University of Jiroft

Biospecies Research

Journal homepage: bsr.ujiroft.ac.ir

Iranian Biology Society

Gene Network Modeling and Promoter Motif Analysis of Hub Genes in Skeletal Muscles of Young Bulls Treated with Steroid Growth Promoters

Saideh Eskandri Nasab[1], Hamideh Nouri Sadegh[1], Zahra Roudbari[*2]

https://doi.org/10.22034/bsr.2026.575234.1015

[1] *Department of Animal Science, Faculty of Agriculture, University of Zabol, Iran.*

[2] *Department of Animal Science, Faculty of Agriculture, University of Jiroft, Iran.*

ARTICLE INFO

Article Type
Original Article

Article History
Received: 02 May 2026
Accepted: 26 May 2026
Published: 31 May 2026

***Corresponding author**
roudbari.zahra@ujiroft.ac.ir

ABSTRACT

Skeletal muscle growth, regulated by complex genetic and hormonal factors, is crucial for livestock productivity. This study identified key hub genes and promoter elements in the skeletal muscle of young bulls treated with dexamethasone (± 17β-estradiol) using the GEO dataset GSE12179. Differentially expressed genes were identified, and a protein-protein interaction network was analyzed using Cytoscape, revealing 11 hub genes as dexamethasone-responsive molecular targets. Promoter motif analysis via MEME Suite identified conserved elements potentially regulated by transcription factors such as SP2, ZEB1, and TFAP2C. Functional enrichment showed these hubs genes are involved in IGF-1/Akt/mTOR and TGF-β/Smad signaling, extracellular matrix remodeling, and ribosome biogenesis. Although glucocorticoid treatments are widely used, these findings suggest that genetic-based approaches such as genomic selection and marker-assisted breeding may provide realistic alternatives for enhancing muscle development. These findings provide novel insights into the molecular mechanisms underlying dexamethasone-associated muscle transcriptional responses and offer a framework for improving livestock traits through targeted genetic strategies rather than hormonal interventions.

Keywords: Skeletal muscle growth, Dexamethasone, Hub genes, Promoter motif analysis.

How to cite this paper

Eskandri Nasab, S., Nouri Sadegh, H., Roudbari, Z., 2026. Gene Network Modeling and Promoter Motif Analysis of Hub Genes in Skeletal Muscles of Young Bulls Treated with Steroid Growth Promoters. *Biospecies Research*, 2, pp. 102-111.

Introduction

Body growth and size, particularly skeletal muscle mass, are critical traits in domestic animals because they are directly associated with productivity, meat quality, and economic profitability in the livestock industry. Consequently, numerous programs have been implemented to improve growth rate and body composition in farm animals, including selective breeding, targeted nutrition, and environmental optimization (Devlin et al., 2009).

In addition to these approaches, the use of bioactive compounds such as growth hormones has emerged as an effective tool for stimulating anabolic pathways and

increasing muscle mass. In this context, steroid growth promoters, both natural and synthetic, play a key role in regulating gene expression and growth-related signaling pathways (Gharahdaghi et al., 2021). Although the use of these compounds is permitted in some countries, it is entirely prohibited in the European Union due to food safety and ethical considerations (Combes and Balls, 2007). Nonetheless, reports of illegal application of these compounds in the livestock industry, particularly in beef cattle, continue to raise concerns regarding public health and production chain monitoring (Nebbia et al., 2011).

Investigating the molecular effects of these compounds can provide deeper insights into the biological mechanisms and regulatory pathways influencing muscle growth. In this regard, gene network modeling, as a systems biology approach, enables the identification of key or hub genes that play central roles in biological interactions and regulatory networks associated with muscle growth. These hub genes are typically located at the core of protein–protein interaction networks and their expression is directly influenced by intracellular signals and environmental factors (Zhang et al., 2023). Identifying such central genes can enhance our understanding of the molecular mechanisms controlling growth and the response to hormonal stimulants.

