EFFECTS OF CONTUSION AND EXHAUSTIVE EXERCISE ON MURF1 AND MAFBX IN THE SKELETAL MUSCLE OF RATS

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EFEITOS DO TRAUMA CONTUSO E DO EXERCÍCIO EXAUSTIVO NO EM MURF1 E MAFBX NO MÚSCULO ESQUELÉTICO DE RATOS

EFECTOS DE LA CONTUSIÓN Y DEL EJERCICIO EXHAUSTIVO SOBRE MURF1 Y MAFBX EN EL MÚSCULO ESQUELÉTICO DE RATAS

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ABSTRACT

Objective: To study the effects of contusion and exhaustive exercise on the expression of degradation-related factors MuRF1 and MAFbx in the skeletal muscle of rats and describe the repair mechanism of skeletal muscle injury. Methods: Forty-two male SD rats were randomly divided into 7 groups. The rats in each group were killed at different time points (0h, 24h, 48h) after exhaustive exercise (E0, E24, E48) and contusion (D0, D24, D48), respectively, and in the resting state in control group (C). The right gastrocnemius muscles were resected and divided into two parts, one for the mRNAs of MuRF1 and MAFbx by real-time PCR, and the other for protein measurement by Western blotting. Results: Compared with the control group, the MuRF1 mRNA and protein expression of the skeletal muscle in the E0 group was markedly increased (P <0.05) and followed by a downward trend in E24 the E48 groups. On the other hand, MuRF1 mRNA expression of the skeletal muscle in the D24 group was significantly upregulated (P <0.01), then decreased in the D48 group (P <0.01). Meanwhile, compared with the C group, MAFbx mRNA gene expression continued to be upregulated in D24 and D48 (P <0.05), but decreased in E24 and E48 (p<0.01). On the other hand, the NF-κB protein contents of the skeletal muscle in the D0, D24, and D48 groups, as well as in the E48 group, were markedly downregulated (P <0.05), and the one in E48 was also remarkably downregulated (P <0.05). Conclusion: NF-κB may negatively regulate the process of protein degradation by the NF-κB / MuRF1 signal pathway. ***Level of evidence III; Therapeutic studies investigating the results of treatment.***

Keywords: Exercise; Contusion; CBL E3 Ubiquitin Protein Ligase.

RESUMO

Objetivo: Estudar os efeitos do trauma contuso e do exercício exaustivo na expressão dos fatores relacionados à degradação MuRF1 e MAFbx no músculo esquelético de ratos e descrever o mecanismo de reparo da lesão muscular esquelética. Métodos: Quarenta e dois ratos SD machos foram divididos aleatoriamente em 7 grupos. Os ratos de cada grupo foram mortos em diferentes momentos (0h, 24h, 48h) após exercício exaustivo (E0, E24, E48) e trauma contuso (D0, D24, D48), respectivamente, e no estado de repouso no grupo controle (C). Os músculos gastrocnêmios direitos foram ressecados e divididos em duas partes, uma para os mRNAs de MuRF1 e MAFbx por PCR em tempo real e outra para a medição de proteínas a partir do Western blot. Resultados: Em comparação com o grupo controle, o mRNA de MuRF1 e a expressão proteica do músculo esquelético no grupo E0 foram acentuadamente aumentados (P <0,05) e seguidos por uma tendência descendente nos grupos E24 e E48. Por outro lado, a expressão do mRNA de MuRF1 do músculo esquelético no grupo D24 foi significativamente regulada para cima (P <0,01), depois diminuiu no grupo D48 (P <0,01). Enquanto isso, em comparação com o grupo C, a expressão gênica do mRNA de MAFbx continuou regulada para cima em D24 e D48 (P <0,05), mas diminuiu em E24 e E48 (p<0,01). Por outro lado, os teores de proteína NF-κB do músculo esquelético nos grupos D0, D24 e D48, bem como no grupo E48, foram marcadamente regulados para baixo (P <0,05), e o do grupo E48 também foi notavelmente regulado para baixo (P <0,05). Conclusão: NF-κB pode regular negativamente o processo de degradação da proteína pela via NF-κB / MuRF1. ***Nível de evidência III; Estudos terapêuticos que investigam os resultados do tratamento.***

