frontiers | Frontiers in Physiology

TYPE Opinion
PUBLISHED 05 July 2023
DOI 10.3389/fphys.2023.1228318

OPEN ACCESS

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RECEIVED 24 May 2023
ACCEPTED 27 June 2023
PUBLISHED 05 July 2023

CITATION
Xu J and Velleman SG (2023), Critical role of the mTOR pathway in poultry skeletal muscle physiology and meat quality: an opinion paper.
Front. Physiol. 14:1228318.
doi: 10.3389/fphys.2023.1228318

Critical role of the mTOR pathway in poultry skeletal muscle physiology and meat quality: an opinion paper

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KEYWORDS

meat quality, mTOR, muscle growth, poultry, satellite cells, skeletal muscle

Skeletal muscle is the major component of meat, and is primarily composed of muscle fibers bounded by multiple connective tissue layers (Velleman and McFarland, 2014). These connective tissue layers function as an essential support and functional system, incorporating components like blood vessels and extracellular matrix macromolecules. Consequently, muscle development and growth, morphological structure, and biochemistry are crucial aspects in the determination of meat yield and quality. The modern poultry industry has had one area of focus on selection for enhanced growth performance, specifically emphasizing increased body weight and skeletal muscle yield (Havenstein et al., 2007; Collins et al., 2014). Structural abnormalities, such as diminished connective tissue spacing and reduced capillary density resulting from excessive muscle fiber hypertrophy, have been observed in the breast muscle of modern rapid-growing poultry lines (Velleman et al., 2003; Joiner et al., 2014). The loss of connective tissue spacing and presence of oversized myofibers result in direct contact between muscle fibers, and this condition is correlated with a greater occurrence of muscle fiber degeneration (Wilson et al., 1990; Velleman et al., 2003). Furthermore, insufficient capillary supply in the breast muscle could limit the removal of anaerobic respiration byproducts, such as lactic acid. The residual lactic acid in the breast muscle can lead to a decrease in pH, potentially exacerbating muscle degeneration. In addition to the structural flaws, the breast muscle of modern fast-growing poultry breeds exhibits conditions such as Wooden Breast (Sihvo et al., 2014) and White Stripping (Soglia et al., 2018), which adversely affect the quality of the breast meat. Muscle growth and structure are primarily determined by muscle cell biology and biochemistry, which are influenced by signal transduction pathways. One of the key players involved in muscle function is the mechanistic target of rapamycin (mTOR) pathway, which is critical in regulating muscle hypertrophic growth and mass accretion in poultry (Vignale et al., 2015; Ma et al., 2018). This opinion paper will discuss how the mTOR pathway modulates skeletal muscle growth, structure, and biochemistry, and ultimately can affect poultry meat yield and quality.

Muscle fiber number is fixed by the time of hatch (Smith, 1963). Post-hatch muscle grows through the hypertrophy of existing muscle fibers. Accumulation of intracellular protein in existing muscle fibers is the most likely mechanism for post-hatch muscle hypertrophic growth. With regard to the molecular mechanisms, mTOR is a key regulator controlling muscle size and mass accretion in mammals and poultry (Bodine et al., 2001; Vignale et al., 2015). It has been broadly hypothesized that mTOR promotes myofiber hypertrophy by stimulating protein synthesis (Wang and Proud, 2006; Wang et al., 2015; You et al., 2019). A schematic illustration of possible mechanisms of mTOR pathway in skeletal muscle function is presented in Figure 1. Using mammalian models, the mTOR protein kinase has been found to function in two distinct multiprotein complexes: mTOR