Promoter motif analysis of hub genes is a useful approach for identifying conserved DNA motifs and transcription factors involved in gene regulation under different physiological and treatment conditions. This approach facilitates the exploration of upstream transcriptional regulatory mechanisms and helps reveal shared regulatory patterns associated with steroid exposure. Dexamethasone (Dex), a synthetic glucocorticoid, has been reported to influence skeletal muscle gene expression and, when administered at subtherapeutic doses, has occasionally been used illegally as a growth promoter in beef cattle (Nebbia et al., 2011).

Although several studies have investigated the effects of steroid compounds on gene expression and muscle physiology, an integrated analysis combining protein–protein interaction (PPI) networks of differentially expressed genes with promoter motif analysis of hub genes in response to Dex treatment has not yet been comprehensively explored, particularly in young bulls. In the present study, we analyzed hub genes identified in the skeletal muscle of young bulls treated with Dex and investigated their promoter regions to identify common regulatory motifs and potential transcription factors using network-based analysis and motif discovery approaches. This study aims to improve understanding of the transcriptional regulatory mechanisms associated with Dex-induced responses in bovine skeletal muscle and to highlight key genes involved in these processes.

Materials and Methods

To identify differentially expressed genes (DEGs) associated with muscle growth in response to glucocorticoid treatment, gene expression data were retrieved from the Gene Expression Omnibus (GEO) database hosted by NCBI (https://www.ncbi.nlm.nih.gov/gds), a widely used resource for storing and accessing genomic datasets in bioinformatics studies. In this study, the microarray dataset GSE12179 was selected which was originally generated and published by Carraro et al., (20009), and examines gene expression in skeletal muscle of young bulls treated with dexamethasone (Dex) and a combination of dexamethasone with 17β-estradiol (Estr) at sub-therapeutic doses, compared to a control group (untreated). Differential expression analysis was performed using the GEO2R tool, based on the limma package. To correct for multiple testing, the Benjamini–Hochberg method was applied. Genes with $|\log_2 FC| > 1$ and P-value < 0.01 were considered significantly differentially expressed.

The identified DEGs were further subjected to functional annotation and biological clustering using the DAVID Bioinformatics Resources (version 6.8). Functional enrichment analysis included Gene Ontology (GO) categories for Biological Process and Molecular Function, as well as KEGG pathways, with a significance threshold of P-value < 0.05. Subsequently, to explore interactions among genes related to muscle growth and development, a protein–protein interaction (PPI) network

was constructed using data from STRING v10 (http://string-db.org), with a minimum interaction confidence score of 0.15 (low confidence). A low confidence threshold was applied to prevent the exclusion of potential interactions and to maintain network comprehensiveness, as commonly practiced in exploratory network analyses. The extracted interactions were imported into Cytoscape v3.9.1 as TSV files to construct the PPI network. To identify hub genes, the CytoHubba plugin v0.1 was used. Four computational algorithms Maximal Clique Centrality (MCC), Degree, Density of Maximum Neighborhood Component (DMNC), and Maximum Neighborhood Component (MNC) were employed to rank genes and select hub genes in the PPI subnetwork. These algorithms provide complementary analytical approaches, reducing bias that may arise from using a single method. Specifically, MNC and DMNC are based on the cluster structure of the network, Degree relies on the number of edges connected to each node, and MCC evaluates shortest paths between nodes (Elasbali et al., 2024). For promoter motif analysis of hub genes, the 1,000 bp upstream flanking regions (UFRs) of the selected genes were retrieved from Ensembl. The MEME Suite v5.4.1 (https://meme.nbcr.net) was used to identify regulatory motifs. In MEME analysis, up to 10 motifs of 6–50 nucleotides were identified under the Zero or One Occurrence per Sequence (ZOOPS) model, with a significance threshold of P-value < 0.01; all other parameters were set to default. Identified motifs were further analyzed using Tomtom (http://meme-suite.org/tools/tomtom) to match them against known motif databases and remove redundant patterns. Additionally, GOMo (http://meme-suite.org/tools/gomo) was employed to predict the biological functions of motifs and assess their potential roles in regulating genes responsive to steroid treatment.

