytokines and other peptides that are produced, expressed, and released by muscle fibers and exert autocrine, paracrine, or endocrine effects should be classified as myokines [1]. For example, some interleukins (IL-4, IL-6, IL-7, IL-8, and IL-15), growth factors (insulin-like growth factor-1, fibroblast growth factor (FGF)-2, and FGF-21), and other molecules (myostatin, brain-derived neurotrophic factor, follistatin-related protein 1, irisin, and leukemia inhibitory factor) [1] have been identified as myokines. Among these molecules, IL-6 is one of the most well-investigated myokines [2]. It has been reported that MIF secretion is regulated by muscle contraction in humans *in vivo* and in cultured muscle cells [3,4]. Acute treatment of rat L6 muscle cells with IL-6 has been shown to increase basal glucose uptake and translocation of the glucose transporter GLUT4 [5]. Moreover, IL-6 has been shown to increase intramyocellular [5] and whole-body [6] fatty acid oxidation via AMPK [5,7]. These observations suggest that myokines may be responsible for metabolic homeostasis in skeletal muscle.

MIF has emerged as an important regulator of inflammation [8,9], playing a central role in the control of both innate and antigen-specific immunity [10,11] through its receptors CD74, CXCR2, and CXCR4 [12]. Although MIF was initially described as T cell-derived, it has been recently shown to be released by a variety of cell types. Autocrine/paracrine effects of MIF have been reported in heart and adipose tissue. Miller et al. showed that MIF is released from the ischemic heart, where it stimulates AMPK activation

Abbreviations: MIF, macrophage migration inhibitory factor; EDL, extensor digitorum longus; AICAR, 5-aminoimidazole-4-carboxyamide ribonucleoside; AMPK, 5′AMP-activated protein kinase; IL, interleukin; TNF-α, tumor necrosis factor-α; LDH, lactate dehydrogenase; TA, tibialis anterior.

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through CD74, promotes glucose uptake, and protects the heart during ischemia-reperfusion injury [13]. Atsumi et al. showed that the insulin resistance evoked by TNF-α in adipose tissue can be largely explained by the autocrine/paracrine action of MIF [14].

In this study, we examined whether the myokine MIF affects muscle glucose transport induced by insulin or AMPK activation.

2. Materials and methods

2.1. Animals

ICR mice (8–9 weeks old) were obtained from Sankyo Lab (Tokyo, Japan). The mice were housed at 23–25 °C with a 12 h light/dark cycle. The mice received an MF certified diet (Oriental Yeast, Tokyo, Japan) and water ad libitum. Care and use of the laboratory animals were in accordance with the guidelines of the Experimental Animal Committee of Tokyo Metropolitan University and followed the Guidelines for the Proper Conduct of Animal Experiments established by the Science Council of Japan.

2.2. Cell culture

A mouse skeletal muscle cell line, C2C12 myoblasts (American Type Culture Collection, Manassas, VA, USA), was grown on 4-well plates (Nalge Nunc, New York, USA) at a density of 2×10^5 cells/well with 3 ml of growth medium consisting of Dulbecco's Modified Eagle Medium (DMEM; 25 mM glucose; Life Technologies, CA, USA) supplemented with 10% fetal bovine serum (Bio West, Nuaillé, France) and 1% penicillin–streptomycin, at 37 °C under a 5% CO_2 atmosphere until confluence. Differentiation was then induced by switching the growth medium to DMEM supplemented with 2% calf serum (Bio West) and 1% penicillin–streptomycin (day 0). Four days after the initiation of differentiation, the cells were used for experiments. The differentiation medium was changed every 24 h.

2.3. C2C12 myotube contraction by electrical stimulation

A day before the experiment, the cells were washed with PBS twice, followed by addition of 2 ml of serum and phenol red-free DMEM. After incubation for 1 h at 37 °C, the medium was changed to fresh medium again and incubated for 24 h at 37 °C. On the day of the experiment, the medium was changed again to fresh medium and the 4-well plates were placed in the electrical stimulation apparatus, a 4-well C-Dish (Ion Optix Corp., MA, USA) that was connected to an electrical stimulator (Uchida Denshi, Tokyo, Japan) and stimulated with electric pulses of 20 mA at 1 Hz for 30 ms at 970-ms intervals for 1 h in an incubator at 37 °C, as described previously [15]. After the contraction experiment, the conditioned medium was collected and cells were harvested with 300 μl of ice-cold lysis buffer. The conditioned medium was centrifuged for 15 min at 2000*g*, followed by centrifugation for 35 min at 12,000*g* at 4 °C to eliminate cell fragments. The supernatant was concentrated using 3 kDa cut-off centrifugal filters (Millipore, Watford, UK) after filtration with a 0.22-μm filter (Millipore, Watford, UK). The concentrated conditioned medium was used for immunoblotting and a LDH assay after correction for concentrate volume. The harvested cells were sonicated and centrifuged at 14,000*g* for 20 min at 4 °C, and the supernatant was used for immunoblotting.

