EFFECTS OF CONTUSION AND EXHAUSTIVE EXERCISE ON MG53, PTRF IN SKELETAL MUSCLE OF RATS

EFEITOS DA CONTUSÃO E DO EXERCÍCIO EXAUSTIVO SOBRE MG53, PTRF EM MÚSCULOS ESQUELÉTICOS DE RATOS

EFECTOS DE LA CONTUSIÓN Y DEL EJERCICIO EXHAUSTIVO SOBRE MG53, PTRF EN MÚSCULOS ESQUELÉTICOS EN RATONES

Original Article
Artigo Original
Artículo Original

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ABSTRACT

Objectives: To study the effects of contusion and exhaustive exercise on gene expression of MG53, PTRF, Pax7 and β-catenin in skeletal muscle of rats, and reveal the repair mechanism of skeletal muscle injury. Methods: Forty-two male Wistar rats were randomly divided into 7 groups, with 6 rats in each group. All groups were euthanized at different time points after exhaustive exercise and contusion, respectively, while the control group was euthanized in resting state. The right gastrocnemius muscles were measured for mRNAs of MG53, PTRF, Pax7 and β-catenin by real time PCR. Results: MG53 mRNA and PTRF mRNA of skeletal muscle in groups immediately after exhaustive exercise and after contusion increased significantly ($p<0.05$), while the two indices decreased constantly at 24 and 48 hours after injury with a similar change trend. Compared with the control group, Pax7 mRNA of skeletal muscle as a marker showed no significant difference in exhaustive exercise groups, but decreased at 48 hours after contusion ($p<0.05$). β-catenin mRNA of skeletal muscle down-regulated significantly over 24 hours after injury, then activated with an increased value at 48 hours after contusion ($p<0.05$). As a whole, the variations in the above indices in the contusion groups covered a wider range than in the exhaustive exercise groups. Conclusion: The cytomembrane repair mechanism of MG53 and PTRF began immediately after the end of exhaustive exercise and contusion. Activation of Pax7 as the satellite cell marker took longer, and Wnt/β-catenin pathway showed first a decrease and then an increase resulting from the time-dependent gene expression during the repair of skeletal muscle injury. ***Level of evidence III, Therapeutic studies investigating the results of treatment.***

Keywords: MG53; PAX7 Transcription Factor; Wnt Signaling Pathway.

RESUMO

Objetivos: Estudar os efeitos da contusão e do exercício exaustivo sobre a expressão de MG53, PTRF, Pax7 e β-catenina no músculo esquelético de ratos e revelar o mecanismo de reparo da lesão desses músculos. Métodos: Quarenta e dois ratos Wistar machos foram divididos randomicamente em 7 grupos, com 6 ratos em cada grupo. Todos os grupos foram sacrificados em diferentes momentos após exercícios exaustivos e contusão, respectivamente, enquanto o grupo controle foi sacrificado em repouso. O músculo gastrocnêmio direito de todos os ratos foi analisado por PCR em tempo real, quanto ao RNAm de MG53, PTRF, Pax7 e β-catenina. Resultados: O RNAm de MG53 e de PTRF no músculo esquelético dos grupos imediatamente após o exercício exaustivo e após a contusão aumentou significativamente ($p < 0,05$), enquanto a diminuição foi constante 24 e 48 horas depois da lesão, com tendência de mudança semelhante. Comparado com o grupo controle, o RNAm de Pax7 do músculo esquelético não mostrou diferença significativa como marcador nos grupos de exercício exaustivo, mas diminuiu 48 horas depois da contusão ($p < 0,05$). O RNAm da β-catenina do músculo esquelético diminuiu significativamente ao longo de 24 horas após a lesão e, a seguir, voltou para um valor elevado 48 horas depois da contusão ($p < 0,05$). Como um todo, as variações nos grupos de contusão tiveram uma faixa mais ampla do que a dos grupos de exercícios exaustivos. Conclusões: O mecanismo de reparação da citomembrana de MG53 e PTRF começou imediatamente depois do término de exercício exaustivo e contusão. A ativação do Pax7 como marcador das células satélite demorou mais tempo e a via Wnt/β-catenina mostrou primeiro diminuição e depois aumento decorrente da expressão gênica dependente do tempo durante o reparo da lesão muscular esquelética. ***Nível de Evidência III, Estudos Terapêuticos – Investigação de resultados do tratamento.***