Descritores: *Exercício; Contusões; Proteínas Proto-Oncogênicas c-cbl.*

RESUMEN

Objetivo: Estudiar los efectos de la contusión y del ejercicio exhaustivo sobre la expresión de los factores relacionados con la degradación MuRF1 y MAFbx en el músculo esquelético de ratas y describir el mecanismo de reparación de la lesión muscular esquelética. Métodos: Cuarenta y dos ratas macho SD fueron divididas aleatoriamente en 7 grupos. Las ratas de cada grupo fueron sacrificadas en diferentes momentos (0h, 24h, 48h) después del ejercicio exhaustivo (E0, E24, E48) y de la contusión (D0, D24, D48), respectivamente, y en estado de reposo en el grupo de control (C).

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Se resecaron los músculos gastrocnemios derechos y se dividieron en dos partes, una para los ARNm de MuRF1 y MAFbx mediante PCR en tiempo real y la otra para la medición de proteínas mediante Western blot. Resultados: En comparación con el grupo control, el ARNm de MuRF1 y la expresión proteica del músculo esquelético en el grupo E0 se incrementó notablemente (P <0,05) y fueron seguidos por una tendencia a la baja en los grupos E24 y E48. Por otra parte, la expresión del ARNm de MuRF1 del músculo esquelético en el grupo D24 fue significativamente regulada al alza (P <0,01), y luego disminuyó en el grupo D48 (P <0,01). Mientras tanto, en comparación con el grupo C, la expresión génica del ARNm de MAFbx permaneció regulada al alza en D24 y D48 (P <0,05), pero disminuyó en E24 y E48 (p<0,01). Por otro lado, el contenido de proteína NF-κB del músculo esquelético en los grupos D0, D24 y D48, así como en el grupo E48, se vio notablemente regulado a la baja (P <0,05), y el del grupo E48 también se vio notablemente regulado a la baja (P <0,05). Conclusión: NF-κB puede regular negativamente el proceso de degradación de la proteína a través de la vía NF-κB / MuRF1. ***Nivel de evidencia III; Estudios terapéuticos que investigan los resultados del tratamiento.***

Descriptores: *Ejercicio; Contusiones; Proteínas Proto-Oncogénicas c-cbl.*

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INTRODUCTION

E3 ubiquitin ligase muscle ring finger1 (MuRF1) and muscle atrophy F-box (MAFbx) have been shown to be involved in the regulation of skeletal muscle atrophy under various physiological and pathological conditions. MuRF1 is a master regulator of muscle mass.[1,2] The effects of various modifiable factors and lifestyle such as smoking, drinking, exercise, and nutrition on the regulation of MuRF-1 and MAFbx were discussed. Finally, potential strategies for inhibiting the levels of MuRF-1 and MAFbx to prevent skeletal muscle atrophy were explored. NF-κB activation can enhance the expression of MuRF1 and MAFbx which induce muscle proteolysis and atrophy.[3,4]

Blunt trauma can cause relatively obvious muscle fiber swelling. Eccentric exhaustion exercise can lead to ultrastructural changes and micro-damages of keletal muscle which has been proved by previous studies. But the dynamic changes of protein degradation of skeletal muscle under the two injury models are not clear. Through synchronous comparison, the difference of the degradation-related factors MuRF-1 and MAFbx at different phases during the recovery period in two models will be explored and evaluated in this paper. It is of great significance to explore the degradation mechanism of skeletal muscle.

METHODS

Animals

Male Sprague Dawley rats (aged 8 weeks, weighted 130±20 g, n = 6 per group) were obtained from Comparative Medicine Centre, Jiangsu University (Jiangsu, China). Rats were breed and raised in Human Movement Science Laboratory in Yangzhou University. All animal experiments fit in the international agreements (Helsinki Declaration, revised 2013, Guide for the Care and Use of Laboratory Animals) and approved by the Animal Care and Use Committee of Yangzhou University for the treatment of animals (Jiangsu, China).

