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Effect of Treadmill Exercise on Interleukin-15 Expression and Glucose Tolerance in Zucker Diabetic Fatty Rats

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Background: Interleukin-15 (IL-15), a well-known myokine, is highly expressed in skeletal muscle and is involved in muscle-fat crosstalk. Recently, a role of skeletal muscle-derived IL-15 in the improvement of glucose homeostasis and insulin sensitivity has been proposed. However, little is known regarding the influence of endurance training on IL-15 expression in type 2 diabetic skeletal muscles. We investigated the effect of endurance exercise training on glucose tolerance and IL-15 expression in skeletal muscles using type 2 diabetic animal models.
Methods: Male Zucker diabetic fatty (ZDF) and ZDF lean control (ZLC) rats were randomly divided into three groups: sedentary ZLC, sedentary ZDF (ZDF-Con), and exercised ZDF (ZDF-Ex). The ZDF-Ex rats were forced to run a motor-driven treadmill for 60 minutes once a day 5 times per week for 12 weeks. Intraperitoneal glucose tolerance test (IPGTT) was performed after 12 weeks. Expression of IL-15 was measured using ELISA in extracted soleus (SOL) and gastrocnemius medial muscles.
Results: After 12 weeks of treadmill training, reduction of body weight was observed in ZDF-Ex compared to ZDF-Con rats. Glucose tolerance using IPGTT in diabetic rats was significantly improved in ZDF-Ex rats. Furthermore, the expression of IL-15 was significantly increased ($P<0.01$) only in the SOL of ZDF-Ex rats compared to ZDF-Con. Additionally, IL-15 expression in SOL muscles was negatively correlated with change of body weight ($R=-0.424$, $P=0.04$).
Conclusion: The present study results suggest that 12 weeks of progressive endurance training significantly improved glucose tolerance with concomitant increase of IL-15 expression in SOL muscles of type 2 diabetic rats.

Keywords: Exercise; Glucose intolerance; Interleukin-15; Rats, Zucker; Treadmill

INTRODUCTION

Myokines, known as cytokines and peptides, that are produced, expressed, and released by muscle fibers and exertion of these substances in either paracrine or endocrine fashion should be classified [1]. Previously, researchers have searched for a muscle contraction-induced hormonal factor, an exercise factor, which could mediate some of the exercise-induced changes in other organs such as the liver and adipose tissue [1]. Among various myokines, interleukin-15 (IL-15) has been identified as an anabolic factor, which is highly expressed in skeletal muscle [2]. Quinn et al. [3] have proposed an important role of IL-15 in skeletal muscle by demonstrating that IL-15 can stimulate differentiated myocytes and muscle fibers to accumulate increased amounts of contractile proteins. The action of IL-15 stimulates muscle-specific myosin heavy chain

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accumulation by differentiated myocytes and muscle fibers in culture, suggesting a role in skeletal muscle fiber growth *in vivo* [4]. In addition, overexpression of IL-15 in mouse C2C12 cells leads to clear muscle hypertrophy [5]. Recently, the functional role of IL-15 in regulating metabolic diseases, including obesity and diabetes, has been emphasized. Modulation of glucose uptake in incubated skeletal muscles and muscle cell cultures by IL-15 implies that cytokines may play a role in the inhibition of the development of diabetes [4]. Indeed, *in vivo* administration of IL-15 results in an elevation of 2-deoxyglucose uptake in skeletal muscle. Additionally, *in vitro* treatment of IL-15 increases GLUT4 content in muscle cell cultures [6].

These findings suggest the possibility that IL-15 can serve as an important mediator of skeletal muscle fiber growth, hypertrophy, and glucose uptake. One study demonstrated that high intensity resistance training leads to a transient increase in serum IL-15 concentration [7], while another study reported that plasma IL-15 concentration is not altered by heavy resistance training [8]. Endurance exercise did not increase IL-15 mRNA content in skeletal muscle or circulating IL-15 concentration from 1 up to 6 hours after exercise [9-12]. However, a recent study implied that endurance exercise increases circulating IL-15 concentration 10 minutes after the exercise [13]. These findings suggest that exercise-induced IL-15 may mediate the systemic as well as local beneficial effects of endurance exercise, including insulin-sensitizing, antiadipogenic effects, and anabolic actions in skeletal muscle [13].