Descritores: *MG53; Fator de Transcrição PAX7; Via de Sinalização Wnt.*

RESUMEN

Objetivos: Estudiar los efectos de la contusión y del ejercicio exhaustivo sobre la expresión de MG53, PTRF, Pax7 y β-catenina en el músculo esquelético de ratones y revelar el mecanismo de reparación de la lesión de esos músculos. Métodos: Cuarenta y dos ratones Wistar machos fueron divididos aleatoriamente en 7 grupos, con 6 ratones en cada grupo. Todos los grupos fueron sacrificados en diferentes momentos después de ejercicios exhaustivos y contusión, respectivamente, mientras que el grupo control fue sacrificado en reposo. El músculo gastrocnemio derecho de todos

los ratones fue analizado por PCR en tiempo real, cuanto al RNAm de MG53, PTRF, Pax7 y β-catenina. Resultados: El RNAm de MG53 y de PTRF en el músculo esquelético de los grupos inmediatamente después del ejercicio exhaustivo y después de la contusión aumentó significativamente (p < 0,05), mientras que la disminución fue constante 24 y 48 horas después de la lesión, con tendencia de cambio semejante. Comparado con el grupo control, el RNAm de Pax7 del músculo esquelético no mostró diferencia significativa como marcador en los grupos de ejercicio exhaustivo, pero disminuyó 48 horas después de la contusión (p < 0,05). El RNAm de la β-catenina del músculo esquelético disminuyó significativamente a lo largo de 24 horas después de la lesión y, a continuación, volvió para un valor elevado 48 horas después de la contusión (p < 0,05). Como un todo, las variaciones en los grupos de contusión tuvieron una franja más amplia que la de los grupos de ejercicios exhaustivos. Conclusiones: El mecanismo de reparación de la citomembrana de MG53 y PTRF comenzó inmediatamente después del término de ejercicio exhaustivo y contusión. La activación del Pax7 como marcador de las células satélite demoró más tiempo y la vía Wnt/β-catenina mostró primero disminución y después aumento proveniente de la expresión génica dependiente del tiempo durante la reparación de la lesión muscular esquelética. ***Nivel de Evidencia III, Estudios Terapéuticos – Investigación de resultados del tratamiento.***

Descriptores: *MG53; Factor de Transcripción PAX7; Vía de Señalización Wnt.*

DOI: http://dx.doi.org/10.1590/1517-869220192506197718 Article received on 05/04/2018 accepted on 05/03/2019

INTRODUCTION

In the present study, mitsugumin-53 (MG53) as a muscle-specific TRIM family protein(TRIM72), is an important component for regulating membrane repair and to be protective against cardiac Ischemia/reperfusion(I-R) and various forms of skeletal muscle injury.[1-4] MG53 is rapidly recruited to the injury site, and interacts with caveolin-3 to repair membrane damage. Mice lacking MG53 are easily damaged by exercise, and develop a progressive myopathy with atrophy.[5] As a gene known to regulate caveolae membrane structure, Polymerase I and transcript release factor (PTRF) is an essential component of the membrane repair machinery. It play an vital role in the stabilization of caveolins and the formation of caveolae.[6,7,8-10] On the other hand, satellite cells from dystrophic muscle can retain regenerative capacity.[11] The reports showed that paired-box transcription factor 7 (Pax7) and myoblast determination protein (MyoD) expressions were up-regulated after injury by quantitative real-time PCR assays and Western blot) which suggested that Pax7 and MyoD may be potential markers for wound age estimation in skeletal muscle.[12, 13] β-catenin is known as an Armadillo protein that regulates gene expression following WNT pathway activation. In the context of physiopathology, β-catenin is activated genetically or transiently in various cancers, including melanoma where it can be found in the nucleus of tumors.[14, 15] However, there is no report regarding the effects of exhaustive exercise and contusion on MG53 and PTRF of rats skeletal muscles, nor is on Pax7 and β-catenin. So we designed the comparative study investigating the cell membrane repair machinery by measurement of MG53 and PTRF under two models of contusion and a single bout of exhaustive exercise. We also discussed a possible role of Pax7 and Wnt/β-catenin signaling pathway during muscle regeneration under this two models.

