Advances in Molecular Signaling Pathways and Nutritional Regulation of Muscle Fiber Type Transformation (Postprint)

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Abstract

Skeletal muscle is composed of different types of muscle fibers, which are classified into types , a, x, and b based on the myosin heavy chain isoforms. The composition of muscle fiber types in skeletal muscle can affect post-slaughter meat quality, while muscle fiber type transformation is regulated by various intracellular signaling pathways and regulatory factors, as well as dietary nutritional factors. This paper provides a preliminary summary of the molecular signaling pathways underlying muscle fiber transformation and its nutritional regulation, aiming to serve as a reference for future research on regulating meat quality through nutritional strategies.

Full Text

Progress in Molecular Signaling Pathways of Skeletal Muscle Fiber Type Transformation and Their Nutritional Regulation

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Abstract

Skeletal muscle is composed of different types of muscle fibers characterized by myosin heavy chain isoform composition, consisting of four main types: type I, IIa, IIx, and IIb. The composition of muscle fiber types in skeletal muscle influences meat quality after slaughter. Skeletal muscle fiber type transformation can be regulated by various signaling pathways and regulatory factors in vivo, as well as by nutritional factors in the diet. This review summarizes the molecular signaling pathways underlying muscle fiber transformation and certain nutritional factors, providing a reference for understanding how to improve meat quality through nutritional intervention.

Keywords: skeletal muscle; muscle fiber type transformation; signaling pathway; nutritional regulation; meat quality

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Skeletal muscle is composed of different types of muscle fibers. Traditional classification methods use histochemical staining to categorize fibers into slow oxidative (type I), fast glycolytic (type II), and oxidative-glycolytic hybrid types based on metabolic and contractile characteristics [1]. Modern molecular biology methods classify fibers into types I, IIa, IIx, and IIb according to their myosin heavy chain (MyHC) composition, with metabolic profiles transitioning from oxidative to glycolytic and contractile speed increasing sequentially. The proportion of different muscle fiber types affects post-slaughter meat quality [2]. Mammalian muscle fiber number is largely determined before birth, with pigs showing no further change in fiber number after embryonic day 90 [3]. Mature mammalian skeletal muscle exhibits high plasticity, with age, nutrition, hormones, and exercise all capable of inducing fiber type transformation following the pattern I IIa IIx IIb [4]. Muscle fiber transformation is regulated by multiple signaling pathways and numerous cytokines (Figure 1 [Figure 1: see original paper]) [5]. Changes in MyHC expression levels manifest as muscle fiber type transformation. This article summarizes recent research on nutritional regulation—including plant extracts, dietary energy and crude protein levels, and unsaturated fatty acids—to provide a theoretical basis for improving muscle fiber type composition and meat quality through nutritional strategies.

Abbreviations: CaM, calmodulin; CaMK, calmodulin-dependent protein kinase; AMPK, AMP-activated protein kinase; SIRT1, silent information regulator 1; PGC-1α, peroxisome proliferator-activated receptor γ co-activator 1α; MEF2, myocyte-specific enhancer-binding factor 2; CaN, calcineurin; NFAT, nuclear factor of activated T cells; HDACs, histone deacetylases; Fnip1, folliculin interacting protein-1; FNDC5, fibronectin type III domain-containing protein 5; Irisin; FoxO1, forkhead box transcription factor O1; Akt, protein kinase B; PPARs, peroxisome proliferator-activated receptors; ERR, estrogen-related receptor.

1. Signaling Pathways of Muscle Fiber Type Transformation

Muscle fiber transformation is regulated by multiple signaling pathways, primarily through changes in intracellular calcium ion (Ca^{2+}) concentration and metabolic products in skeletal muscle, which activate downstream molecular pathways and subsequently regulate the expression of genes related to muscle fiber types, leading to adaptive transformation.

