Key Genes Regulating Skeletal Muscle Development and Growth in Farm Animals

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Simple Summary: Skeletal muscle mass is an important economic trait, and muscle development and growth is crucial for understanding molecular genetic regulation of muscle growth and can be benefit the meat industry toward the goal of increasing meat yields. During the past years, significant progress has been made for understanding these mechanisms, and thus, we decided to write a comprehensive review covering regulators and (candidate) genes crucial for muscle development and growth in farm animals. Detection of these genes and factors increases our understanding of muscle growth and development and is a great help for breeders to satisfy demands for meat production on a global scale.

Abstract: Farm-animal species play crucial roles in satisfying demands for meat on a global scale, and they are genetically being developed to enhance the efficiency of meat production. In particular, one of the important breeders’ aims is to increase skeletal muscle growth in farm animals. The enhancement of muscle development and growth is crucial to meet consumers’ demands regarding meat quality. Fetal skeletal muscle development involves myogenesis (with myoblast proliferation, differentiation, and fusion), fibrogenesis, and adipogenesis. Typically, myogenesis is regulated by a convoluted network of intrinsic and extrinsic factors monitored by myogenic regulatory factor genes in two or three phases, as well as genes that code for kinases. Marker-assisted selection relies on candidate genes related positively or negatively to muscle development and can be a strong supplement to classical selection strategies in farm animals. This comprehensive review covers important (candidate) genes that regulate muscle development and growth in farm animals (cattle, sheep, chicken, and pig). The identification of these genes is an important step toward the goal of increasing meat yields and improves meat quality.

Keywords: muscle development; myogenesis; adipogenesis; candidate gene; meat yield

1. Introduction

As a complex and heterogeneous tissue, skeletal muscle is considered a vital organ for the muscular system [1]. This very abundant tissue in vertebrates has different but crucial metabolic actions. Lean skeletal muscle mass regulates the body’s rate of energy expenditure [2–4]. Theoretically, increased muscle mass and energy expenditure from muscle protein turnover can prevent obesity [5]. Moreover, skeletal muscle has the highest insulin-stimulated glucose uptake and thus maintains the insulin sensitivity of the whole body [6]. Elevated skeletal muscle development in farm animals is important because it
creates tissue that meets human requirements for meat consumption. The development of fetal skeletal muscle involves primarily myogenesis, fibrogenesis, and adipogenesis [7] derived from mesenchymal stem cells (MSCs). Meat quality also can be enhanced by changing the MSC commitment from muscle to adipocyte development through the provision of more intramuscular fat.

Skeletal muscle development is determined mainly by the proliferation and differentiation of myoblasts, which are precursors of muscle cells. Myogenic regulatory factors (MRFs) and growth promoters are crucial for muscle development in farm animals [8]. Generally, muscle growth, categorized as a heritable feature, can be modulated by fiber type position, especially with regard to metabolism and contractile speed, as well as temperature and food availability [9,10]. Skeletal muscle has a very unique ability to regenerate and remake itself in response to growth and injury, via the activation of muscle stem cells or satellite cells [11,12].

2. Myogenesis

Myogenesis is the complex process of skeletal muscle construction in diverse species, including farm animals. Generally, the aim of myogenesis is the formation of multinucleated myofibers with contractile activity. The time required for each developmental phase varies among species [13]. Typically, myogenesis is regulated by the intricated networking of intrinsic and extrinsic factors [1], monitored by MRF genes in different phases as well as genes that code proteins called kinases [13]. Nutrition also plays an important role in the regulation of myogenesis. Malnutrition and overnutrition during gestation abated fetal myogenesis, but only overnutrition enhanced intermuscular fat accumulation [14,15].

Prenatal muscle development is achieved by the proliferation and differentiation of myogenic factors; postnatal muscle growth is achieved by cascade actions of muscle satellite cells. The formation of muscle in farm animals is accomplished via various biological processes, including protein accretion and muscle cell proliferation [7]. Small proportions of progenitor cells in the myotome proliferate and then differentiate into myoblasts. These myoblasts withdraw from the cell cycle and begin to differentiate and fuse to each other to construct myotubes and primary myofibers [16]. Myoblasts near primary muscle fibers proliferate and fuse to form secondary muscle fibers [17]. Muscle fibers in adult animals are established primarily through secondary myogenesis.