Skeletal muscle is the principle site of glucose uptake under insulin-stimulated conditions and strongly influences glucose intolerance [14]. Impaired glucose transport in skeletal muscles leads to impaired whole-body glucose uptake, and facilitates the development of type 2 diabetes. Subjects with glucose intolerance have an increased risk of type 2 diabetes, therefore improvement of glucose tolerance is considered important for the prevention of diabetes [15,16].

Collectively, the results of previous studies clearly indicate that expression of IL-15 in skeletal muscles may regulate glucose metabolism in various metabolic diseases including diabetes. Although exercise is considered an important preventive measure for patients with diabetes, data regarding the influence of endurance training on IL-15 expression in type 2 diabetic skeletal muscles by fiber types are lacking. Therefore, in the present study, we examined the effect of endurance exercise training on glucose tolerance and IL-15 expression in skeletal muscles using type 2 diabetic rats.

METHODS

Animals

Male and female Zucker diabetic fatty (ZDF, *fa*/+) rats were purchased from Genetic Models (Indianapolis, ME, USA) and allowed to mate. They were housed in conventional cages under adequate temperature (23°C) and humidity (60%), control with a 12-hour light/12-hour dark cycle, and free access to food and water. Purina 5008 rodent diet (7.5% fat) was provided as recommended by Genetic Models Co. (Purina, St. Louis, MO, USA). The *fa* gene genotype was determined using the strategy described in our previous study [17]. Twenty-four male lean (ZDF lean control, ZLC, +/+) and diabetic (ZDF, *fa/fa*) Zucker rats (8-week-old) were separated into three groups, lean control (sedentary ZLC, ZLC-Con, $n=8$), diabetic control (sedentary ZDF, ZDF-Con, $n=8$), and diabetic exercise-trained (exercised ZDF, ZDF-Ex, $n=8$).

All animals in the training group had a treadmill adaptation period of 1 week. At 8 weeks (pre-exercise) and 20 weeks (postexercise) of age, body weight (mettle instrument AG CH-8606; Mettler Toledo, Greifensee, Switzerland) and fasting plasma glucose level (Roche Diagnostics Ltd., Mannheim, Germany) were measured in all animals. The handling and caring procedures for the animals adhered to the guidelines in compliance with the current international law and policies (National Institutes of Health [NIH] Guide for the Care and Use of Laboratory Animals, NIH Publication No. 85-23, 1985, revised 1996). All experiments were conducted to minimize the number of animals used and the suffering caused by the procedures in the present study.

Progressive endurance exercise training

The rats in the ZDF-Ex were forced to run a motor-driven treadmill for 60 minutes once a day 5 times per week for 12 weeks. The ZDF-Ex rats were acclimated to the treadmill exercise before training. The exercise intensity (running speed) was set at the speed of 15 to 20 m/min at their lactate threshold [18]. The initial treadmill speed was set to 15 and 2 m/min was added every 2 weeks to simulate the intensity and effect of exercise training. The maximal treadmill speed was limited to 20 m/min in the last 2 weeks.

Tissue collection

Skeletal muscle tissue collection was performed 2 days after the last session of the exercise training program. Rats were anesthe-

tized by Zoletil 50 (intraperitoneal injection, 10 mg/kg; Vibac Laboratories, Carros, France) and sacrificed. The tissues were collected from the soleus (SOL) and the gastrocnemius medial (GM) muscles. The samples were quickly weighed, frozen with liquid nitrogen, and then stored at -80°C until used. Each tissue was homogenized in radio immunoprecipitation assay buffer. The homogenized tissues were then centrifuged at 14,000 rpm for 20 minutes at 4°C, and the total protein concentration of the supernatant was determined using the Bradford assay.

IL-15 protein analysis

Protein extracts from the skeletal muscle were prepared by centrifugation of the tissue homogenates according to the manufacturer's specifications (Rat IL-15 ELISA Kit; Cusabio Biotec Co., Ltd., Newark, DE, USA). Detection range was 1.56 to 100 pg/mL for each assay. All samples were assayed in duplicate to guarantee the precision of the results, and all samples were run within the range of the standard curve. The results were expressed as concentration of IL-15 (pg/mL) read from standard curves.