Grouping and sampling

42 Sprague Dawley rats were randomly divided into 7 groups: (1) sedentary control group (C, n=6), (2) immediately after contusion group (D0, n=6), (3) 24 hours after contusion group (D24, n=6), (4) 48 hours after contusion group (D48, n=6), (5) immediately after exhaustive exercise group (E0, n=6), (6) 24 hours after exhaustive exercise group (E24, n=6), (7) 48 hours after exhaustive exercise group (E48, n=6). For sample collection, all rats were euthanized by sodium pentobarbital overdose (200 mg/kg, intraperitoneal) and killed at different time points according to above groups. The right gastrocnemius muscles of the hind limbs were taken and stored at −80°C, then the middle section of the sample for Real-time PCR and Western blotting.

A single bout of exhaustive treadmill exercise

The graded exhaustive exercise protocol was adapted by a modification of the method of Lin et al.[5] The treadmill installed electric shock grid on the rear obstacle to give the animal power to exercise. In the exhaustive exercise groups, the rats were tested for 15 - 20 minutes of accommodate treadmill exercise at 15 - 30 meters / minute for 6 day. During the exercise test, they were asked to run in six lanes inclined treadmill (-10 °). The treadmill speed were increased gradually to 10, 15, 20, 25m/min for 10min in each gear, and then accelerated to 30m/min until exhaustion of rats. The exhaustion standard is that the rats can no longer keep pace with the treadmill at the last speed 30 meters / minute, and can't stand erect when placed on the back at rest. The average exhaustion time was 110 minutes in our experiment.

Contusion Injury

The contusion injury to the rat hind-limb was produced using the mass-drop model injury first described by Kami et al.[6] and optimized for our laboratory. This contusion injury was moderately severe, did not result in bone injury or affect gait in the injured animals. Briefly, the technique entails dropping a 200 g weight of cylinder (Diameter of basal surface is 1cm with 1.0J of kinetic energy) from the height of 50 cm onto the medial surface of right gastrocnemius muscles of anaesthetized rats with ethyl ether.

Real-time reverse transcription-PCR

In the present study, the mRNA expression of MuRF1 and MAFbx was assessed by real-time reverse transcription-polymerase chain reaction (RT-PCR). Using RNAiso Plus (Takara Bio, Japan), total RNA was extracted from the middle section of right gastrocnemius muscles according to the manufacturer's instructions. Using the firststrand cDNA Synthesis kit, Samples (-10 ng of RNA) were reverse-transcribed according to the manufacturer's protocol [PrimeScript RT Master Mix (Perfect Real Time) for mRNA, Takara Bio, Japan].

GAPDH was used as an internal standard, to normalize the amount of total RNA present in each reaction. The real-time cycle conditions were 95°C for 30 sec, followed by 40 cycles at 95°C for 5 sec, and at 60°C for 34 sec for mRNA. Expression levels for each mRNA transcript were determined by normalizing each group to the sedentary group by the $2^{-\Delta\Delta CT}$ method. Primers used for detection of rat cDNA were as follows, which were designed by Sangon Biotech (Shanghai, China).

MURF1	forward: 5´-CCATCCTGGACGAGAAGAAG-3´
	reverse: 5´-GCTTGGTCGACTTTTCCAAC-3´
MAFbx	forward: 5´-AGCTTGTGCGATGTTACCCA-3´
	reverse: 5´-AGCTTGTGCGATGTTACCCA-3´
GAPDH	forward: 5´-TGGGTGTGAACCACGAGAA-3´
	reverse: 5´-GGCATGGACTGTGGTCATGA-3´

Western blot analyses

An appropriate amount of right gastrocnemius muscles were taken and shred. The supernatant sample was prepared at 20 ug / time, and SDS polyacrylamide gel electrophoresis was performed (electrophoresis instrument 325BR051391, BIO-RAD, USA. Separating gel concentration 12%), then transferred to a PVDF membrane for 1 hour and blocked with 5% skim milk. The primary antibody Anti-MuRF1 (Sangon Biotech Co.,China, D261009, 1:500), Anti-NF-kB p65 antibody (Abcam, ab19870, 1:500) and the internal reference Anti-GAPDH (Sangon Biotech Co.,China, D110016, 1:10000) were diluted with 5% skim milk according to the ratio of antibody instructions. Then the membrane was soaked, and incubated at 4°C in a three-dimensional shaker overnight. The membrane was washed 4 times and incubated the secondary antibody (Sangon Biotech Co.,1:5000) for 1 h. Then the membrane developed by ECL (ECL Plus Ultra Sensitive Kit, Phygene Life Sci Co.,China). The target protein and GAPDH are evaluated in the same membrane. The final result was expressed as the OD ratio of the target protein LC3 to the internal reference GAPDH. Image Lab5.1 software was used to analyze the gray value.