METHODS

Animals and grouping

Male Wistar rats (aged 6–8 weeks, weighted 130±20 g, n = 6 per group) were obtained from Comparative Medicine Centre ,Yangzhou University (Jiangsu, China). Rats were raised and breed in Human Movement Science Laboratory in Yangzhou University. All animal experiments were approved by the Animal Care and Use Committee of Yangzhou University (Jiangsu, China) and followed the 'Guide for the Care and Use of Laboratory Animals' (NIH Publications no. 8023, revised 1978) guidelines for the treatment of animals. All rats were housed in a home cage 30 ×41 cm and 25 cm height in a clean room controlled at approximately 22°C with a 12/12 h light–dark cycle. Solid diet and water were provided ad libitum.

Grouping: 42 Wistar rats were randomly divided into 7 groups: (1) sedentary control group (C, n=6), (2) immediately after exhaustive exercise group (E0, n=6), (3) 24 hours after exhaustive exercise group (E24, n=6), (4) 48 hours after exhaustive exercise group (E48, n=6), (5) immediately after contusion group(D0, n=6), (6) 24 hours after contusion group (D24, n=6), (7) 48 hours after contusion group (D48, n=6). For sample collection, all rats were euthanized by sodium pentobarbital overdose (200 mg/kg, intraperitoneal) at different time points according to above groups. Exhaustive exercise group and contusion group sampling: Wistar rats were sampled immediately or 24 and 48 hours later. The left gastrocnemius muscles were harvested and stored at −80°C for Real-time PCR analyses.

A single bout of exhaustive treadmill exercise

The graded exhaustive exercise protocol was adapted by a modification of the method of Lin et al.[16] 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. The treadmill installed electric shock grid on the rear obstacle to give the animal power to exercise. During the exercise test, they were asked to run in six lanes inclined treadmill (-10 °), running to exhaustion at the last speed 30 meters / minute until it can no longer keep pace with the treadmill. So it's exhausted because the rat can't stand erect when placed on the back.

Contusion Injury

The contusion injury to the rat hind-limb was produced using the mass-drop model injury first described by Kami et al[17] and optimized for our laboratory. Briefly, the technique entails dropping a 200 g weight of cylinder from the height of 50 cm (Diameter of basal surface is 1cm with 1.0J of kinetic energy) onto the medial surface of the left gastrocnemius muscle of anaesthetized rats with ethyl ether. This contusion injury was moderately severe, did not result in bone injury or affect gait in the injured animals.

Real-time reverse transcription-PCR

In the present study, the mRNA expression of MG53, PTRF, Pax7, β-catenin was assessed by real-time reverse transcription-polymerase chain reaction (RT-PCR). Total RNA was extracted from the proximal portion of gastrocnemius muscle using RNAiso Plus(Takara Bio, Japan) according to the manufacturer's protocol. Samples (~10 ng of RNA) were reverse-transcribed using the firststrand cDNA Synthesis kit according to the manufacturer's instructions [PrimeScript RT Master Mix (Perfect Real Time) for mRNA, Takara Bio, Japan]. Synthesized cDNA was applied to real-time RT-PCR (ABI 9700 Thermal Cycler Dice, USA) using Takara SYBR Premix Ex Taq TMII for mRNA, and analyzed with 7500 Real-Time PCR System (ABI,USA).