Intraperitoneal glucose tolerance test

Glucose tolerance was assessed using the intraperitoneal glucose tolerance test (IPGTT) in rats during the last week of the training session. IPGTT was performed by injecting glucose (2 g/kg in 20% solution) intraperitoneally in overnight-fasted rats. Blood samples were obtained by cutting the tile tip before and 0, 15, 30, 60, 90, and 120 minutes after glucose administration. Blood glucose concentration was measured using an Accu-Chek glucose analyzer (Roche Diagnostics Ltd., Mannheim, Germany).

Statistical analysis

Statistical analysis was performed using the Origin 8.0 and SPSS version 18.0 software package (IBM Co., Armonk, NY, USA). Data were analyzed using two samples *t*-test to examine the body weight, fasting glucose levels, IL-15 levels, and area under the curve (AUC) of IPGTT. Data were presented as mean±standard error of mean with significance set at $P<0.05$. Associations of IL-15 expression in SOL with body weight and fasting blood glucose were calculated with Pearson correlation coefficient.

RESULTS

As shown in Fig. 1A, the body weight of ZDF-Con rats was markedly increased ($P<0.05$) compared to ZLC-Con rats at the end of exercise training. After the 12-week treadmill exercise program, body weight was lower ($P<0.05$) in the ZDF-Ex group compared to ZDF-Con group. However, there was no significant change in body weight following the treadmill exercise in ZLC rats (data not shown). The fasting blood glucose concentration in ZDF-Con rats (297.2±18.5 mg/dL) was significantly higher ($P<0.05$) than in ZLC-Con rats (78.4±5.4 mg/dL). After the last exercise session, the fasting blood glucose level was lower in ZDF-Ex (178.2±12.9 mg/dL) than in ZDF-Con rats (Fig. 1B).

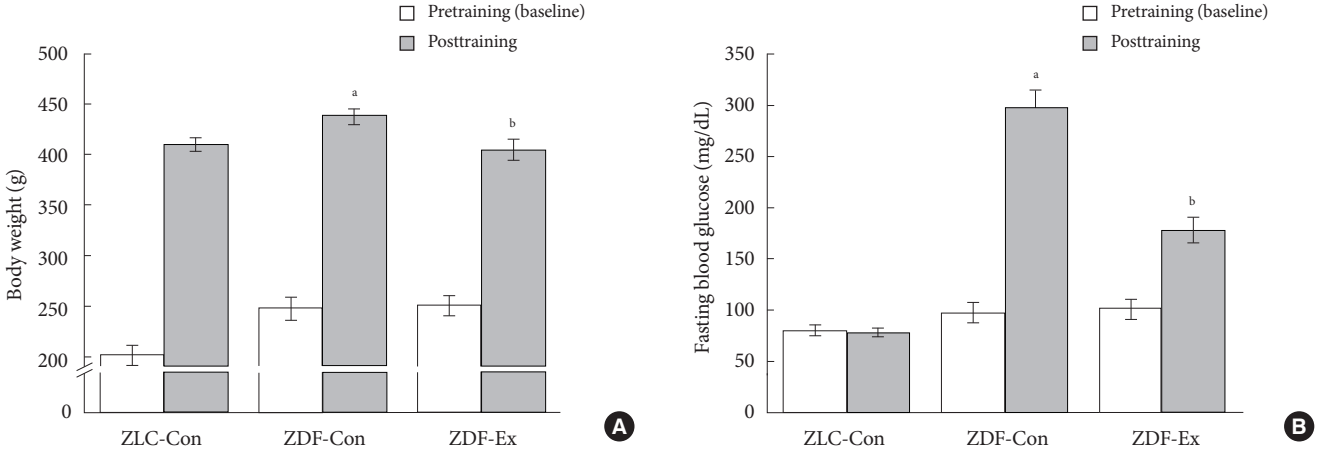

Fig. 1. Effect of 12 weeks of (A) treadmill exercise on body weight and (B) fasting blood glucose concentration. Values are mean±standard error of mean for $n=8$ in each group. ZLC-Con, sedentary Zucker diabetic fatty lean control; ZDF-Con, sedentary Zucker diabetic fatty; ZDF-Ex, exercised Zucker diabetic fatty. [a]$P<0.05$ compared with ZLC-Con group, [b]$P<0.05$ compared with ZDF-Con group.