Results

Analysis of gene expression profiles between young bulls treated with dexamethasone (± 17β-estradiol) and the control group revealed a substantial number of genes exhibiting significant differential expression. In total, 445 genes were upregulated ($|\log_2 FC| > 1$, P-value < 0.01) and 580 genes were downregulated in the treated group compared to controls. These expression changes indicate the broad effects of glucocorticoid treatment (dexamethasone) on gene regulation in bovine muscle tissue.

To identify key genes within the protein–protein interaction (PPI) network, network analysis was performed using the CytoHubba plugin. Based on the results from four algorithms MNC, DMNC, Degree, and MCC a total of 11 hub proteins with the highest levels of connectivity and central roles in the network were identified (Figure 1). The characteristics and biological functions of these hub proteins are summarized in Table 1.

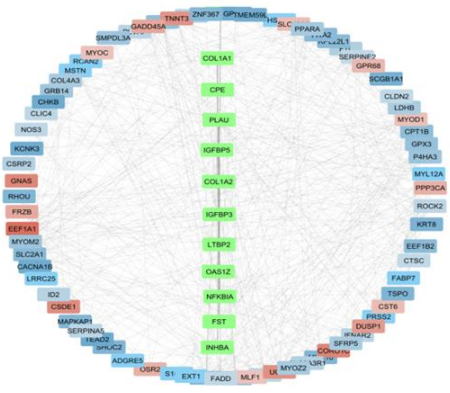

Figure 1. Gene co-expression network of hub genes in skeletal muscles of young bulls treated with steroid growth promoters.

In this study, to investigate the regulatory mechanisms of the identified hub genes and to identify potential transcriptional regulatory elements, the promoter regions of these genes were analyzed. Motif analysis revealed that among the promoter sequences of the hub genes, eight conserved motifs ranging from 8 to 62 base pairs in length were identified (Table 2). These motifs may represent potential transcription factor binding sites and could be associated with the regulation of genes responsive to dexamethasone, as well as biological processes related to muscle growth, development, and tissue remodeling. The identification of these conserved motifs suggests the presence of shared regulatory patterns among key genes in the protein–protein interaction network that may contribute to the transcriptional response to dexamethasone treatment.

Table 1. Hub genes identified in the gene co-expression network of skeletal muscles in young bulls treated with steroid growth promoters.

Rank	Gene symbol	Method	(|logFC| > 1	P-value < 0.01	Gene discription
1	OAS1Z	DMNC	2.155456	0.000607	ENSBTAG00070032649
1	NFKBIA	MNC	1.644063	2.99E-05	ENSBTAG00070002974
2,1	PLAU	DMNC- MCC	-1.03886	0.032873	ENSBTAG00070028590
4	FST	DMNC	-1.94367	0.004001	ENSBTAG00070019948
2	CPE	MNC	-3.76218	0.001029	ENSBTAG00070006277
3,1,4	IGFBP5	Degree-MNC-MCC	1.365756	0.015781	ENSBTAG00070001801
2	LTBP2	Degree	-1.46046	0.006171	ENSBTAG00070023359
1,1,2	INHBA	Degree-DMNC- MCC	-1.06888	0.011863	ENSBTAG00070016353
4,1	IGFBP3	DMNC- MCC	-1.26046	0.001539	ENSBTAG00070016065
1,2,4	COL1A1	Degree-MNC-MCC	2.465887	0.000668	ENSBTAG00070016905
3,2	COL1A2	Degree-MNC	1.818516	0.014556	ENSBTAG00070001070

Table 2. Promoter motifs and associated transcription factors identified in hub genes of skeletal muscles in young bulls treated with steroid growth promoters.