1.1 AMPK/PGC-1α/SIRT1 Signaling Pathway

AMPK is a crucial regulatory kinase that balances cellular energy, often referred to as the "cellular energy regulator." During exercise, AMPK is essential for maintaining energy supply. AMPK is regulated by various metabolic signals, such as high AMP/ATP ratios and exercise. Once activated by phosphorylation, AMPK can regulate multiple downstream target pathways in the body, including skeletal muscle tissue. Mice with AMPK gene deletion show reduced capacity for transforming type IIb to IIa and IIx fibers during endurance training [6]. PGC-1α is highly expressed in skeletal muscle and plays an important role in muscle fiber transformation. As a key downstream target of AMPK, PGC-1α can be directly phosphorylated by AMPK and promotes mitochondrial biogenesis, aerobic metabolism, and slow-twitch fiber formation [7]. Lin et al. [8] found that mice with skeletal muscle-specific overexpression of PGC-1α showed increased type I fiber content in glycolytic fibers, increased oxidative metabolism-related proteins, and improved muscle fatigue resistance. Arany et al. [9] also found that PGC-1α transgenic mice exhibited increased fatigue resistance and induced transformation of type IIx to type I fibers, while skeletal muscle-specific knockout of PGC-1α promoted fiber transformation from oxidative types I and IIa to glycolytic types IIx and IIb [10]. SIRT1 is another important energy sensor in the body. As a nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylase, SIRT1 is involved in energy metabolism regulation, free radical metabolism, and other physiological processes. AMPK can activate SIRT1 by regulating nicotinamide phosphoribosyltransferase activity, increasing the NAD^+/NADH ratio [11]. Overexpression of SIRT1 in mouse skeletal muscle promotes fast-to-slow fiber transformation and increases PGC-1α levels [12]. SIRT1 can affect muscle fiber differentiation by regulating myogenic regulatory factors (MRFs). The MRF family includes MyoD, myogenin, Myf5, and MRF4. MRFs regulate the differentiation of myoblasts into different lineages, altering muscle fiber types. MRF4 is continuously highly expressed in slow-twitch fibers of adult individuals after birth, suggesting its involvement in muscle fiber phenotype regulation [13]. MyoD can affect MyHC gene expression by regulating myocyte-specific enhancer-binding factor 2 (MEF2), thereby altering fiber types. SIRT1 can specifically inhibit the expression of myogenic differentiation marker genes MyoD and MEF2, blocking satellite cell differentiation and ultimately changing muscle fiber type [14].

1.2 Ca^{2+}/Calcineurin (CaN)/Calmodulin-Dependent Protein Kinase (CaMK) Signaling Pathway

In skeletal muscle, Ca^{2+}-dependent transport pathways play an important role in muscle fiber transformation by activating transcription factors and regulating mitochondria-encoded genes, thereby inducing fiber type conversion [15]. The calcineurin (CaN) signaling pathway is an important Ca^{2+}-dependent transport mechanism. Calcineurin is a Ca^{2+}/calmodulin (CaM)-dependent serine/threonine protein phosphatase. When muscle fibers generate action potentials, intracellular Ca^{2+} content increases continuously, binding to CaM and activating CaN, which subsequently dephosphorylates nuclear factor of activated T cells (NFAT), causing its translocation into the nucleus where it binds to target genes and promotes slow-twitch fiber gene expression [16]. Exercise can affect muscle fiber transformation by regulating the CaN signaling pathway. Wu [17] found that loaded eccentric exercise could activate Ca^{2+} and regulate muscle fiber transformation through CaN. Mice with CaN knockout showed decreased type I fiber proportions, while CaN overexpression increased type I and IIa fiber proportions in skeletal muscle [18]. McCullagh et al. [19] found that NFAT promoted slow-twitch fiber gene expression while inhibiting fast-twitch fiber gene expression. CaMK can be activated by increased intracellular Ca^{2+}, inducing muscle fiber type transformation. During strength exercise, CaMKII activity increases and rises with exercise intensity, indicating that Ca^{2+}/CaMK participates in muscle fiber type transformation. The regulatory pathway involves activated CaMK interacting with histone deacetylases (HDACs), which then translocate to the nucleoplasm, activating MEF2 and inducing slow-twitch fiber gene expression [18-20]. CaMKII also serves as an upstream signaling molecule of AMPK to regulate oxidative metabolic capacity in mouse muscle [21].