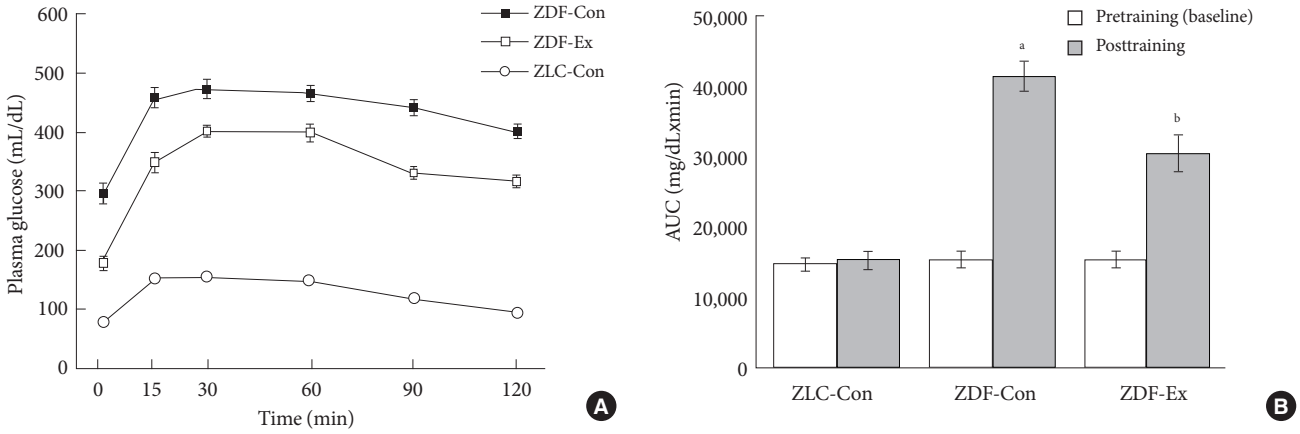

Fig. 2. Effect of 12 weeks of treadmill exercise on glucose tolerance in diabetic rats. (A) Blood glucose concentration was measured at various time points after dextrose (2 g/kg) treatment. (B) Area under the curve (AUC) of intraperitoneal glucose tolerance test was calculated for quantified comparison. Values are mean±standard error of mean for $n=8$ in each group. ZDF-Con, sedentary Zucker diabetic fatty; ZDF-Ex, exercised Zucker diabetic fatty; ZLC-Con, sedentary Zucker diabetic fatty lean control. [a]$P<0.05$ compared with ZLC-Con group, [b]$P<0.05$ compared with ZDF-Con group.

IPGTT was performed on every weekend to verify the improvement of glucose tolerance. The representative result was found at the last measurement, 2 days after the last session of the exercise program. The significant increase of blood glucose concentration was found within 30 minutes after dextrose injection (2 g/kg, intraperitoneal) in all experimental groups (Fig. 2A). In ZLC-Con rats, the increased blood glucose due to injection of dextrose was gradually eliminated within 2 hours, whereas, the regulatory capacity of blood glucose was significantly attenuated in ZDF-Con rats (Fig. 2A). In parallel, the AUC values of blood glucose levels during IPGTT in ZDF-Con rats were increased to approximately 2.8-fold compared to ZLC-Con rats (Fig. 2B). However, the blood glucose levels in ZDF-Ex rats were significantly reduced during IPGTT, and the total AUC for the glucose response was markedly lower compared to ZDF-Con rats (Fig. 2B).

The expressions of IL-15 in SOL and GM muscles were measured at the end of the 12-week endurance training. In SOL muscle, there was no significant change of IL-15 proteins between ZLC-Con and ZDF-Con rats. In addition, the expression of IL-15 in SOL of ZDF-Ex rats was higher compared to ZDF-Con rats ($P<0.05$) (Fig. 3). However, no significant effects of diabetes and endurance training were detected in IL-15 expression in GM muscle. Additionally, we found a negative correlation between expression of IL-15 in SOL muscle and body weight ($R=-0.424$, $P=0.04$) (Fig. 4A), whereas, statistical correlation between IL-15 expression in SOL muscle and concentration of fasting blood glucose was not observed ($R=-0.328$, $P=0.118$) (Fig. 4B).