2.4. Expression vector construction

Mouse MIF cDNA was cloned by a RT-PCR based method. To ensure that the cDNA was tagged with HA at its C-terminus, the forward primer used for its amplification included the *Eco*RI enzyme restriction site (GAATTC) and Kozac sequence (GCCACC) before the start codon of the coding sequence for mouse MIF (5′-GAATTCGCCACCATGTTCATCGTGAACACCAATGTT-3′). The reverse primers included recognition sites for the restriction enzymes *Xho*I (CTCGAG) and *Bgl*II (AGATCT), the complement of the HA sequence, and the complement of the coding sequence for the C-terminal end of mouse MIF (5′-AGATCTCTCGAGTCAAGCGTAATCTGGAACATCG-TATGGGTAAGCGAAGGTGGAACCGTTCCAGCCC-3′). The PCR cycling condition was 25 cycles of 98 °C for 10 s, 60 °C for 5 s and 72 °C for 10 s. Amplified fragments were cloned into the pCR-Blunt vector (Life Technologies, CA, USA), digested with the restriction enzymes *Eco*RI and *Xho*I, and then subcloned into the pCAGGS vector before analysis of the sequence. All DNA preparations were performed using the EndoFree Plasmid Mega Kit (Qiagen, Hilden, Germany), and the concentration and purity of the plasmid preparations were determined using a spectrophotometer (Thermo Fisher Scientific, MA, USA).

2.5. DNA injection into skeletal muscle and in vivo electroporation

DNA injection and *in vivo* electroporation were performed using a modification of the method of Aihara and Miyazaki [16]. Female mice were anesthetized intraperitoneally (100 mg of pentobarbital per kg of body weight). The plasmid DNA was diluted in 0.9% saline to a final concentration of 4 μg/μl. An insulin syringe was used to inject 25 μl or 50 μl of DNA solution intramuscularly each into the TA muscle or the gastrocnemius muscle along the long axes of the muscle fibers. Immediately after injection of the DNA, an electrode and a pair of stainless steel needles were inserted into the skeletal muscle, which was then stimulated with eight square wave electric pulses (200 V/cm), each with a frequency of 1 Hz and duration of 20 ms, delivered using an electrical pulse generator. At 2 weeks after electroporation of the muscle tissues, the serum was collected and the muscles were dissected and immediately frozen in liquid nitrogen.

2.6. In vitro muscle incubation and glucose transport

Male mice were sacrificed, and the EDL and soleus muscles were rapidly removed and treated for *in vitro* muscle incubation as previously described [17]. Briefly, both ends of the muscle strips (tendons) were tied with sutures and mounted on an incubation apparatus. The muscles were preincubated for 2 h in 1.3 ml of Krebs–Ringer bicarbonate buffer (KRB) containing 2 mM pyruvate with or without 1 μg/ml MIF (R&D Systems, Minneapolis, USA). The muscles were then incubated in KRB with or without 50 mU/ml or 200 μU/ml insulin (Eli Lilly, Indianapolis, USA) for 30 min, or with 2 mM or 250 μM AICAR (Wako, Osaka, Japan) for 20 min in the presence or absence of MIF. The buffers were kept at 37 °C throughout the experiment and gassed continuously with 95% O_2 and 5% CO_2.