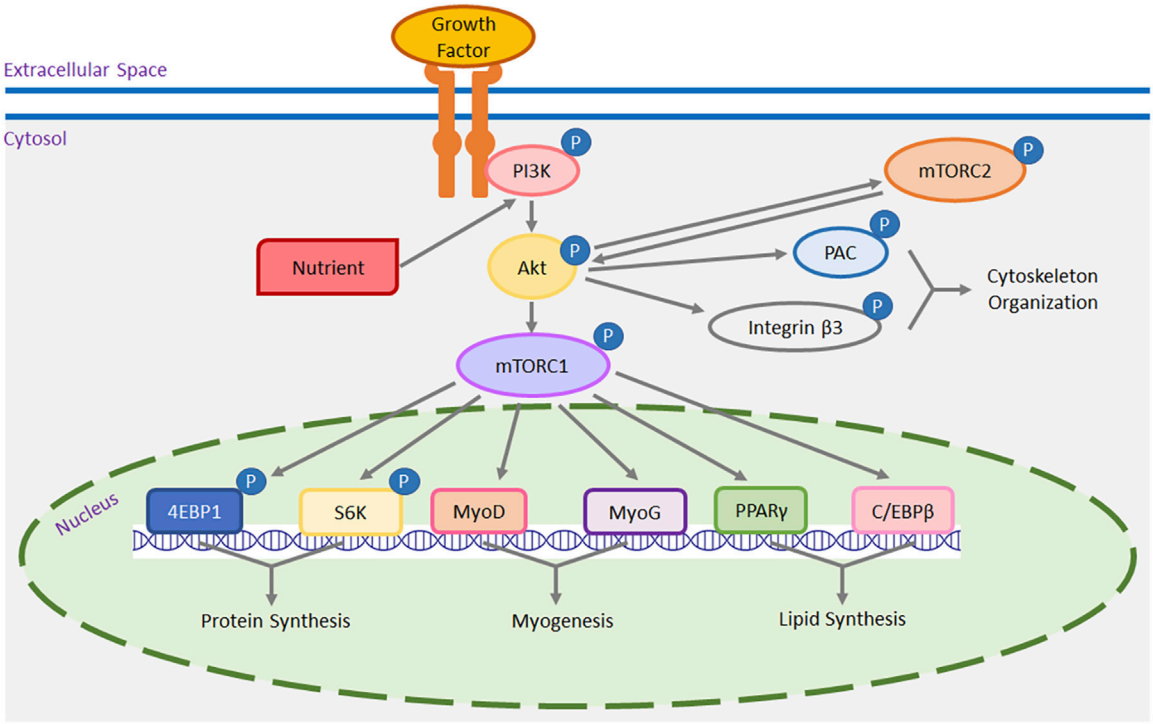

FIGURE 1
A schematic representation of the mTOR pathway in muscle cells. Both growth factors, through their receptors, and intracellular nutrients trigger the activation (or phosphorylation) of phosphoinositide 3 kinase (PI3K). Once activated, PI3K in turn activates protein kinase B (Akt) and mTOR complex 1 (mTORC1). Nutrients and growth factors, via the PI3K/Akt pathway, can also stimulate mTOR complex 2 (mTORC2), which, once activated, can further stimulate mTORC1 via Akt. Moreover, activated mTORC2 phosphorylates cytoplasmic p21-activated kinase (PAK) and integrin β3 via Akt, contributing to cytoskeleton organization and migration. Downstream targets of mTORC1 include but are not limited to p70 S6 kinase (S6K), eukaryotic initiation factor 4E binding protein 1 (4EBP1), myoblast determination factor 1 (MyoD), myogenin (MyoG), peroxisome proliferator-activated receptor-gamma (PPARγ), and CCAAT/enhancer-binding protein-beta (C/EBPβ). Both S6K and 4EBP1 are implicated in the initiation of gene expression for protein synthesis. MyoD and MyoG are myogenic transcriptional regulatory factors promoting myogenesis, while PPARγ and C/EBPβ are adipogenic factors that stimulate the transcription of genes involved in lipid synthesis.

complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (Hara et al., 2002; Sarbassov et al., 2004). As an intracellular nutrient sensor (Tesseraud et al., 2006; Vignale et al., 2015), mTORC1 has been found to promote protein synthesis with the stimulation of intracellular nutrients including amino acids (Kop-Bozbay and Ocak, 2019), vitamins (Vignale et al., 2015), fatty acids (Yoon et al., 2011), and glucose (Patel et al., 2001) in birds and mammals. In addition to nutrients, extracellular growth factors also stimulate the activation of mTORC1 via specific transmembrane growth factor receptors (Rommel et al., 2001). Both nutrients and growth factors activate mTORC1 via the phosphoinositide 3 kinase (PI3K)/protein kinase B (Akt) signaling. For mTORC2, it can also be activated by nutrients (Tato et al., 2011) and growth factors (García-Martínez and Alessi, 2008) through the PI3K/Akt pathway in mammalian cells. Activated mTORC2 indirectly activates mTORC1 through Akt (Sarbassov et al., 2005; Moschella et al., 2013). Downstream mTOR effectors for protein synthesis are p70 S6 kinase (S6K) (Brown et al., 1995; Ohanna et al., 2005; Vignale et al., 2015) and eukaryotic initiation factor 4E binding protein 1 (4EBP1) (Hara et al., 1998; Wang et al., 2015). As the amount of intracellular protein directly determines the size of myofibers, both mTOR/S6K and mTOR/4EBP1 signaling plays an essential role in regulating the hypertrophic growth of poultry skeletal muscle (Zhang et al., 2014; Wang et al., 2015). Notably, using human models, Cuthbertson et al. (2006) reported that it is the myofibrillar proteins and not the sarcoplasmic proteins which promote hypertrophic growth of muscle fibers. Abou Sawan et al. (2018) also showed that mTORC1 increased muscle myofibrillar protein synthesis but not mitochondrial protein synthesis via the S6K and 4EBP1 in human muscle fibers. In avian species, the mTOR pathway may also promote muscle fiber hypertrophy and muscle mass accretion by upregulating myofibrillar proteins synthesis in an S6K- and 4EBP1-dependent manner. Future studies will be needed to test this hypothesis.

