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Skeletal muscle cell transformation and its influencing factors

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Abstract. The composition of muscle fiber type is closely related to pork quality, and the pork quality with high proportion of slow muscle fiber is relatively good. In the study, various regulatory factors were found to act on key genes that determine the type of skeletal muscle fibers. The results show that there are many transcription factors affecting the transformation of muscle fiber types, including calcineurin-NFAT signaling pathway, MEF2-HDACs signaling, AMPK-PGC1 α and nuclear receptor PPAR α/PPAR β. However, the underlying mechanism of individual regulators is still unclear. The mechanism of action of PGC-1 α, MicroRNA and PPAR β (δ) and the synergistic effects of MEF2 and PPAR β with PGC-1 α and PPAR β (δ) and ERR γ were analyzed. Relevant results were obtained such as PGC-1 α gene expression can induce the conversion of type IIx muscle fibers to type I muscle fibers, and miR-133a regulates the conversion of slow muscle fibers to fast muscle fibers by targeting TEAD1; MiR-208b regulates the transformation of slow muscle fibers by targeting and inhibiting METTL8. PPAR β (δ) drives the formation of functional type I muscle fibers. In this paper, there is still a gap in the deep molecular mechanism, in the follow-up study, we can further clarify the factors of the key genes to determine the type of muscle fibers, as well as the deep influence mechanism between each factor. Future research and exploration can focus on the regulation factor proposed in this paper.

Keywords: Skeletal muscle, cell transformation, transcriptional regulators.

1. Introduction

As one of the major sources of protein for human beings, meat has a high proportion in the diet. Therefore, the quality of meat is of great concern to consumers and the market. The main source of domestic animal meat is skeletal muscle, which is an important part of domestic animal body [1]. Different types of skeletal muscle directly affect the physiological characteristics of animal body and meat quality after slaughter, such as the apparent color of meat, meat tenderness and the use of taste and so on [2]. Up to now, there are many methods to classify fiber types, including histochemical method, dominant enzyme pathway, fatigue, twitch contraction velocity, myosin heavy chain (MYHC) subtype expression, etc [3]. Myosin heavy chain isoforms are the most commonly used classification criteria among them, MyHC has different isoforms, corresponding to different atpase activities, and the number of MyHC isoform proteins corresponds to different muscle fiber types, therefore, it is considered as a molecular marker of fiber type [4]. Four subtypes of MyHC in skeletal muscle are MYH7(type I), MYH2(type II a), MYH1(type II X) and MYH4(type II B), [1] type I and type IIA muscle fibers can

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promote the muscle to present the good phenotype characteristics such as flesh color, pH and water system, and thus to present the better meat quality, while type IIB muscle fibers can do the opposite [5].

Pgc-1α is a transcriptional coactivator involved in the peroxisome of mitochondrial proliferation and the transformation of muscle fiber types and cardiac development. The peroxisome proliferator-activated receptor β (δ) [PPAR β (δ)] not only plays an important role in regulating the glucose-lipid balance in the body, moreover, it also plays an important regulatory role in enhancing muscle endurance and explosive force, and promoting the transformation of muscle fiber types [3]. Fibroblast growth factor 21(FGF21) can significantly or extremely significantly increase the expression of genes critical for myogenic differentiation [4]. The theme of this paper is to study the mechanism of muscle fiber type transformation and it's influencing factors to explore the regulatory factors affecting livestock meat quality.

In this study, we investigated the effects of PGC-1 α, CIRCMYLK4, FGF21 and NUDT3 on skeletal muscle fiber type transformation at molecular and genetic levels, this study lays a foundation for further understanding the factors that regulate the transformation of skeletal muscle fiber types and the interactions between them.

2. Transformation of skeletal muscle fibers

2.1. The structure and type of skeletal muscle fibers

The research on skeletal muscle has been going on for many years, and many classification methods have been derived, such as histochemical method and MyHC subtype expression method. In addition to their effects on muscle function, the different muscle fiber compositions also have important effects on the aforementioned meat quality.

Four subtypes of MyHC in skeletal muscle are MYH7(type I), MYH2(type II a), MYH1(type II X) and MYH4(type II B) [1]. Type I muscle fibers, namely oxidative fibers, belong to slow muscle fibers, which have slower contraction speed and higher oxidation capacity. Its energy source is mainly ATP, which is used to maintain the basic metabolic activity and metabolic stability of the body, the content of intramuscular fat is high, with high anti-fatigue and endurance. Type IIb fiber (MyHC 2b) is a kind of fast muscle fiber, which has low activity of aerobic metabolic enzymes, and its energy source is glycogen fermentation. [6] the characteristics of the IIx fiber (MyHC 2x) are similar to those of the IIB fiber, except that the oxidation degree of the IIX fiber is slightly higher and the shrinkage degree is slightly lower. Type IIa fiber (MyHC 2A), which is capable of both oxidative and fermentative metabolism, has metabolic and contractile characteristics intermediate between type IIX and type I fibers [7].