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. To normalize the amount of total RNA present in each reaction, GAPDH was used as an internal standard. Expression levels for each mRNA transcript were determined by the 2–ΔΔCT method by normalizing each group to the sedentary group.The primers were designed by Sangon Biotech (Shanghai, China). Primers used for detection of rat cDNA were as follows:
MG53 forward: 5'-CGAGCAGGACCGCACACTT-3'
reverse: 5'-CCAGGAACATCCGCATCTT-3'
PTRF forward: 5'-CCGCCCTTTACCTTCCAT-3'
reverse: 5'-CCAACCTCGTCGTCATCAG-3'
Pax7 forward: 5'-GCGAGAAGAAAGCCAAACAC-3'
reverse: 5'-CTCAGCCGTGAATGTGGTC-3'
β-catenin forward: 5'-CTTACGGCAATCAGGAAAGC-3'
reverse: 5'-GACAGACAGCACCTTCAGCA-3'
GAPDH forward: 5'- TGGGTGTGAACCACGAGAA-3'
reverse: 5'- GGCATGGACTGTGGTCATGA-3'

Statistical analysis

Data are expressed as mean ± standard error of mean (SEM). Significance was evaluated using one-way ANOVA test (SPSS 13.0, SPSS Inc) followed by Tukey post hoc multiple comparisons test for unpaired values. $P < 0.05$ was considered statistically significant.