Statistical analysis

Statistical significance was evaluated by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test to correct for multiple comparisons (SPSS 21.0, SPSS Inc). Data are expressed as mean ± standard error of mean (SEM). P < 0.05 was considered statistically significant.

RESULTS

MuRF1 mRNA expression after exhaustive exercise and blunt contusion

Real-Time PCR results showed that compared with group C, the MuRF1 mRNA of the skeletal muscle in E0 group was remarkably increased (P <0.01) and followed by a downward trend in E24,E48. On the other hand, MuRF1 mRNA expression of the skeletal muscle in D24 group was significantly upregulated (P <0.01), then decreased in D48 group (P <0.01). (Table 1)

MAFbx mRNA expression after exhaustive exercise and blunt contusion

Real-Time PCR results showed that compared with group C, the MAFbx mRNA expression in D24 and D48 groups was remarkably upregulated (P <0.05), but there was no remarkable change in the D0. On the other hand, the expression of the MAFbx mRNA in the E24 and E48 were remarkably downregulated (P <0.01), but there was no remarkable change in the E0. (Table 1)

MuRF1 protein expression after exhaustive exercise and blunt contusion

Western Blot results showed that compared with group C, MuRF1 protein expression in skeletal muscle of D24 and D48 groups was remarkably reduced (P <0.01), but there was no remarkable difference in D0 group. On the other side, MuRF1 protein in E0 group Significantly increased (P <0.01), but MuRF1 protein in the E24 group was remarkably downregulated (P <0.01), and there was no remarkable difference in the E48 group. (Figure 1)

Table 1. Genes expression at different time points in all groups after contusion(D0,-D24,D48) and exhaustive exercise(E0,E24,E48).

Group (n=6)	MuRF1 mRNA	MAFbx mRNA
C	1.000±1.683	1.000±0.719
D0	1..534±1.159	1.777±1.010
D24	9.331±0.550^{**bb}	2.027±0.516*
D48	0.204±0.019^{**bb}	4.806±0.649^{**bb}
E0	10.118±0.747**	1.267±0.866
E24	1.138±0.792^{aa}	0.202±0.395^{**aa}
E48	0.556±0.392^{**aa}	0.595±0.499**

[*] P < 0.05, [**] P < 0.01, Significant difference compared with control. [aa] P < 0.01, Significantly compared with E0. [bb] P < 0.01, Significantly compared with D0. n = 6/group.

NF-κB protein expression after exhaustive exercise and blunt contusion

The results showed that compared with group C, the NF-κB protein contents of the skeletal muscle in the D0, D24, and D48 groups were remarkably downregulated (P <0.05), and the one in E48 was also remarkably downregulated (P <0.05), but there was no remarkable difference in the E0 and E24 groups (P> 0.05). (Figure 2)

DISCUSSION

Blunt trauma can cause relatively obvious muscle fiber swelling. Eccentric exhaustion exercise can lead to ultrastructural changes and micro-damages of keletal muscle which has been proved by previous studies. There also have been reports of ultrastructural changes in the previous work of our laboratory. But the dynamic changes of protein