For glucose transport, the incubated muscles were transferred to KRB containing 1 mM 2-deoxy-D-glucose (1.5 μCi/ml) and 7 mM d-[14C]mannitol (0.45 μCi/ml) (PerkinElmer Life Sciences, MA, USA) at 30 °C and incubated for 10 min. MIF, insulin, and AICAR were added to each glucose transport buffer at a concentration equal to that of the incubation buffer. Glucose transport was terminated by dipping the muscle tissue in KRB at 4 °C, and the muscle tissue was frozen in liquid nitrogen. The muscle tissue was weighed and digested by incubation in 250 μl of 1 N NaOH at 80 °C for 10 min. The digests were neutralized with 250 μl of 1 N HCl, and particulate matter was precipitated by centrifugation at 13,000*g* for 5 min. The radioactivity in aliquots of the digested muscles was determined by liquid scintillation counting for dual labels, and the extracellular and intracellular spaces were calculated as previously described [18].

2.7. Western blot analysis

Frozen muscle tissue was pulverized and homogenized in lysis buffer and centrifuged at 12,000*g* for 20 min at 4 °C, and the supernatant was used for immunoblotting. The protein concentration was determined by the Bradford method. The samples were separated by SDS–PAGE and transferred to polyvinylidene fluoride membranes. The membranes were blocked with Tris-buffered saline containing 0.1% Tween 20, 2.5% non-fat dry milk, and 2.5% bovine serum albumin (for proteins in lysates), 7.5% non-fat dry milk (for MIF in serum), or 5% bovine serum albumin (for HA-tagged protein in serum). The membranes were incubated overnight with appropriate primary antibodies (anti-MIF, anti-CXCR2 (R&D Systems, Minneapolis, USA), anti-CD74 (BD Biosciences, California, USA), anti-CXCR4 (Abcam, Massachusetts, USA), and anti-GAPDH (Cell Signaling, Massachusetts, USA)), followed by incubation with rabbit (GE Healthcare, Buckinghamshire, UK), goat (Millipore, Watford, UK), or rat (Cell Signaling) secondary antibodies conjugated to horseradish peroxidase or with an anti-HA antibody conjugated to horseradish peroxidase (Cell Signaling). The signal was detected by enhanced chemiluminescence.

2.8. LDH assay

LDH activity in the conditioned medium, a marker of cell damage, was measured using an LDH assay kit following the manufacturer's instructions (Roche, Basel, Switzerland).

2.9. Statistical analysis

Data are shown as mean ± SEM values. Student's *t*-test was performed to compare the two groups. For multiple comparisons, data were analyzed using an one-way ANOVA followed by the Bonferroni *post hoc* test, and $p < 0.05$ was considered to be significant.

3. Results

3.1. Confirmation of MIF expression and secretion in skeletal muscles

Only a few reports have focused on MIF in skeletal muscles [19,20]. To confirm MIF expression in skeletal muscles, muscle tissues (gastrocnemius, soleus, EDL, and TA muscles) and the heart dissected from a mouse in addition to C2C12 myotubes were subjected to immunoblotting. MIF (12 kDa) was detected in all muscles, the heart, and C2C12 myotubes (Fig. 1A). To determine whether MIF is secreted from C2C12 myotubes, the conditioned culture medium was collected after incubation of the myotubes at 37 °C for 1 h, concentrated, and subjected to immunoblotting. As shown in Fig. 1B, MIF was detected in the conditioned medium.

Next, we investigated whether MIF is secreted from skeletal muscles *in vivo*. To distinguish blood–borne MIF secreted from skeletal muscles from that secreted from other tissues, the TA and gastrocnemius muscles of mice were transfected with expression vectors that encode MIF tagged with HA at the C-terminal end (HA-MIF). Expression of HA-MIF protein was confirmed in the skeletal muscles of the mice by immunoblotting with a MIF-specific antibody (Fig. 1C, upper band), and the band was distinguished from that of endogenous MIF (Fig. 1C, lower band). In contrast, only endogenous MIF and not HA-MIF was observed in serum collected from the mice on immunoblotting with a MIF-specific antibody, although immunoblotting with a HA-specific antibody did detect an HA signal in the serum (Fig. 1D). These results suggest that although MIF is secreted from skeletal muscle, it does not contribute to total serum MIF content because the amount of MIF secreted by skeletal muscles is much less than that secreted by other tissues. Therefore, it is possible that muscle MIF is a myokine that functions in an autocrine/paracrine manner rather than an endocrine manner.