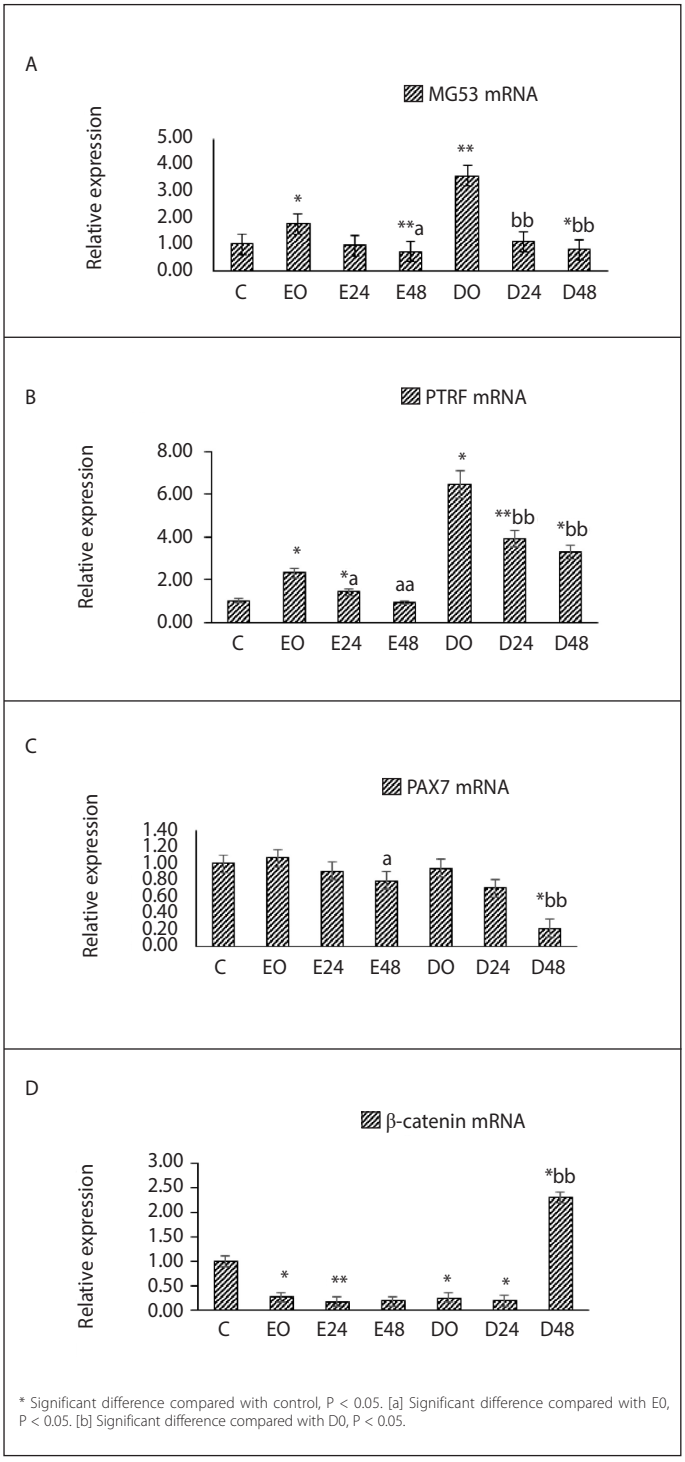
RESULTS

In order to investigating the cell membrane repair machinery, MG53 was measured by qRT-PCR. (Figure 1A) Comparing with group C, MG53 mRNA of skeletal muscle in group E0 and D0 increased significantly ($p<0.05$,$p<0.01$), but decreased significantly in group E48 and D48 ($p<0.05$,$p<0.01$).Comparing with group E0, MG53 mRNA of skeletal muscle in group E48 decreased significantly($p<0.05$). Comparing with group D0, MG53 mRNA of skeletal muscle in group D24 and D48 also decreased significantly($p<0.01$). Comparing with exhaustive exercise groups, MG53 mRNA of skeletal muscle in contusion groups changed much more obviously. (Figure 1A, Table 1)

Figure 1B showed PTRF qRT-PCR results of dynamic changes: comparing with group C, PTRF mRNA of skeletal muscle in group E0, E24, D0, D24 and D48 all up-regulated significantly ($p<0.05$, $p<0.01$).Comparing with group E0, PTRF mRNA of skeletal muscle in group E24 and E48 down-regulated significantly($p<0.05$,$p<0.01$). Comparing with group D0, PTRF mRNA of skeletal muscle in group D24 and D48 also down--regulated significantly($p<0.01$). Comparing with exhaustive exercise groups, PTRF mRNA of skeletal muscle in contusion groups changed with a larger range. (Figure 1B, Table 1)

On the other hand, we also investigated a possible role of Pax7 and Wnt/β-catenin signaling pathway during muscle regeneration. The results as follow: Pax7 mRNA of skeletal muscle had no difference significantly amomg exhaustive exercise groups, but decreased at 48 hours after contusion ($p<0.05$). At the same time, that in E48 decreased significantly comparing with E0 ($p<0.05$), and the expression in group D48 also decreased significantly Comparing with group D0 ($p<0.01$), which indicated that the marker of satellite cells were yet not activated because it need a longer time. Furthermore, comparing with exhaustive exercise groups, Pax7 mRNA of skeletal muscle in contusion groups decreased much more obviously. (Figure 1C, Table 2)

β-Catenin qRT-PCR results: comparing with group C, β-catenin mRNA of skeletal muscle in groups E0,E24,D0 and D24 down-regulated significantly($p<0.05$, $p<0.01$), but up-regulated significantly in group D48 ($p<0.05$) with a time-dependent expressions. Comparing with group D0, β-catenin mRNA of skeletal muscle in group D48 up-regulated significantly($p<0.01$) , which was higher than those of all exhaustive exercise groups. (Figure 1D, Table 2)



* Significant difference compared with control, $P < 0.05$. [a] Significant difference compared with E0, $P < 0.05$. [b] Significant difference compared with D0, $P < 0.05$.

Figure 1. Gene expression in all groups at different time points after exhaustive exercise(E0, E24, E48) and contusion(D0, D24, D48). (A) MG53 ,(B) PTRF, (C) Pax7, (D) β-catenin gene expressions were measured using qRT-PCR. Date are mean ± SEM, n = 6/group,

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

Group(n=6)	MG53 mRNA	PTRF mRNA
C	1.00±0.11	1.00±0.15
E0	1.76±0.11*	2.29±0.11*
E24	0.95±0.15	1.40±0.29*[a]
E48	0.71±0.29**[a]	0.93±0.34[aa]
D0	3.59±0.07**	6.44±0.43*
D24	1.11±0.57[bb]	3.90±0.52**[bb]
D48	0.79±0.50*[bb]	3.29±0.40*[bb]

[*]Significant difference compared with control, $P < 0.05$. [a] Significant difference compared with E0, $P < 0.05$. [b] Significant difference compared with D0, $P < 0.05$. n = 6/group.