At the periphery of each muscle fiber, there exists a specific population of muscle stem cells known as satellite cells (Mauro, 1961). Satellite cells act as the exclusive cell reservoir for post-hatch muscle hypertrophy, and this occurs through satellite cell proliferation, differentiation, and donation of cell nuclei to existing muscle fibers (Moss and Leblond, 1971; Cardiasis and Cooper, 1975). In poultry, satellite cell mitotic activity peaks during the first week after hatch (Mozdziak et al., 1994; Halevy et al., 2000), after which it gradually diminishes, eventually reaching a mitotically quiescence state in mature muscle (Schultz and Lipton, 1982). With damage to muscle fibers (Bischoff, 1975; Snow, 1977),

the mitotically inactive satellite cells re-enter the cell cycle and repair the damaged muscle fibers. Numerous studies have suggested that mTORC1 promotes satellite cell myogenesis by inducing the expression of myogenic transcriptional factors such as myoblast determination factor 1 (MyoD) and myogenin (MyoG) (Han et al., 2008; Vignale et al., 2015; Xu et al., 2022a; Xu and Velleman, 2023) (Figure 1). In chicken breast muscle, impaired proliferation and differentiation with decreased expression of *mTOR, MyoD,* and *MyoG* were observed in the breast muscle satellite cells of a current faster-growing broiler chicken line compared to two historical chicken lines from 1990s (Xu and Velleman, 2023). Insufficient myogenesis by satellite cells may result in a higher incidence of myofiber degenerative and fibrotic myopathies like Wooden Breast, as satellite cells with impaired regeneration potential are unable to fully restore the necrotic myofibers to their original size (Velleman and Clark, 2015; Clark and Velleman, 2016; Velleman et al., 2018). In contrast, Wooden Breast has not been observed in modern faster-growing turkeys. This difference can be partially explained by increased satellite cell myogenesis facilitated by an enhanced mTOR/S6K pathway in turkeys (Xu et al., 2022a). The other complex, mTORC2, promotes mouse satellite cell myogenesis, primarily through the activation of Akt/mTORC1 signaling (Matheny Jr et al., 2012) (Figure 1). In addition, mTORC2-triggered Akt activation influences actin polymerization, which in turn affects cytoskeleton organization and cell migration through its downstream effectors including p21-activated kinase (PAK) (Zhou et al., 2003) and integrin β3 (Kirk et al., 2000) in mammals (Figure 1). Satellite cell alignment, a prerequisite for their fusion to form multinucleated myotubes, requires migration (Chazaud et al., 1998). Taken together, the mTOR pathway plays a multifaceted role in muscle biology; it not only directly regulates protein synthesis in muscle fibers but also modulates muscle hypertrophy and regeneration potential of damaged fibers by controlling the myogenic or regenerative potential and migration of satellite cells.

In addition to regulating muscle growth and regeneration, the mTOR pathway also governs the possible adipogenesis of muscle satellite cells. This is accomplished by regulating the expression of adipogenic regulatory factors like peroxisome proliferator-activated receptor-gamma (PPARγ) (Kim and Chen, 2004) and CCAAT/enhancer-binding protein-beta (C/EBPβ) (Kim et al., 2014) (Figure 1). As multipotential stem cells, satellite cells can spontaneously transdifferentiate to an adipocyte-like lineage and synthesize lipid content with appropriate extrinsic stimuli (Asakura et al., 2001; Shefer et al., 2004). As shown by Xu et al. (2021; 2022a), heat stress significantly increased the activity of the mTOR/S6K pathway, which is accompanied by increased lipid synthesis in turkey breast muscle satellite cells. Furthermore, knocking down the expression of *mTOR* significantly decreased lipid accumulation and suppressed the expression of both *PPARγ* and *C/EBPβ* in turkey satellite cells (Xu et al., 2022b). In in vivo studies, the increased intracellular lipid content has been associated with the increased intramuscular fat deposition in chicken breast muscle (Piestun et al., 2017; Patael et al., 2019), potentially influencing protein-to-fat ratio in poultry breast muscle. The increase in intramuscular fat depots may also be associated with fat-associated myopathies like White Striping.