2.2. Transformation of skeletal muscle fiber types

Muscle fibers are not static during skeletal muscle development and can be converted under certain exteRNAl and inteRNAl conditions, for example, it is highly variable under different pathological conditions (such as exercise and obesity), age, nutrition and environmental conditions [8]. Studies have shown that oxidative muscle fibers increase significantly at low temperatures. In addition to the daily intake of nutrients and certain intensity of physical exercise can also change the composition of muscle fibers. This paper mainly discusses the influence of molecular mechanism in the process of fiber change. It was reported that there was no effect on muscle fiber type after systemic knockout of PGC-1 α in mice, but when it was subjected to muscle-specific knockout, there is a clear shift in muscle fibers from oxidative to glycolytic [9]. The results indicate that pgc-1α plays an important role in the transformation of muscle fibers. The transformation order of muscle fiber type was from slow muscle to fast muscle, fast muscle to intermediate fast muscle, and finally to white muscle. In general, myofiber transformation follows Type I, type II, Type III, Type III, Type III, and Type II.

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3. Regulating the influencing factors of skeletal muscle fiber transformation

3.1. PGC-1α

PGC-1 α is a multifunctional transcriptional regulator of protein co-transcription factors, which is expressed in skeletal muscle and fat and participates in mitochondrial biosynthesis, energy metabolism and glycolipid metabolism, to regulate the process of mitochondrial genesis and energy metabolism. The expression of PGC-1 α gene can induce the transformation of type IIX muscle fibers into type I muscle fibers [3]. It was found that the skeletal muscle of the muscle-specific transgenic mice was transformed into a new type of muscle fiber. Overexpression of skeletal muscle PGC-1 α gene increased mitochondrial respiration and fatty acid oxidation, type II fibers turn red and mitochondrial aerobic metabolism is activated [2]. The muscles of type II fibers exhibit features characteristic of type I fibers, for example, increased expression of the TroponinI and MyoG genes [3]. At the same time, myocyte experiments demonstrated that PGC-1 α is a transcriptional co-activator of MEF2 protein and serves as a downstream substrate of CaN signaling, thereby regulating the expression of slow muscle fiber genes.

3.2. microRNA

MicroRNAs (miRNAs) are small non-coding RNAs 21-23 nucleotides long that regulate target mRNA cleavage or only inhibit its translation after transcription. MiRNAs preferentially expressed in striated muscles are called myomiR [6]. The group currently includes eight miRNAs: Mir-1, Mir-133a, Mir-133b, Mir-206, Mir-208a, miR-208b, miR-486, and miR-499 [7] . Experiments in C2C12 cells showed that Mir-1 and miR-206 promote MYOBLAST differentiation by downregulating HDAC4 and the P180 subunit of DNA polymerase α. Studies have shown that zero miRNAs are expressed differently in slow and fast muscles, suggesting that miRNAs may play a key role in the transition of muscle fiber types. Liu et al found that miR-133a-1 and miR-133a-2 did not significantly affect skeletal muscle development in the case of individual knockout, but simultaneous knockout resulted in fast muscle fiber disease, as well as muscle fiber transformation [7]. Mir-133a regulates the conversion of slow to fast muscle fibers by targeting TEAD1 [8]. Mir-208b regulates the transformation of slow muscle fibers by targeting and inhibiting METTL8. Mi-r-204-5p can significantly reduce the proportion of slow muscle fiber genes in myoblasts by targeting MEF2C and err γ, overexpression or inhibition of miR-2-12p expression in C204C5 cells after induction of myogenic differentiation [8]. The differential expression of miR-103 and miR-144 in the fast and slow muscles of Chinese perch suggests that their roles in regulating muscle fiber development or performance are also different [9]. It was found that overexpression of miR-22-3p inhibited the expression of myosin heavy chain I (MyHC I) and MYHC IIA, and promoted the expression of MyHC IIb. However, the effect of MIR-22-3P inhibitor was reversed. Mir-22-3p regulates skeletal muscle fiber type switching by inhibiting the AMPK/SIRT1/PGC -1 signaling pathway [10].

3.3. PPARβ(δ)

PPAR β (δ) is a transcription factor that drives the formation of functional type I muscle fibers in muscle tissue, indicating that overexpression of PPAR β (δ) in skeletal muscle can promote the conversion of more fermentative muscle fibers into oxidative ones, the expression of genes related to oxidative metabolism was significantly increased [11]. In skeletal muscle ,PPARβ is expressed ubiquitously as the most abundant PPAR isotype. Increases of PPARβ activity through ligand activation, PPARβ overexpression have recently suggested it could be physiologically involved in muscle fiber-type switching [12].