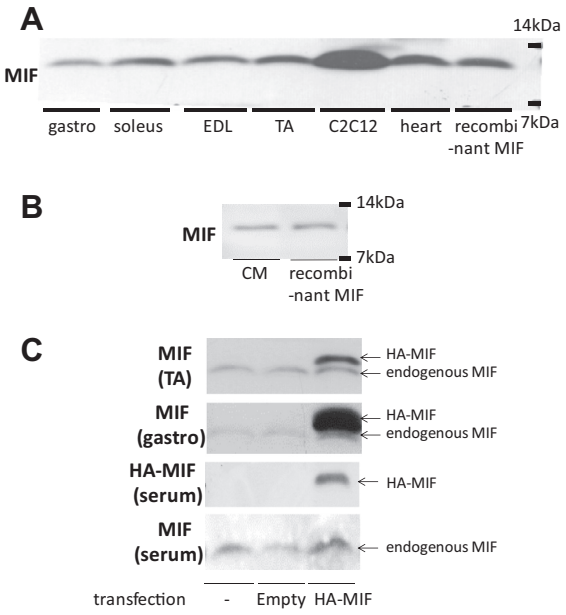

Fig. 1. (A) Expression of MIF in skeletal muscles and C2C12 myotubes. MIF was detected in lysates from different types of skeletal muscle in addition to C2C12 myotubes and heart tissue by Western blotting. (B) Secretion of MIF from C2C12 myotubes. MIF was detected in the conditioned medium (CM) after incubation for 1 h. Recombinant MIF was used as a positive control. (C) Detection of HA-MIF in the skeletal muscles and serum of mice transfected to express HA-MIF. Electroporation was used to transfect the empty or HA-MIF expression vector into the TA and gastrocnemius muscles in both legs of mice. Western blotting using a MIF-specific antibody detected endogenous MIF and HA-MIF in each type of muscle. Western blotting using a HA-specific antibody, but not a MIF-specific antibody, detected HA-MIF only in the serum of HA-MIF transfected mice.

3.2. MIF supplementation diminishes glucose transport induced by insulin in the soleus muscle and by AICAR in the EDL muscle

Because it has been reported that MIF secreted from adipose tissue and the heart affects glucose metabolism of these tissues in an autocrine manner [13,14] and because the skeletal muscles are the primary consumers of blood glucose [21], we focused on the role of MIF in muscle glucose transport. First, to determine the role of MIF in insulin sensitivity in skeletal muscle, isolated soleus and EDL muscles were incubated in KRB with or without 1 μg/ml MIF. MIF itself had no effect on glucose transport in both types of skeletal muscle. However, glucose transport induced by a submaximal dose (200 μU/ml) of insulin was significantly diminished in the presence of MIF in the soleus muscle (Fig. 2A). This inhibitory effect was not observed with the maximal dose (50 mU/ml) of insulin. Moreover, the inhibitory effect of MIF was not observed in the EDL muscle with both doses of insulin (data not shown). In agreement with the glucose transport findings, MIF significantly diminished Akt phosphorylation (Thr308) induced by the submaximal dose of insulin in the soleus muscle ($p < 0.01$, data not shown). The role of MIF in AMPK-stimulated glucose transport in the soleus and EDL muscles was also examined using the maximal dose of AICAR (2 mM) or a submaximal dose of AICAR (250 μM). Glucose transport induced by the maximal dose of AICAR, but not by the submaximal dose of AICAR, significantly decreased in the presence of MIF in the EDL muscle (Fig. 2B). In agreement with the glucose transport findings, phosphorylation of AMPK induced by the maximal dose of AICAR was significantly diminished by MIF treatment in EDL muscle ($p < 0.05$, data not shown). We could not determine

