（学位第３号様式）

学 位 論 文 要 旨

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題　目	Studies on molecular mechanisms that regulate the skeletal muscle mass in meat type chickens （肉用鶏における骨格筋量の個体差を支配する要因の解明と鶏肉生産への応用）

Skeletal muscle mass is controlled through a delicate balance between protein synthesis and protein degradation. In chickens, it has been considered that the muscle protein degradation rate is one of the major factors that affects muscle growth, because fast-growing strains and/or individuals show a lower protein degradation rate compared with slow-growing counterparts. However, the molecular mechanisms for regulating protein degradation rates in the skeletal muscle of chickens remain unclear. The aim of this study was to investigate the mechanisms by which regulate the different growth rate between fast- and slow-growing chicks.

Based on their body weight gain from 1 to 5 days of age, 5-day-old chicks (*Gallus gallus domestics*) were divided into a slow-growing and a fast-growing group. The rates of degradation of myofibrillar proteins in the chicks were determined by measurement of 3-methylhistidine (3-MeHis) in excreta. The muscle protein degradation rate was lower in the fast-growing than in the slow-growing chicks. Concordantly, lower mRNA expression of *Atrogin-1/MAFbx*, which is one of the limiting factors for the ubiquitin–proteasome system of muscle protein degradation, and higher phosphorylation (inactivation) levels of the transcriptional factor FoxO1, which has a critical role to control muscle protein degradation rate, were observed in the skeletal muscle of the fast-growing chicks. Moreover, the mRNA expression of β_2-adrenergic receptor (β_2-AR) was significantly higher in the skeletal muscle of the fast-growing group compared with that of the slow-growing group. These results suggest that the lower muscle protein degradation rate might contribute to growth of the fast-growing chicks, and β_2-AR expression levels might be involved in the control of muscle protein degradation.

Next, the roles of each subtype of β-AR in the skeletal muscle of chicks were evaluated. Among 3 β-AR subtypes, only β_2-AR suppressed gene expression encoding *Atrogin-1/MAFbx* mRNA in the skeletal muscle. Then, to investigate the intracellular signaling mechanisms by which β_2-AR reduces muscle protein degradation, the phosphorylation level and intracellular localization of FoxO1 were examined both in the skeletal muscle of chicks and C2C12 myotubes. Consequently, the β_2-AR agonist increased phosphorylated FoxO1 protein accompanied by decreased plasma 3-MeHis concentration, an index of muscle protein degradation. Furthermore, the β_2-AR agonist also decreased *FoxO1* mRNA expression and FoxO1 protein abundance accompanied by increase in 64 microRNAs (miRNAs) in C2C12 myotubes. Among these miRNAs, transfection with miR-374b-5p and miR-7a-1-3p mimics decreased FoxO1 mRNA expression and protein abundance. These results indicate that the β_2-AR signaling suppresses FoxO1 transcriptional activity towards its target genes (i.e., *Atrogin-1/MAFbx*) via the dual mechanisms of altering FoxO1 protein expression and phosphorylation.

In conclusion, in the skeletal muscle of chicks, the β_2-AR plays a significant role in regulating muscle protein degradation by suppressing FoxO1 transcriptional activity. And, the fast-growing chicks showed higher expression of *β_2-AR* mRNA in the skeletal muscle accompanied by lower *Atrogin-1/MAFbx* mRNA expression level, compared with the slow-growing chicks, suggesting that *β_2-AR* mRNA expression might be physiologically significant in controlling the level of muscle protein degradation.