In the process of transforming muscle fiber types regulated by PPAR β (δ) , the possible underlying mechanism is mainly the PGC-1α/PPAR β (δ)/ERR γ/miRNA pathway. Studies by Luquet et al have revealed that PGC-1α can rapidly activate PPAR β (δ) in the absence of a ligand. The activation of PPAR β (δ) by PGC-1α occurs through protein-protein interactions [5]. This suggests that PGC-1α effects muscle fiber type conversion by activating its downstream effector, PPAR β (δ) [9]. PPARb in skeletal muscle myocytes induces a functional muscle fiber-type switching toward less oxidative fibers [12]

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PGC-1 α coactivates many transcription factors, including PPARs, ERR, NRF1/2, and MEF2[4]. PGC-1α directly interacts with its transcription factors to recruit molecules that mediate staining, chromatin remodeling, and by recruiting components of the transcriptional machinery through histone acetyltransferase activity; Such as RNA polymerase II to achieve gene transcription. Mir-22-3p regulates skeletal muscle fiber type switching by inhibiting the AMPK/SIRT1/PGC -1 signaling pathway. PPAR β (δ) can produce a variety of signal events by binding to other activators, kinase cascades, etc. These signals change the transcriptional activity of key nuclear receptors in the body, the stability of miRNAs, etc., finally induced skeletal muscle fiber type transformation [7].

4. The correlation between factors

4.1. The synergism of PPAR β and PGC-1 α

Luquet et al showed that PGC-1α can rapidly activate PPAR β (δ) in the absence of ligand. This indicates that PGC-1α has a high probability of transforming muscle fiber types by activating its downstream effector PPAR β (δ). The trends in PGC-1α and PPAR β (δ) mRNA expression in skeletal muscle were consistent with changes in oxidative muscle fiber content, suggesting that PPAR β (δ) may be regulated by PGC-1α, thereby affecting aerobic metabolism in skeletal muscle as well as the transformation of muscle fiber types [8]. PPARb/RXRa heterodimers efficiently bound the PGC1a PPRE; no binding could be observed when it was mutated in its 30 and 50 repeated motifs. Addition of the PPARb-specific agonist GW501516 stimulated luciferase activity 2-fold, when its PPRE was mutated this ligand-dependent stimulation of PGC1a promoter activity was abolished.

4.2. Synergism of pgc-1 α and MEF2

The MEF2 family belongs to the MADS-box family of evolutionarily conserved transcription factors, which are essential for cell growth and differentiation in a variety of tissues, including the brain. It was originally found in muscle tissue. [13] it has been described as a protein activity that binds to a DNA sequence that, unlike the MRF binding site, is present in the CRM of the (MCK) gene, which is responsible for MCK expression during muscle cell differentiation. The Mef2-binding DNA sequence was found in almost all known muscle-specific genes in CRM [13].

The overexpression of PGC-1α also increased the expression of Myoglobin and troponin, indicating that PGC-1α could induce more complete transformation of muscle fiber types This was accompanied by a significant increase in MEF2 expression, which revealed that PGC-1α and MEF2 could cooperatively activate transcriptional processes during myofiber transformation [6].

4.3. PPAR β (δ) and ERR γ acted synergistically

PPAR β (δ) and ERR γ synergize with transcription capable of activating MYH7 and MYH7B genes, thus playing a critical role in energy metabolism in oxidized muscle fibers [4] . There was a positive correlation between the expression of ERR γ and the expression of MCK-PPAR β (δ) I type muscle fiber marker gene. ERR γ has been shown to promote the formation of type I muscle fibers in skeletal muscle, and ERR γ can directly, through highly conserved ERR response elements, activate the transcription of Myh7(miR-208b) and Myh7b (miR-499) genes, therefore, ERR γ is considered as a bridge between PPARs and miR-208b, miR-499, and PGC-1α may play a role in this regulatory mechanism through its synergistic activation of ERR γ and PPAR β (δ) [9].

5. Conclusion

The different types of skeletal muscle fibers and their mutual transformation are introduced in this paper. Furthermore, the important factors regulating fiber type transformation were introduced, and the mechanism of each factor and their relationship were listed. We can see that PGC-1 α, MicroRNA and PPAR β (δ) can all regulate muscle fiber types, and these factors are related to each other and form a complex system to regulate the transformation of muscle fibers. In the follow-up study, we can further identify the factors to determine the type of muscle fiber key genes, as well as the factors between the

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deep-seated mechanism. There is still a gap in the deep-seated molecular mechanism in this paper. In the future, we can focus on the regulatory factors proposed in this paper, in order to improve meat quality and increase production benefit, more economical and convenient ways to adjust and control the influencing factors are explored.

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