Table 2. Gene expression in all groups at different time points after exhaustive exercise(E0,E24,E48) and contusion(D0,D24,D48).

group(n=6)	Pax7 mRNA	β-ceatenin mRNA
C	1.00±0.31	1.00±0.09
E0	1.07±0.23	0.27±0.56*
E24	0.90±0.42	0.17±0.68**
E48	0.79±0.24[a]	0.19±0.38
D0	0.94±0.20	0.27±0.17*
D24	0.70±0.18	0.19±0.31*
D48	0.22±0.21*[bb]	2.30±0.42*[bb]

[*]Significant difference compared with control, $P < 0.05$. [a] Significant difference compared with E0, $P < 0.05$. [b] Significant difference compared with D0, $P < 0.05$. n = 6/group.

DISCUSSION

MG53, PTRF expression

The data show that it is indispensable for molecular complexes formed by MG53, dysferlin and Cav3 for repair of muscle membrane injure, which provide therapeutic targets for the treatment of cardiovascular and muscular diseases associated with damaged membrane repair.[2,18,19] MG53 overexpression can attenuate hypoxia- and H2O2-induced myocardial membrane injury, whereas knockdown of MG53 show progressive muscular dystrophy.[20] Recombinant MG53 protein can modulate therapeutic cell membrane repair in treatment of muscular dystrophy when provided in the extracellular space.[3, 21] The recent study also showed MG53 played a role of damage repair in other organ such as liver, kidney and the cortex.[2, 22] Activity can attenuate skeletal muscle fiber damage after ischemia and reperfusion.[23]

However, there is yet no report regarding the effects of one-time exhaustive exercise and contusion on MG53 and PTRF of rats skeletal muscles. Their modulatory mechanism of skeletal muscle injury and repair are still unclear. To our knowledge, this is the first comparative study investigating the cell membrane repair machinery by measurement of MG53 and PTRF through two models of one-time exhaustive exercise and contusion. In our rat models, we found that PTRF/MG53 mRNA of skeletal muscle in groups immediately after exhaustive exercise and contusion group increased significantly, which indicated that PTRF/MG53 of skeletal muscle may induce cytomembrane repair mechanism to work at the early time after injury. PTRF/MG53 mRNA decreased constantly after 24 and 48 hours in exhaustive exercise groups and contusion groups, because of a following consumption period of them. Comparing with exhaustive exercise groups, PTRF/MG53 launched more sensitively in contusion groups. There was a similar dynamic changes trend between PTRF and MG53, which showed that PTRF is an indispensable component as a docking protein of MG53 served for potential membrane repair.

Loading-associated expression of TRIM72(G53) and caveolin-3 in antigravitational soleus muscle in mice had been reported, and the results demonstrated that 2-week hindlimb unloading caused to down-regulate the expression level of IRS-1(insulin receptor substrate-1) mRNA, TRIM72, Cav-3, and p-Akt in mouse soleus muscle. In addition, the mean expression of them was up-regulated by 1-week reloading following unloading.[5] Recent reports have demonstrated the role of TRIMs in regulation of inflammatory pathways including NF-κB.[24]

Pax7, β-catenin expression

Satellite cells that express Pax7 can regenerate most of the muscle cell in adult life. Pax7 plays a role to control muscle regeneration mediated by muscle satellite cells at different levels in a non-stratified regulatory network. Relatively small amounts of stem cells in the muscle are enough to effectively repair skeletal muscle.[25] Stem cell research proved that the satellite cells from dystrophic muscle retained regenerative capacity.[11]