Motif	Logo	Gene Symbol	Predictions	Top 5 specific predictions
MA0079.5 (SP1)		CPE	40	BP translation CC nucleus BP protein transport MF structural constituent of ribosome CC ribosome
MA0103 (ZEB1)		COL1A1	8	MF isomerase activity CC cytoplasmic part BP cellular macromolecule biosynthetic process CC intracellular membrane-bounded organelle BP regulation of transcription, DNA-dependent
MA0516.3 (SP2)		CPE	62	BP translation BP protein transport MF structural constituent of ribosome CC ribosome BP regulation of transcription, DNA-dependent
MA0685.2 (SP4)		CPE	39	BP translation CC nucleus BP protein transport MF structural constituent of ribosome CC ribosome
MA0740.2 (KLF14)		INHBA	40	BP translation CC nucleus BP protein transport MF structural constituent of ribosome CC ribosome
MA0742.2 (KLF12)		COLA1A	40	BP translation CC nucleus BP protein transport MF structural constituent of ribosome CC ribosome
MA0814.2 (TFAP2C)		PLAU	56	BP translation CC nucleus BP RNA processing MF structural constituent of ribosome CC ribosome
MA1511.2 (KLF10)		IGFBP5	40	BP translation CC nucleus BP protein transport MF structural constituent of ribosome CC ribosome

Discussion

In this study, network analysis highlighted several hub genes associated with the transcriptional response to dexamethasone in bovine skeletal muscle. These findings suggest that the response to dexamethasone involves coordinated changes in gene regulatory networks, rather than the regulation of individual genes alone, potentially influencing processes related to muscle growth and tissue remodeling.

Given the increasing demand for improved production efficiency in the livestock industry, various hormonal compounds have been investigated for their effects on muscle growth and metabolism. Dexamethasone, a synthetic glucocorticoid, has been reported to influence muscle physiology and metabolic regulation in cattle (Vascellari et al., 2012). Unlike anabolic agents, dexamethasone primarily exerts catabolic effects, modulating gene expression pathways in skeletal muscle that are involved in protein turnover, tissue remodeling, and metabolic adaptation. Understanding the transcriptional networks responsive to dexamethasone may therefore provide insights into glucocorticoid-associated muscle regulation in bovine species.

In recent years, genomic and transcriptomic approaches have enabled the identification of key or hub genes within co-expression networks. These hub genes, acting as central nodes in regulatory networks, play pivotal roles in controlling cellular functions and thus represent valuable targets for investigating the molecular mechanisms underlying hormonal responses (Tian et al., 2024). In the present study, protein–protein interaction network analysis led to the identification of a set of hub genes associated with pathways involved in muscle growth, differentiation, and tissue remodeling, which are likely critical for mediating the physiological effects of dexamethasone in beef cattle.

Among these genes, IGFBP5 exhibited a significant upregulation ($\log_2$FC = 1.365756) in response to dexamethasone treatment, highlighting its central role in regulating skeletal muscle growth in young bulls. Increased IGFBP5 expression may modulate the bioavailability of insulin-like growth factors (IGFs), fine-tuning the IGF-1/Akt/mTOR signaling pathway. By binding to IGF-1, IGFBP5 not only protects it from degradation but also spatially and temporally regulates its distribution in muscle tissue, thereby maintaining the

balance between myoblast proliferation and differentiation (Sadkowski et al., 2009).

Furthermore, elevated IGFBP5 expression has been reported to enhance myogenic differentiation under certain conditions, promoting the maturation of muscle fibers a process essential for increasing functional muscle mass. Therefore, changes in IGFBP5 expression in response to dexamethasone likely reflect an adaptive regulation of the muscle gene network to steroid signals, optimizing muscle growth through the modulation of IGF activity (Foulstone et al., 2003). Consequently, IGFBP5 can be considered a key indirect transcriptional regulator in the dexamethasone response of bovine skeletal muscle, with its upregulation linked to enhanced myogenesis and increased muscle mass.