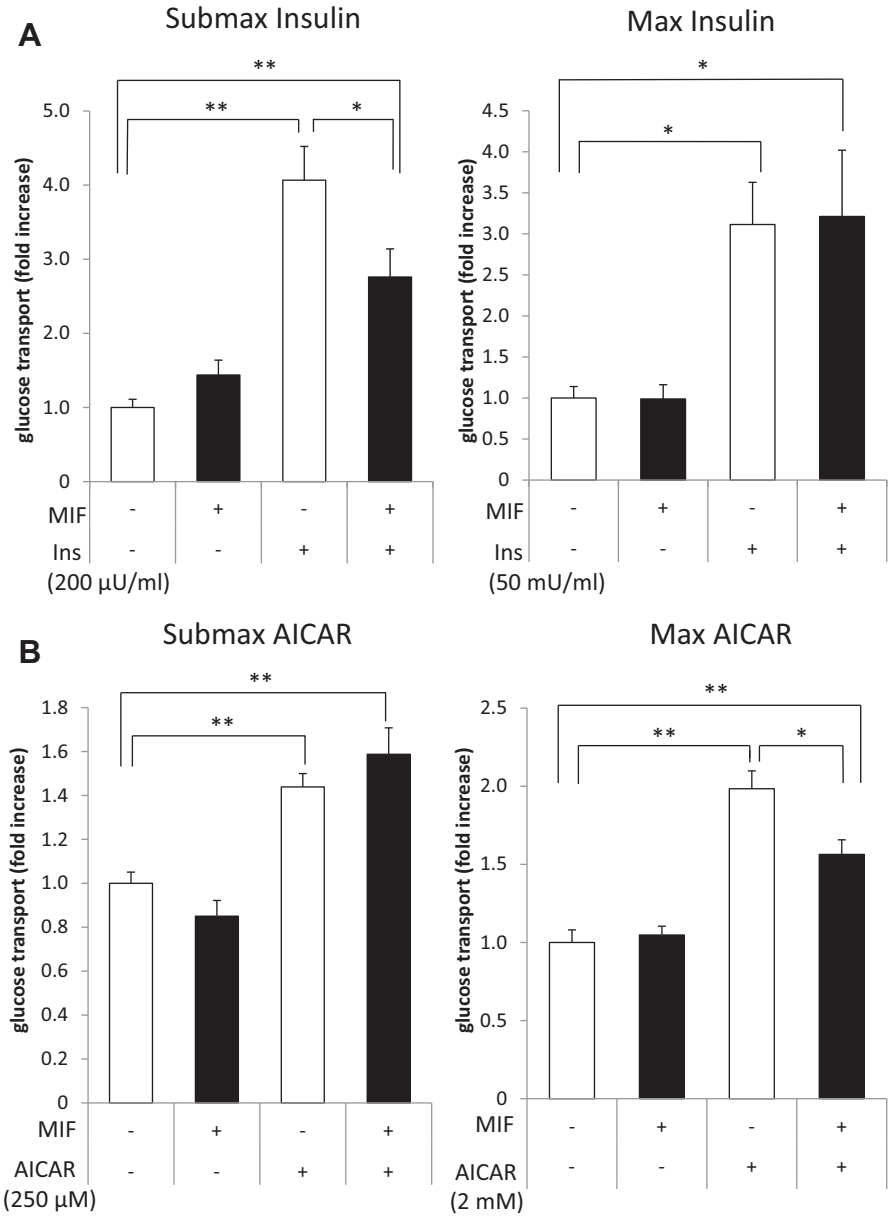

Fig. 2. (A) Effect of MIF supplementation on glucose transport induced by insulin in the soleus muscle. Isolated soleus muscles were incubated in KRB with or without MIF (1 μg/ml) and insulin. The graph shows the fold increase over the basal value for glucose transport (μmol/ml/h). MIF did not affect the increase of glucose transport induced by 50 mU/ml insulin (n = 6–7) but inhibited the increase of glucose transport induced by 200 μU/ml insulin (n = 11–14). (B) Effect of MIF supplementation on glucose transport induced by AICAR in the EDL muscle. The graph shows the fold increase of glucose transport over the basal value (μmol/ml/h). MIF inhibited the increase in glucose transport induced by 2 mM AICAR (n = 8) but not 250 μM AICAR (n = 7–8). Data are shown as the mean ± S.E.M. $^{*}p < 0.05$, $^{**}p < 0.01$.

the role of MIF in AMPK-activated glucose transport in the soleus muscle because neither dose of AICAR increased glucose transport in the muscle (data not shown). We also did not observe an increase in glucose transport by 2,4-dinitrophenol and rotenone, which generally activate AMPK in many cells and tissues [17].

3.3. Expression of the MIF receptors CD74 and CXCR2/4 in the EDL and soleus muscles

MIF diminished the increase in glucose transport induced by insulin in the soleus muscle and by AICAR in the EDL muscle, possibly indicating that the expression pattern of MIF receptors is different between these two muscles. Indeed, expression of both isoforms of CD74 (p31 and p41) was significantly higher in the soleus muscle than in the EDL muscle. In contrast, expression of CXCR2 was significantly higher in the EDL muscle than in the soleus muscle. Expression of CXCR4 was not different between these muscles (Fig. 3).