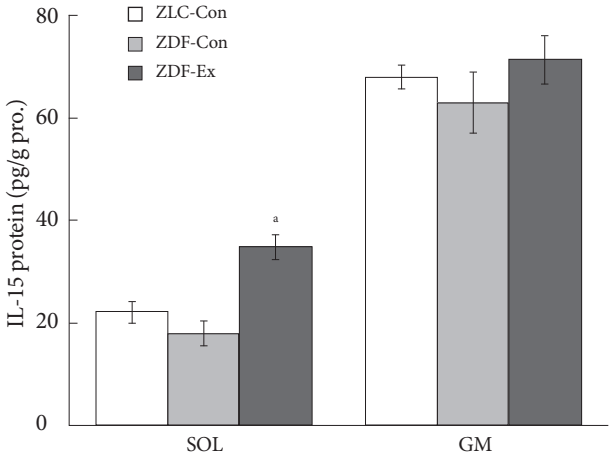

Fig. 3. Effect of 12 weeks of treadmill exercise on expression of interleukin-15 (IL-15) in soleus (SOL) and gastrocnemius medial (GM) muscles. Values are mean±standard error of mean for $n=8$ in each group. ZLC-Con, sedentary Zucker diabetic fatty lean control; ZDF-Con, sedentary Zucker diabetic fatty; ZDF-Ex, exercised Zucker diabetic fatty. [a]$P<0.05$ compared with ZDF-Con group.

DISCUSSION

In the present study, we investigated whether 12 weeks of physical exercise training improves glucose tolerance and expression of IL-15 in diabetic skeletal muscles. Our data demonstrated that body weight and fasting blood glucose levels were positive-

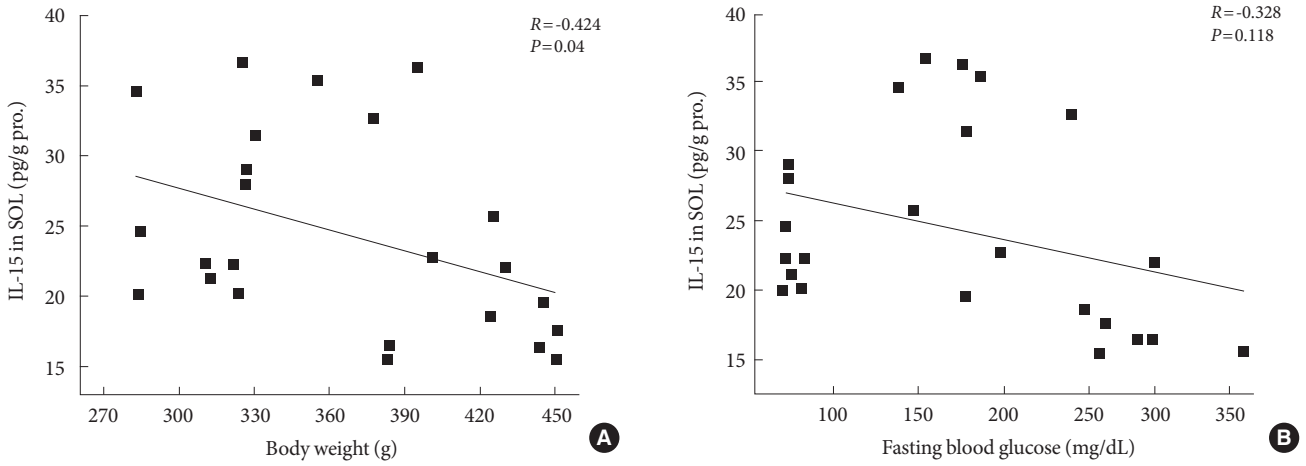

Fig. 4. Association of interleukin-15 (IL-15) expression in soleus (SOL) with body weight and fasting blood glucose levels. Pearson correlation coefficients of IL-15 expression in SOL with (A) body weight and (B) concentration of fasting blood glucose are shown. Pearson correlation coefficients and *P* values are shown in each graph.

ly changed in trained diabetic rats. Additionally, the glucose tolerance significantly improved following 12 weeks of treadmill exercise training. The expression of IL-15 in skeletal muscles, especially in the SOL muscle, significantly increased after treadmill exercise in diabetic animals. To our knowledge, this is the first study to investigate the effect of exercise training on the expression of IL-15 in skeletal muscles with concomitant improvement of glucose tolerance in transgenic diabetic animals.