The INHBA gene, another key gene identified in this study, is a member of the TGF-β superfamily and plays a crucial role in regulating muscle cell proliferation and differentiation, tissue remodeling, and muscle homeostasis (Huang et al., 2024). The present results showed that the expression of this gene significantly decreased in response to dexamethasone treatment ($\log_2$FC = −1.06888). Reduced INHBA expression may lead to weakened Smad signaling, a pathway typically associated with inhibition of muscle growth and induction of anti-myogenic signals. This change may create a permissive environment for the activation of anabolic pathways and enhanced muscle growth. In this context, the relative suppression of INHBA may act as a regulatory mechanism that diminishes the inhibitory effects of the TGF-β pathway on myoblast differentiation, thereby facilitating increased muscle growth and hypertrophy. Previous evidence has shown that inhibition of TGF-β signaling can promote anabolic pathways and enhance the muscle response to growth factors (Huang et al., 2024). Therefore, the observed downregulation of INHBA in this study likely reflects a skeletal muscle gene network reprogramming toward reduced growth-inhibitory signaling. Overall, these findings suggest that dexamethasone not only promotes growth through the activation of growth pathways but also shifts the balance of cellular signaling toward increased muscle mass by selectively inhibiting anti-myogenic genes such as INHBA in young beef cattle.

In addition, the COL1A1 and COL1A2 genes, which play key roles in type I collagen synthesis and extracellular matrix (ECM) organization, were identified with significantly increased expression, showing $\log_2$FC = 2.465887 and 1.818516, respectively. The upregulation of these genes may indicate ECM remodeling and enhanced structural integrity of skeletal tissue in response to dexamethasone, a process essential for mechanical support of muscle growth. Since dysregulation of these genes is associated with disorders such as Osteogenesis Imperfecta, their upregulation is critical for maintaining skeletal tissue integrity (Rauch et al., 2020). It has also been reported that COL1A1 and COL1A2 expression is regulated by the TGF-β pathway, suggesting potential interactions between steroid signaling and ECM regulatory pathways (Kimoto et al., 2004).

Alongside these genes, PLAU, which plays an important role in ECM degradation, cell migration, and tissue remodeling, was identified with reduced expression in this study ($\log_2$FC = −1.03886). Decreased PLAU expression may indicate reduced proteolytic activity associated with ECM remodeling and consequently the stabilization of tissue structure during later stages of muscle and bone growth. Considering PLAU's role in facilitating tissue repair and early growth, its relative suppression may reflect a transition from active remodeling to structural stabilization in response to dexamethasone (Mahmood et al., 2018). Additionally, since PLAU is involved in regulating immune responses and interactions with viral agents such as PPRV, its downregulation may reflect steroid-mediated modulation of the immune response, indirectly contributing to tissue homeostasis and sustainable growth in livestock (Connolly et al., 2010; Wu et al., 2024).

Overall, these findings indicate that dexamethasone, by modulating key molecular pathways including IGF-1/Akt/mTOR, TGF-β/Smad, and ECM remodeling (through COL1A1/2 and PLAU), can influence skeletal muscle growth in beef cattle. These genes not only serve as molecular markers of the response to dexamethasone

treatment but may also represent potential targets for improving growth efficiency and enhancing livestock health in the animal husbandry industry.

One of the key approaches to understanding the regulatory mechanisms of hub gene expression is the analysis of their promoter regions and the identification of regulatory motifs. Motifs are short, conserved DNA sequences that serve as binding sites for transcription factors and play a critical role in determining gene expression patterns. Identifying these motifs can provide a more precise understanding of the regulatory pathways activated by growth stimuli such as dexamethasone and reveal the key transcription factors involved in these processes (Bussemaker et al., 2000). For instance, studies have shown that specific motifs in promoter regions can interact with transcription factors that regulate gene expression in response to hormonal treatments (Wang et al., 2022).