1.3 Other Signaling Molecules

1.3.1 Folliculin Interacting Protein 1 (Fnip1) Fnip1 is a protein that interacts with folliculin in vivo. Baba et al. [22] found that in kidney cells, Fnip1 can be phosphorylated by AMPK, and its phosphorylation level decreases when AMPK inhibitors are added, suggesting that Fnip1 may be involved in energy sensing mediated by AMPK. Building on this, Park et al. [23] found that compared with wild-type mice, Fnip1-deficient mice showed increased AMPK levels in pre-B cells, along with increased AMPK-related mitochondrial metabolic genes and glucose uptake, indicating that Fnip1 is important for maintaining metabolic balance after metabolic stress in pre-B cells. Park et al. [23] also found that Fnip1 is highly expressed in skeletal muscle. Reyes et al. [24] found that Fnip1 deficiency in skeletal muscle cells leads to increased mitochondrial oxidative phosphorylation levels, enhanced mitochondrial function, and increased oxidative fibers, resulting in muscle fiber type transformation. Fnip1 may regulate mitochondrial biogenesis and muscle fiber type by modulating AMPK through direct or indirect pathways.

1.3.2 Forkhead Box Transcription Factor O1 (FoxO1) FoxO1 is a major regulatory factor in the FoxO family, regulated by various phosphorylation kinases, and plays an important role in myoblast proliferation, differentiation, and muscle fiber type transformation. Schachter et al. [25] found that FoxO1 is regulated by phosphorylated protein kinase B (Akt). In skeletal muscle, FoxO1 regulates carbohydrate catabolism to provide energy during fasting [26]. Kamei et al. [27] found that mice transgenic for human FoxO1 showed reduced muscle mass and weight, with paler muscle color. Shi et al. [28] found that shRNA interference of FoxO1 expression promoted MyHC I expression in porcine myoblasts, consistent with Zhang et al. [29] who found that FoxO1 inhibited MyHC I expression in porcine skeletal muscle. Acute or chronic eccentric exercise altered FoxO1 mRNA expression levels in the superficial region of fast skeletal muscle, thereby changing muscle fiber types [30].

1.3.3 Peroxisome Proliferator-Activated Receptors (PPARs) PPARs are a class of nuclear receptors that regulate gene expression at the transcriptional level. Wang et al. [31] found that oral administration of PPARδ agonists in mice increased mitochondrial synthesis and type I fiber content, indicating that PPARδ may be a key molecule in the muscle fiber transformation process. Luquet et al. [32] found that skeletal muscle-specific overexpression of PPARδ promoted fiber transformation from type II to type I and enhanced skeletal muscle oxidative metabolic capacity. Endurance training elevated PPARγ and PGC-1α to different levels in various fiber types, possibly related to changes in mitochondrial content and oxidative profile [33]. Schuler et al. [34] found that knockout of PPARβ in mice decreased muscle fiber oxidative capacity, while PPARβ also stimulated PGC-1α expression. PPARγ may be activated through protein-protein interactions with PGC-1α [35]. PPARs promote slow-twitch fiber expression through direct or indirect interactions with estrogen-related receptors (ERR) [36].

2. Nutritional Regulation

2.1 Natural Plant Extracts

Natural plant extracts often contain various polyphenolic compounds that can increase AMPK phosphorylation in skeletal muscle, thereby promoting PGC-1α phosphorylation and activation. It is speculated that natural plant extracts may regulate muscle fiber type transformation through the AMPK pathway [37]. Dietary supplementation with Eucommia polyphenol extract significantly increased type I fiber-related gene expression while decreasing type IIb fiber expression in porcine longissimus dorsi muscle [38]. Oral administration of salidroside and Rhodiola rosea in mice promoted fast-to-slow muscle fiber transformation [39]. Dietary supplementation with 5% apple polyphenols in mice increased the proportion of slow-twitch fibers, with subsequent studies showing that 0.5% supplementation also promoted slow-twitch fiber formation [40-41]. Murase et al. [42] found that dietary supplementation with polyphenol-rich green tea

extract improved muscle endurance and oxidative capacity. Wang et al. [43] found that dietary supplementation with epigallocatechin gallate in finishing pigs decreased type I fiber content and reduced AMPK and PGC-1α expression, possibly related to extract type and dosage.