Our result demonstrated a body weight reduction in ZDF-Ex rats. Based on our observation, we could not find any significant differences in food and water intake between control and exercise groups (data not shown). Additionally, there was no visible symptom of under nutrition during the entire training program. Although the change of body composition was not measured in our study, regular physical exercise is known to decrease body fat mass which leads to weight reduction. The results showing body weight reduction and lower fasting blood glucose levels are typical results obtained from exercise in type 2 diabetic models, indicating the training program was adequately designed and implemented.

In previous IL-15 metabolism studies, IL-15 reportedly stimulated glucose uptake and lipid oxidation in muscle tissue [6,19]. Furthermore, systemic injection of IL-15 reduced fat deposition in normal and obese rodents, which was associated with inhibition of lipogenesis in the liver and adipose tissues [20,21]. Additionally, circulating IL-15 protein regulated body composition including adipose tissue deposition [22]. A recent study reported that IL-15 improves glucose homeostasis and insulin sensitivity in obese mice [23]. In the present study, we found the increase of IL-15 expression in SOL muscle with concomitant improvement of glucose tolerance in diabetic rats after training. Systemic effect of exercise-induced IL-15 on improvement of glucose metabolism is unknown, and IL-15 may be a potent mediator to elucidate the beneficial effect of exercise on metabolic diseases such as obesity or type 2 diabetes.

Previous studies showed inconsistent results regarding the effects of exercise on IL-15 expression in skeletal muscle and plasma [24]. Nieman et al. [12] reported no changes in muscle IL-15 mRNA following 2 hours of intensive strength training. Similarly, Ostrowski et al. [11] observed no changes in plasma IL-15 following 2 hours of treadmill running. In contrast, plasma IL-15 levels increased following resistance exercise [8,25] and treadmill running in healthy young men [13]. To date, however, most of the previous research subjects were normal individuals, and alteration of IL-15 expression in diabetic skeletal muscle was not found. Only one study reported that treadmill exercise promotes IL-15 expression in skeletal muscle of high-fat induced obese rats [26]. In our results, IL-15 expression was increased in skeletal muscle following exercise training especially in the SOL muscle when using a transgenic diabetic model.

Having an important role in the determination of carbohydrate and lipid metabolism, skeletal muscle is affected by insulin resistance in diabetic conditions. In patients and animals with type 2 diabetes, skeletal muscles showed lower oxidative enzyme activity than normal subjects [27-29]. Additionally, the alteration of muscle fiber types and fiber specific oxidative enzyme activities in skeletal muscles of patients with type 2 di-

abetes have been reported [30]. In various type 2 diabetic animals including Otsuka Long Evans Tokushima Fatty, Goto-Kakizaki, and ZDF rats, skeletal muscle had a lower percentage of type IIA fibers compared to age-matched nondiabetic rats [31,32]. Additionally, Yasuda et al. [33] reported the SOL muscle in ZDF rats has a lower percentage of type IIA fibers than lean controls. Due to different metabolic properties of the muscle fiber classification, type I (slow-twitch, oxidative) and type II (fast-twitch, glycolytic) skeletal muscles are differently affected by diabetes. In the present study, IL-15 expression was markedly increased in SOL (mostly type I fiber) but not in GM (type II dominant) muscles. Based on our results, in diabetic skeletal muscle, response of type I muscle fibers may be more sensitive to IL-15 expression than type II muscle fibers following exercise training.

Although this study investigates a new perspective of exercise-induced improvement in type 2 diabetes, several limitations in the experimental design and variables remain. IL-15 expression should have been measured in both skeletal muscle and circulating plasma following exercise training. However, not enough plasma was obtained to analyze insulin and plasma IL-15 levels in this experiment.

In conclusion, our data showed that 12 weeks of treadmill exercise induced an increase of IL-15 expression in SOL muscle with concomitant improvement of glucose tolerance. Based on the current knowledge, including our own findings, increased IL-15 following endurance exercise might be a potent mediator of glucose regulation in type 2 diabetes. Further studies will be required to investigate the mechanisms by which different expressions of IL-15 are regulated by different muscle fiber types under diabetic conditions, and how the increased expression of IL-15 exerts preventive effects including improvement of glucose tolerance in diabetic models.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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