The analysis of motifs identified in the promoter regions of hub genes indicates the involvement of key transcription factors in regulating muscle growth pathways in response to dexamethasone treatment. One of the most prominent motifs is MA0516.3, 62 base pairs in length, which is associated with the transcription factor SP2. Although direct studies on SP2's role in skeletal muscle are limited, its membership in the Sp/KLF family, which regulates multiple structural and metabolic genes, suggests that SP2 may play a role in controlling growth, differentiation, or muscle regeneration under growth-stimulating conditions such as dexamethasone treatment (Cai et al., 2024).

Another identified motif, MA0814.2, 56 base pairs long, is associated with the transcription factor TFAP2C. TFAP2C is involved in various cellular processes, including differentiation and hormonal responses, and has been shown to regulate the expression of estrogen receptor alpha (ERα) and other genes related to hormone signaling pathways. This suggests that TFAP2C may influence muscle growth and differentiation in response to steroid treatments such as dexamethasone (Woodfield et al., 2010). Although its direct role in skeletal muscle is not well-defined, its involvement in hormone signaling and cellular differentiation supports the idea that it may contribute to the regulation of muscle growth. For example, TFAP2C has been implicated in controlling genes critical for cell growth and differentiation, processes essential for muscle development (Zhang et al., 2024).

The motif MA0103.3, related to ZEB1, was also observed among the identified elements. ZEB1 acts as a regulator of the balance between differentiation and self-renewal in muscle cells, playing a key role in muscle growth dynamics and tissue regeneration (Elasbali et al., 2024). The presence of this factor in the promoters of hub genes may indicate precise regulation of muscle repair and remodeling pathways in response to injury or hormonal stimulation.

Beyond identifying transcription factors, GOMo analysis revealed that the identified motifs are associated with diverse biological functions, classified into the three main GO categories: Biological Process (BP), Molecular Function (MF), and Cellular Component (CC). Regarding biological processes, these motifs were associated with protein transport, macromolecular biosynthesis, and DNA-dependent transcription. From a molecular function perspective, these elements were linked to ribosomal structural activity and enzymatic functions such as isomerase activity. At the cellular component level, the nucleolus and ribosomes were identified as enriched sites in the GO analysis.

Protein transport plays a particularly crucial role in skeletal muscle growth regulation, especially in response to dexamethasone, as it not only mediates the trafficking of growth factors and hormone receptors but also supports the delivery of structural proteins to functional regions of the muscle (Biolo et al., 2002). The presence of this process in the transcriptomic data underscores that muscle growth in young bulls is directly influenced by the regulation of pathways related to protein transport and translation. Structural ribosomal activity, as an indicator of cellular protein synthesis capacity, is also increased under growth-stimulating treatments, reflecting the readiness of muscle cells to enter hypertrophy. This upregulation is likely mediated through the activation of

signaling pathways such as mTOR and IGF-1(Yoshida and Delafontaine, 2020).

Finally, the enrichment of the nucleolus and ribosomes, as key components of protein synthesis, directly contributes to muscle hypertrophy. Increased nucleolar activity enhances ribosome biogenesis, providing the cellular machinery required to expand translational capacity in response to growth stimuli (Wen et al., 2016).

Conclusion

The results of this study demonstrate that dexamethasone, a synthetic glucocorticoid, induces broad transcriptional changes in skeletal muscle of young bulls. The identification of 11 hub genes through protein–protein interaction (PPI) network analysis underscores the importance of systems-level approaches for understanding the molecular responses triggered by glucocorticoid exposure. Promoter motif analysis further revealed conserved regulatory elements associated with transcription factors such as SP2, ZEB1, and TFAP2C, suggesting their potential involvement in coordinating muscle-related molecular responses to dexamethasone. Functional enrichment results highlighted key biological processes, including protein transport, ribosome biogenesis, and nucleolar activity, which may contribute to cellular adaptation under glucocorticoid influence. Collectively, these findings provide insight into the regulatory architecture underlying the glucocorticoid-responsive gene network in bovine skeletal muscle. Future studies should focus on experimental validation of the implicated transcription factors and on evaluating temporal gene expression dynamics following dexamethasone treatment.