Considering the crucial role of the mTOR pathway in skeletal muscle growth, structure, and physiology, numerous extrinsic factors have been investigated for their potential effects on mTOR activity. Nutrients such as phosphatidic acid (Yoon et al., 2011), vitamin D (Vignale et al., 2015) and leucine (Kop-Bozbay and Ocak, 2019) and specific growth factors like epidermal growth factor (EGF) (Cao et al., 2009) and insulin-like growth factor-1 (IGF-1) (Rommel et al., 2001) are well-known activators of the mTOR pathway in birds and mammals, which may in turn stimulates muscle protein synthesis. The mTOR pathway is also significantly influenced by various cellular stressors. For example, the mTOR pathway can sense and respond to thermal stress (Xu et al., 2022a) and oxygen stress (Chaillou and Lanner, 2016), subsequently adjusting protein synthesis in skeletal muscle. Nonetheless, the regulation of the mTOR pathway is tissue- and species-specific in poultry muscle, relying on a delicate balance of various factors. Different timing, intensity, or duration of these stimuli can also result in distinct cellular responses. Taking temperature effect as an example, Xu et al. (2022a) reported that cold stress (5°C colder than the control) inhibited the activity of the mTOR/S6K pathway in breast muscle satellite cells of one-week-old turkeys. However, an increase in mTOR activity was observed when newly hatched chickens were constantly challenged with chronic cold stress (5.3°–12.3°C colder than the control) during the first week after hatch in the chicken leg muscle (Nguyen et al., 2015). Comprehending how the extrinsic factors are involved in the regulation of the mTOR pathway is critical in optimizing poultry skeletal muscle growth and structure.

The mTOR pathway is undeniably critical in poultry skeletal muscle growth and physiology by stimulating myofiber protein accumulation (Wang and Proud, 2006) and regulating satellite cell myogenesis and adipogenesis (Xu et al., 2022a; b). These mTOR functions may have a direct impact on poultry meat quality. Gaining a deeper understanding of the mTOR pathway and its regulatory mechanisms will enable the poultry industry to develop strategies for optimizing poultry muscle growth and enhancing meat quality. For example, providing feed with higher vitamin D (Vignale et al., 2015), arginine (Yu et al., 2018), leucine (Kop-Bozbay and Ocak, 2019) might achieve the nutritional stimuli necessary for mTOR activity in poultry skeletal muscle. Introducing a heat stress with appropriate intensity and duration, particularly during the first week after hatch when satellite cells exhibit peak mitotic activity and temperature sensitivity (Mozdziak et al., 1994; Halevy et al., 2001), will significantly increase the activity of the mTOR pathway (Xu et al., 2022a), which in turn, will stimulate satellite cell myogenesis and protein synthesis, resulting in increased muscle mass accretion and preventing myofiber necrotic and fibrotic myopathies like Wooden Breast. Nevertheless, as indicated by Ma et al. (2018), it is vital to avoid chronic high-intensity heat stress to mitigate negative effects on mTOR activity. Furthermore, the elevation in mTOR activity induced by heat stress at an early age also promotes fat accumulation, particularly in the breast muscle satellite cells of rapid-growing poultry (Xu et al., 2022b). Increased intramuscular fat deposition could be associated with fat-associated myopathies like White Striping, impacting the quality of breast meat. As poultry breast muscle is a favored consumer source of high-protein and low-fat meat, fluctuating

between heat and cold stress in the first week post-hatch could potentially augment mTOR-mediated protein synthesis, while inhibiting mTOR-driven fat production. Continued research is necessary to discover the appropriate strategies of controlling the mTOR pathway in response to various stimuli, ultimately improving poultry skeletal muscle growth while producing a high-quality meat product.

Author contributions

The paper represents the opinion of JX and SV and does not include new data. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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