3.4. MIF secretion from C2C12 myotubes into conditioned medium is inhibited during contraction

To determine whether MIF secretion is altered by muscle contraction, C2C12 myotubes were contracted by electrical pulses (20 mA, 1 Hz, 30 ms) for 1 h at 37 °C using our original system [15]. MIF secretion was significantly reduced by 70% with myotube contraction (Fig. 4A). LDH activity in the conditioned medium was not affected by myotube contraction, which indicates that the myotubes were not injured by electrical pulses or muscle contraction (Fig. 4B).

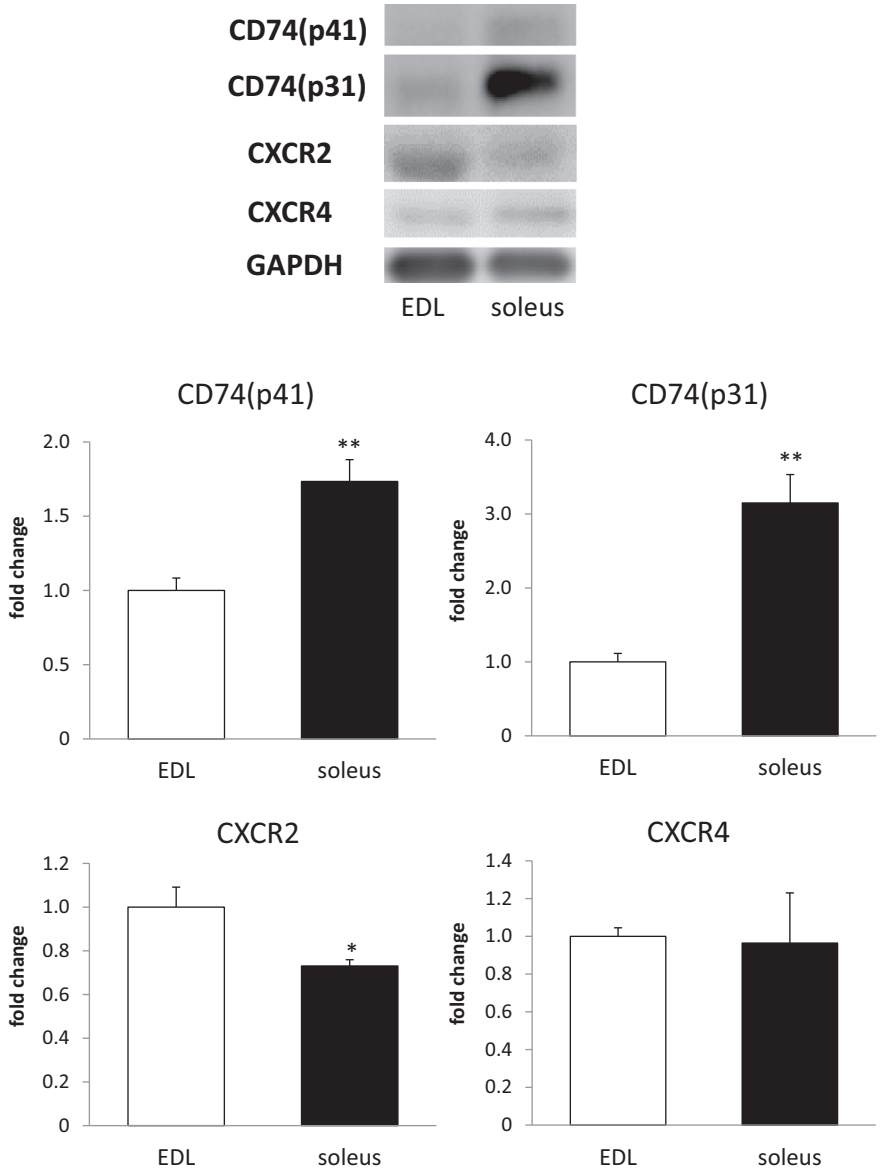

Fig. 3. Expression of CD74 and CXCR2/4 in the EDL and soleus muscles. Representative blots of CD74 (p31 and p41) and CXCR2/4 and the relative expression level in each muscle are shown. Significant increases in both isoforms of CD74 and CXCR2 were detected in the soleus muscle and EDL muscle ($n = 5$). Data are shown as the mean ± S.E.M. $^{*}p < 0.05$, $^{**}p < 0.01$.