Reference

Biolo, G., Fleming, R.D., Maggi, S.P., Nguyen, T.T., Herndon, D.N., Wolfe, R.R.J.T.J.o.C.E., and Metabolism., 2002. Inverse regulation of protein turnover and amino acid transport in skeletal muscle of hypercatabolic patients. *The Journal of Clinical Endocrinology and Metabolism* 87, 3378-3384.

Bussemaker, H.J., Li, H., and Siggia, E.D.J.P.o.t.N.A.o.S., 2000. Building a dictionary for genomes: identification of presumptive regulatory sites by statistical analysis. *Proceedings of the National Academy of Sciences* 97, 10096-10100.

Cai, B., Ma, M., Yuan, R., Zhou, Z., Zhang, J., Kong, S., Lin, D., Lian, L., Li, J., Zhang, X.J.C., *et al.,* 2024. MYH1G-AS is a chromatin-associated lncRNA that regulates skeletal muscle development in chicken. *Cellular and Molecular Biology Letters* 29, 9.

Carraro, L., Ferraresso, S., Cardazzo, B., Romualdi, C., Montesissa, C., Gottardo, F., Patarnello, T., Castagnaro, M. and Bargelloni, L., 2009. Expression profiling of skeletal muscle in young bulls treated with steroidal growth promoters. *Physiological Genomics*, 38(2), pp.138-148.

Combes, R., and Balls, M.J.A.t.L.A., 2007. Comments on the sub-group reports of the EU technical expert working group on the revision of directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes. *Alternatives to Laboratory Animals* 35, 155-175.

Connolly, B.M., Choi, E.Y., Gårdsvoll, H., Bey, A.L., Currie, B.M., Chavakis, T., Liu, S., Molinolo, A., Ploug, M., and Leppla, S.H.J.B., The Journal of the American Society of Hematology., 2010. Selective abrogation of the uPA-uPAR interaction in vivo reveals a novel role in suppression of fibrin-associated inflammation. *Blood, The Journal of the American Society of Hematology* 116, 1593-1603.

Devlin, R.H., Sakhrani, D., Tymchuk, W.E., Rise, M.L., and Goh, B.J.P.o.t.N.A.o.S., 2009. Domestication and growth hormone transgenesis cause similar changes in gene expression in coho salmon (Oncorhynchus kisutch). *Proceedings of the National Academy of Sciences* 106, 3047-3052.

Elasbali, A.M., Al-Soud, W.A., Adnan, M., Alhassan, H.H., Mohammad, T., and Hassan, M.I.J.M.N., 2024. Discovering promising biomarkers and therapeutic targets for Duchenne muscular dystrophy: a

multiomics meta-analysis approach. *Molecular Neurobiology* 61, 5117-5128.

Foulstone, E.J., Savage, P.B., Crown, A.L., Holly, J.M., and Stewart, C.E., 2003. Role of insulin-like growth factor binding protein-3 (IGFBP-3) in the differentiation of primary human adult skeletal myoblasts. *Journal of cellular physiology* 195, 70-79.

Gharahdaghi, N., Phillips, B.E., Szewczyk, N.J., Smith, K., Wilkinson, D.J., and Atherton, P.J. ,2021. Links between testosterone, oestrogen, and the growth hormone/insulin-like growth factor axis and resistance exercise muscle adaptations. *Frontiers in physiology* 11, 621226.

Huang, X., Bao, Y., Yang, F., Li, X., Wang, F., and Zhang, C., 2024. miR-134-3p Regulates Cell Proliferation and Apoptosis by Targeting INHBA via Inhibiting the TGF-β/PI3K/AKT Pathway in Sheep Granulosa Cells. *Biology* 14, 24.