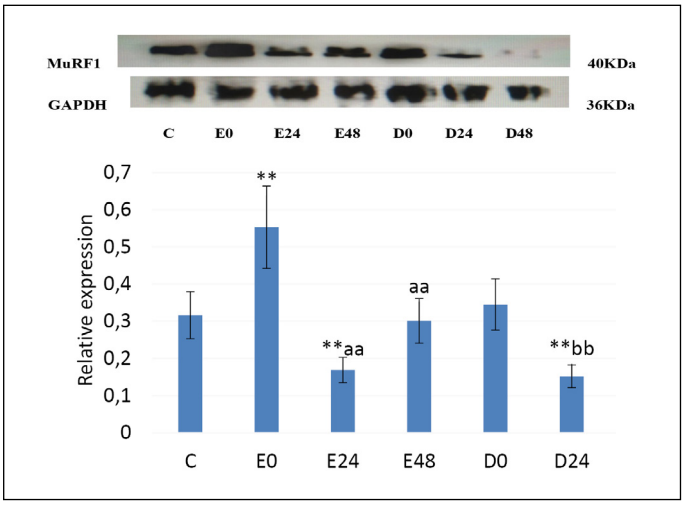

Figure 1. Protein expression of MuRF1 were measured by Western Blot at different time points in all groups after contusion (D0, D24, D48) and exhaustive exercise (E0, E24, E48). Date are mean ± SEM, n = 6/group, [**] P < 0.01, Significant difference compared with control. [aa] P < 0.01, Significantly compared with E0. [bb] P < 0.01, Significantly compared with D0.

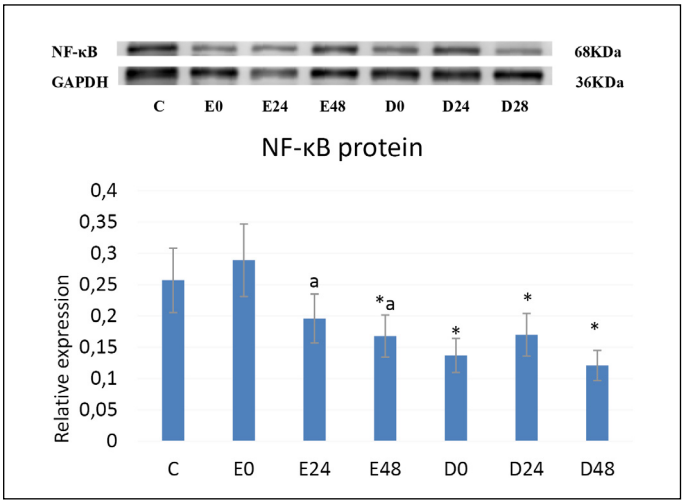

Figure 2. Protein expression of NF-κB were measured by Western Blot at different time points in all groups after contusion (D0, D24, D48) and exhaustive exercise (E0, E24, E48). Date are mean ± SEM, n = 6/group, [*] P < 0.05, Significant difference compared with control. [a] P < 0.05, Significantly compared with E0.

degradation of skeletal muscle under the two injury models are not clear, which has motivated this study. Through synchronous comparison, the difference of the degradation-related factors MuRF1 and MAFbx in two models will be explored and evaluated.

Activation of NF-κB signaling pathway can activate autophagy-lysozyme system (ALS) and ubiquitin proteolysis system (UPS), leading to protein degradation and muscle atrophy.[7,8] However, there are few reports about the changes of MuRF-1 and MAFbx during muscle injury. The aim of this study is to explore the changes of MuRF1, MAFbx, NF-κB in skeletal muscle at different phases after exhaustive exercise and blunt contusion, and related mechanisms of muscle degradation.

Effects of blunt contusion and exhaustive exercise on MuRF1 and MAFbx

How did the exercise effect on MuRF1 and MAFbx in skeletal muscle, Kim et al.[9] studied and found that the combined treatment of low-intensity exercise and ursolic acid (UA) improved muscular atrophy related diseases, remarkably downregulated the expression of atrophy-related genes of atrogin-1 and MuRF1. The other research[10,11] observed the effect of a single aerobic exercise on skeletal muscle protein turnover in mice. As a result, the breakdown-related proteins, such as the phagocytic marker LC3 were immediately upregulated after exercise, but did not increase in recovery period. Meanwhile, MuRF1 level was upregulated in gastrocnemius with an increased polyubiquitination during recovery.