2.2 Dietary Energy and Crude Protein Levels

Dietary energy and crude protein levels and sources can regulate muscle fiber type composition. Harrison et al. [44] found that malnutrition had no effect on fiber type content in the longissimus dorsi muscle of 3-7 week-old pigs but significantly increased type I fiber proportion in the rhomboid muscle, suggesting that nutritional levels may have differential effects on fiber transformation in different muscle locations, exhibiting tissue-specific characteristics. Lefaucheur [45] found that malnutrition in piglets significantly increased type IIb fiber proportion while decreasing type IIa fiber proportion in longissimus dorsi muscle, whereas feed restriction significantly increased type I fiber proportion. Li et al. [46] found that different dietary energy sources affected muscle fiber types in finishing pigs, with low-starch, high-fat, and high-fiber diets increasing type I and IIa fibers while decreasing type IIx and IIb fibers, indicating that low-starch, high-fiber diets can reduce glycolytic fiber proportion and improve meat quality. Sun [47] found that high-energy diets increased type IIa and IIx fiber proportions while decreasing type IIb fiber proportion compared with low-energy diets. Chen [48] found that higher dietary crude protein levels increased muscle fiber diameter in Duroc-Yorkshire-Landrace crossbred pigs. Li et al. [49] found that reducing dietary crude protein from 16% to 13% significantly increased type IIa fiber proportion in longissimus dorsi and psoas major muscles and type I fiber proportion in biceps femoris muscle. Yang et al. [50] found no significant effect of nutrition levels on fiber type composition in longissimus dorsi muscle of Rongchang and Duroc-Landrace-Yorkshire pigs, suggesting that discrepancies may be related to breed and growth stage. Additionally, protein source affects muscle fiber type-related gene expression, with beef extract promoting slow-twitch fiber gene expression in mouse extensor digitorum longus muscle, while fish protein decreased PGC-1α content and type I fiber gene expression in mouse soleus muscle [51-52]. As an important cellular energy sensor, AMPK regulates energy output, and both dietary energy and crude protein levels can alter muscle fiber composition, possibly through AMPK-mediated energy sensing networks.

2.3 Unsaturated Fatty Acids

Recent studies have shown that fatty acid composition and ratio in dietary fat also affect muscle fiber type transformation. Ren [53] found that unsaturated fatty acids promoted type I fiber gene expression in mice, possibly through the AMPK pathway. Maternal supplementation with unsaturated fatty acids during late gestation and lactation promoted related gene expression and increased oxidative fiber proportion in suckling piglets through maternal effects [53]. Un-

saturated fatty acid treatment of muscle cells significantly upregulated AMPK gene expression, suggesting that promotion of oxidative fiber formation may be related to AMPK pathway activation [53]. The type of unsaturated fatty acid also affects fiber transformation. Tian [54] found that n-3 family unsaturated fatty acid supplementation promoted type I and IIa fiber-related gene expression in porcine muscle tissue, improving fiber type composition. Compared with soybean oil rich in n-6 polyunsaturated fatty acids, dietary fish oil rich in n-3 polyunsaturated fatty acids significantly increased type IIx fiber proportion while decreasing type IIb fiber proportion in mouse extensor digitorum longus muscle [55].

Muscle fiber transformation is influenced by multiple signaling pathways and regulatory factors, with nutritional factors exerting varying degrees of regulatory effects. In recent years, besides deepening research on inducing myofiber transformation, studies on inducing directional differentiation of muscle satellite cells to regulate muscle fiber types have also been ongoing. Genome-wide temporal expression profiling of satellite cells has revealed their continuous involvement in muscle stem cell formation and function maintenance [56]. Satellite cells can differentiate into different subpopulations, including fast-twitch, slow-twitch, and convertible subpopulations [57]. Under normal physiological conditions, satellite cells remain quiescent between the basal lamina and plasma membrane. When physiological status changes, satellite cells enter the cell cycle under cytokine stimulation, forming new myofibers [58]. Controlling satellite cell directional differentiation provides a new research direction for regulating muscle fiber type transformation. Advances in muscle fiber type transformation research establish theoretical foundations for precision feeding and targeted nutritional regulation of meat quality in animal production, while also providing references for treating human myopathies.

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