Kimoto, K., Nakatsuka, K., Matsuo, N., Yoshioka, H.J.I.o., and science, V., 2004. p38 MAPK mediates the expression of type I collagen induced by TGF-β2 in human retinal pigment epithelial cells ARPE-19. *Investigative ophthalmology and visual science* 45, 2431-2437.

Mahmood, N., Mihalcioiu, C., and Rabbani, S.A., 2018. Multifaceted role of the urokinase-type plasminogen activator (uPA) and its receptor (uPAR): diagnostic, prognostic, and therapeutic applications. *Frontiers in oncology* 8, 24.

Nebbia, C., Urbani, A., Carletti, M., Gardini, G., Balbo, A., Bertarelli, D. and Girolami, F., 2011. Novel strategies for tracing the exposure of meat cattle to illegal growth-promoters. *The Veterinary Journal*,189(1), pp.34-42.

Rauch, D., Robinson, M.-E., Seiltgens, C., Sutton, V.R., Lee, B., Glorieux, F., and Rauch, F., 2020. Assessment of longitudinal bone growth in osteogenesis imperfecta using metacarpophalangeal pattern profiles. *Bone* 140, 115547.

Sadkowski, T., Jank, M., Zwierzchowski, L., Oprządek, J., and Motyl, T., 2009. Comparison of skeletal muscle transcriptional profiles in dairy and beef breeds bulls. *Journal of applied genetics* 50, 109-123.

Tian, R., Mahmoodi, M., Tian, J., Esmailizadeh Koshkoiyeh, S., Zhao, M., Saminzadeh, M., Li, H., Wang, X., Li, Y., and Esmailizadeh, A., 2024. Leveraging functional genomics for understanding beef quality complexities and breeding beef cattle for improved meat quality. *Genes* 15, 1104.

Vascellari, M., Capello, K., Stefani, A., Biancotto, G., Moro, L., Stella, R., Pozza, G., and Mutinelli, F., 2012. Evaluation of thymus morphology and serum cortisol concentration as indirect biomarkers to detect low-dose dexamethasone illegal treatment in beef cattle. *BMC Veterinary Research* 8, 129.

Wang, J., Li, B., Yang, X., Liang, C., Raza, S.H.A., Pan, Y., Zhang, K., and Zan, L., 2022. Integration of RNA-seq and ATAC-seq identifies muscle-regulated hub genes in cattle. *Frontiers in Veterinary Science* 9, 925590.

Wen, Y., Alimov, A.P., and McCarthy, J., 2016. Ribosome biogenesis is necessary for skeletal muscle hypertrophy. *Exercise and sport sciences reviews* 44, 110-115.

Woodfield, G.W., Chen, Y., Bair, T.B., Domann, F.E., and Weigel, R., 2010. Identification of primary gene targets of TFAP2C in hormone responsive breast carcinoma cells. *Genes, Chromosomes and Cancer* 49, 948-962.

Wu, J., Yang, W., Li, L., Wu, J., He, J., Ru, Y., Ren, J., Wang, Y., Zheng, H., and Shang, Y. ,2024. Plasminogen activator urokinase interacts with the fusion protein and antagonizes the growth of Peste des petits ruminant's virus. *Journal of Virology* 98, e00146-00124.

Yoshida, T., and Delafontaine, P.J.C. 2020. Mechanisms of IGF-1-mediated regulation of skeletal muscle hypertrophy and atrophy. *Cells* 9, 1970.

Zhang, D., Wu, D., Zhang, S., Zhang, M., Zhou, Y., An, X., Li, Q., and Li, Z., 2024. Transcription factor AP-2 gamma affects porcine early embryo development by regulating epigenetic modification. *Reproductive biomedicine online* 49, 103772.

Zhang, J., Sheng, H., Pan, C., Wang, S., Yang, M., Hu, C., Wei, D., Wang, Y., and Ma, Y., 2023. Identification of key genes in bovine muscle development by co-expression analysis. *PeerJ* 11, e15093.