However, there is also no report regarding the effects of one-time exhaustive exercise and contusion on Pax7 and β-catenin. In this paper, we also discussed a possible role of Pax7 and Wnt/β-catenin signaling pathway during muscle regeneration under two models of one-time exhaustive exercise and contusion. Based on our qRT-PCR results of dynamic changes, we noted that Pax7 mRNA of skeletal muscle had no difference significantly among exhaustive exercise groups, and decreased at 48 hours after contusion which indicated that satellite cells of skeletal muscle were yet not activated and differentiated because the procedure may need a longer time. There were reports regarding the time-dependent expressions of Pax7 and MyoD during skeletal muscle wound healing. The relative quantity of Pax7 protein peaked at 5 days after injury and decreased thereafter.[12]

Pax7 was weakly expressed in differentiated C2C12 cells in vitro. MyoG was expressed in a later stage of myogenesis. During the C2C12 myoblasts fusion process, the changes of promoter and exon 1 methylation of Pax7, MyoD and Myf5 genes were observed. [13] On the other hand, roles of Notch1 Signaling in regulating satellite cell fates choices and postnatal skeletal myogenesis had been confirmed, and human skeletal muscle fibroblasts can stimulate in vitro myogenesis and in vivo muscle regeneration.[26]

Wnt/β-catenin signalling also paly a important role to promote stem cells to repair injured tissue. In a previous in vitro study, the results showed that the canonical Wnt/β-catenin pathway promoted the differentiation of Mesenchymal stem cells (MSCs) into type II alveolar epithelial cells.[27] About regeneration of the injured tendon, the other report found that the number of β-catenin-positive cells was increased at the injured site, suggesting involvement of Wnt/β-catenin signaling in tendon healing.[28]

But there were rarely reports investigating the change of β-catenin under the models of exhaustive exercise and contusion. In our rat models, we found that β-catenin mRNA of skeletal muscle decreased significantly during 24 hours after injure, which indicated that Wnt/β-catenin passageway in skeletal muscle satellite cells of both exhaustive exercise and contusion rats may be depressed, then activated with a increased value at 48 hours after contusion, which maybe regulate target gene so that skeletal muscle satellite cells can differentiate by a time-dependent expressions. Comparing with exhaustive exercise groups, Wnt/β-catenin passageway were activated apparently in contusion groups. β-Catenin is also the key element in VSMC (vascular smooth muscle cell)proliferation induced by hyperlipidemia through the Wnt signaling pathway.[29] The other experiment suggested that aberrant Fibroblast growth factor (FGF) signaling cooperates with WNT/β-catenin in suppression of chondrocyte differentiation.[30] As a whole, β-catenin play a important role in canonical Wnt signaling pathway which promoted to repair injury. The regulatory mechanism of Wnt/β-catenin signaling pathway during muscle regeneration under our two models needs to be investigated in the future.

CONCLUSIONS

The gen expression of MG53/PTRF of skeletal muscle in groups immediately after exhaustive exercise and after contusion increased significantly, then decreased constantly at 24 and 48 hours after injury with a similar change trend. Comparing with the control group, Pax7 mRNA of skeletal muscle as a marker of satellite cell had no difference significantly in exhaustive exercise groups, and decreased at 48 hours after contusion which was yet not activated. On the other hand, β-catenin mRNA of skeletal muscle decreased significantly during 24 hours after injure, then activated with a increased value at 48 hours after contusion by a time-dependent expressions. As a whole, above indexes in contusion groups changed with a larger range than in exhaustive exercise groups.

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

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. TP (0000-0003-3597-2160)*, XT (0000-0002-5945-079X)* conceived and designed the experiments. TP (0000-0003-3597-2160)*, XT (0000-0002-5945-079X)* performed the experiments. XT (0000-0002-5945-079X)* analyzed the data. LY (0000-0001-9292-6772)*, MJ (0000-0003-2637-9437)*, JJ (0000-0002-4171-3416)*, contributed reagents/materials/analysis tools. Tongbin Pan wrote the manuscript. All authors read and approved the manuscript. *ORCID (Open Researcher and Contributor ID).

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