4. Discussion

In the current study, we used HA tagging to directly show that MIF is secreted from skeletal muscle. Immunoblotting of serum samples indicated that the amount of MIF derived from skeletal muscle is much lower than that derived from other tissues. This observation strongly suggests that muscle MIF acts on skeletal muscle itself in an autocrine manner, rather than acting on remote organs in an endocrine manner.

We found that MIF is a negative regulator of glucose transport in skeletal muscle. In detail, MIF decreased glucose transport induced by insulin in the soleus muscle and by AICAR in the EDL muscle. Expression of both isoforms of CD74 was significantly higher in the soleus muscle than in the EDL muscle, which may explain why the inhibitory effect of MIF on insulin-stimulated glucose transport was observed in the soleus but not in the EDL. In contrast, the expression of CXCR2 was significantly higher in the EDL muscle than in the soleus muscle. CXCR2 is a G-protein-coupled receptor and interacts with $G\alpha_i$ protein [22], which inhibits adenyl cyclase and reduces cAMP levels [23]. It has been reported that elevated cAMP levels lead to AMPK activation in muscle cells [24]. Therefore, CXCR2 may mediate the inhibitory effect of MIF on AMPK-mediated glucose transport as a result of decreased cAMP levels in skeletal muscle. Additionally, the MIF activation threshold may be different between the CD74 and CXCR2 receptors, resulting in the difference in the response to insulin and AICAR observed in the EDL and soleus muscles.

Secretion of MIF from C2C12 myotubes was reduced by contraction of the myotubes. Muscle contraction activates AMPK, which induces acute glucose transport [25]. It is also well known that muscle contraction increases insulin sensitivity on glucose transport [26]. Therefore, downregulation of MIF secretion by muscle contraction may contribute to further facilitation of glucose transport induced by muscle contraction by decreasing the inhibitory effect of MIF on glucose transport stimulated by insulin and AMPK activation.

In this study, we demonstrated that MIF is a myokine secreted from C2C12 myotubes and skeletal muscles. In addition, MIF is a

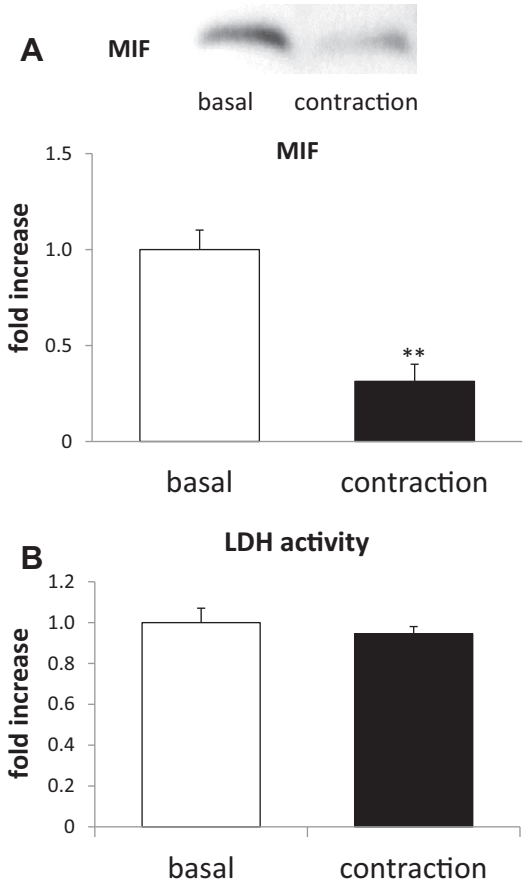

Fig. 4. (A) Secretion of MIF from C2C12 myotubes treated with or without electrical stimulation for 1 h. The amount of MIF secreted from C2C12 myotubes into the conditioned medium was compared for the basal and contracted conditions. Electric pulses were given with parameters of 20 mA, 1 Hz, and 30 ms for 1 h at 37 °C. Representative blots and the quantified expression levels of MIF in the conditioned medium are shown. Significant decreases of MIF were detected 1 h after contraction ($n = 3$). (B) LDH activity in the conditioned medium. There was no significant difference between the basal and the contraction groups ($n = 3$). Data are shown as the mean ± S.E.M. $^{**}p < 0.01$.

negative regulator of insulin- and AMPK-induced glucose transport in skeletal muscle, suggesting that it is a target molecule that improves glucose homeostasis.

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