MuRF1 and MAFbx gene expression can cause muscle atrophy, and knocking out any of these genes can alleviate muscle atrophy. Lecker et al.[12] found that under the state where catabolism was greater than anabolic, muscle proteins were significantly reduced, and MuRF1 expression in skeletal muscle increased sharply by 8-20 times. The report showed that the skeletal muscle protein degradation and MuRF1 expression in rats significantly increased after a high-intensity training.[13] However, other studies have indicated that long-term endurance training can reduce the occurrence of skeletal muscle atrophy and inhibit NF-κB activation, and reduce the expression of MAFbx and MuRF1.[8] The Previous studies also found that 4-week intermittent exercise can significantly improve skeletal muscle mass, skeletal protein, increase cell cross-sectional area, reduce expression of MuRF1, MAFbx, and improve skeletal muscle function in myocardial infarction rats.[14] Labeit et al.[15] reported that small molecules targeting MuRF1 may be useful in attenuating skeletal muscle strength loss conditions and regulating glucose metabolism in T2DM.

The results of our study showed that MuRF1 gene expression in skeletal muscle was significantly up-regulated immediately after exhaustive exercise and 24 hours after blunt contusion. MuRF1 is closely related to protein degradation, suggesting that the muscle protein degradation may be enhanced at different phases, then gradually down-regulated. On the other hand, MAFbx mRNA continued to increase for 24 hours and 48 hours after blunt contusion. This factor is also a sensitive indicator of protein degradation, suggesting that blunt contusion was more severe than exhaustive exercise and caused more durable degradation of skeletal muscle protein.

NF-κB / MuRF1 pathway and mechanisms of muscle atrophy

NF-κB is one of the most critical molecules that mediate muscle atrophy. It exists in eukaryotes and is a protein family consisting of complex peptide subunits. NF-κB gene knockout can effectively delay skeletal muscle atrophy caused by braking, chronic diseases, etc.[7,16,17] Studies found that NF-κB activation can increase the expression of MuRF1 in muscle cells under the conditions such as braking, nerve injury and heart failure, but inhibiting NF-κB activity can decrease proteasome expression. MuRF1 expression was reduced in NF-κB deficient mice, and muscle loss was also significantly reduced, suggesting that NF-κB is a necessary step to activate MuRF1 expression. MuRF1 can targets for degradation several myofibrillar proteins, and UBE2L3 exhibited a high affinity for MuRF1.[18,19] Intermittent exercise can reduce the expression of MuRF1 by inhibiting NF-κB to improve the degradation of skeletal muscle protein. Similarly, endurance training can also inhibit the activation of NF-κB, thereby reducing the expression of MAFbx and MuRF1, and reducing the occurrence of skeletal muscle atrophy.[8] However, the exhaustive exercise and blunt contusion model used in this study were different from the above reports, and the results at different phases were also inconsistent. The expression of NF-κB protein in the blunt contusion groups continued to decrease, showing a negative regulation trend, which may play a role in mitigating protein degradation. The dynamic regulation mechanism of NF-κB / MuRF1 signal needs further study.

Regarding how to improve muscle protein breakdown or muscle atrophy, Maarman et al.[20] described melatonin therapy effects for strenuous exercise and blunt trauma, involving the regulated mechanis of cytokines, Akt, NFκB, MURF-1 and MAF (BX). Sakai et al.[21] observed that treadmill exercise can improve prognosis and at least partially alleviate cisplatin-induced muscle atrophy. In addition, Baumert et al.[22] reported that gene polymorphism of TRIM63 (MuRF-1) is related to biomarkers of muscle injury exercise induced.

CONCLUSIONS

Skeletal muscle MuRF1 gene expression was significantly up-regulated immediately after exhaustive exercise, but 24 hours after blunt contusion, which may trigger the protein degradation mechanism at different phases. On the other hand, MAFbx mRNA gene expression continued to increase after 24 hours and 48 hours of blunt contusion, which may indicate that blunt contusion is more severe than exhaustive exercise and makes the degradation process of skeletal muscle protein last longer. However, the content of NF-κB protein in the blunt contusion group continued to decrease compared with the control group, which may negatively regulate this degradation process, and its NF-κB / MuRF1 signal regulation mechanism needs further study.

All authors declare no potential conflict of interest related to this article

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. TP, YW: conceived and designed the experiments; TP, YW: performed the experiments; LY, YW: analyzed the data; QW, FY, CQ, LY: contributed reagents/materials/analysis tools; TP wrote the manuscript. All authors read and approved the manuscript.

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