In the late fetal stage, some myogenic cells become quiescent, leading to the formation of satellite cells. Thus, the number of myoblasts not only conditions the quantity of muscle fibers but also influences the amount of satellite cells present during postnatal growth [14]. As the number of muscle fibers does not change after birth in most cases, fetal myogenesis is critical for efficient muscle growth in farm animals [7]. Satellite cells first proliferate and then differentiate and fuse with existing muscle fibers, leading to postnatal growth in size or hypertrophy. Satellite cells in adult animal muscles remain quiescent unless activated by extrinsic stimuli (i.e., injury and exercise). Activated satellite cells repair or regenerate fibers in affected muscle. Some age-related diseases reduce the number of satellite cells leading to impaired regeneration and muscle degeneration [18].

Effects of Transcription Factors and the Myogenic Kinome on Myogenesis

Myogenesis is controlled mainly by specific muscle-related transcription factors, including MRFs (MYF5, MYOD, myogenin, and MRF4), PAX7, and PAX3. These factors act as terminal influencers of signaling procedures and contribute to proper development of each stage specific transcripts. Paired-box transcription factors are expressed first in mesoderm cells, followed by the expression of MYF5 and MYOD [19]. PAX3 expression is indispensable for skeletal muscle development; it upregulates the expression of MYOD during skeletal myogenesis. PAX7 keeps satellite cells quiescent and, along with the expression of MYF5, plays a critical role in the development of activated myoblasts [13,20]. Rehfeldt et al. [10] noted that MYOD and MYF5 are essential for the formation of muscle cell types, whereas myogenin and MRF4 are needed to stimulate differentiation and muscle fiber
Animals of the same age, and the expression of MYF5 and CDK2 analyzed by qRT-PCR showed a significant difference in expression between Dzhalginsky Merino sheep and Angus cattle. 
PAX3 phosphorylation of ME2 protein promotes the expression of myogenic factors, including MYF5, p27, FOXO1, and p38a. Phosphorylation of Rb is required for proper myocyte fusion and the suppression of myoblast differentiation; in late myogenesis, it continues expression of cell-cycle-related genes. In addition, phosphorylated Rb and 4 ME2 suppress the activity of MYOD, which triggers S phase entry, allowing for the suppression of differentiation by IGF. 
PAX3, MYOD, and MYFG were greater in LWS than in HWS chickens on the hatching day, and the expression of PAX7, MYF5, MYOD1, and MYFG was greater in HWS than in LWS birds at day 28. Quantitative real-time reverse-transcription polymerase chain reaction (qRT-PCR) analysis of samples from Dzhalginsky Merino sheep showed that MYOD1 was among 17 of 48 evaluated genes with the greatest expression in the loin muscle. MYF5, another important regulator of myogenesis, was shown to be associated with traits related to meat quality in cattle and pigs. Several regulatory transcription factors, such as MYOD1, were identified in the biceps femoris and longissimus dorsi muscles (LDMs) of purebred (IB) and Duroc-crossbred (IB × DU) pigs; MYOD1 was expressed in two developmental stages (birth and growth) and thus can crucially impact phenotypes. For this reason, it must be considered an important candidate gene for muscle growth in pigs.

Myogenesis is not regulated solely by muscle-related transcription factors, which contribute to complex signaling cascades that precipitate the process. Protein kinases, which form a family of enzymes, modify the actions of target proteins via basic and reversible phosphorylation, a fundamental part of myogenesis. Many protein kinases have been shown to participate in different stages of myogenesis; thus, their activation or inhibition can directly affect muscle cell behavior. Protein kinase A (PKA) is required in different muscle developmental stages and is indispensable for the construction of myogenic precursors in the dermomyotome; its involvement leads to myotome construction by myogenic factors, such as PAX3, MYOD, and MYFG, in dermomyotome cells. This activity is initiated with the involvement of Wnt1 and Wnt7a, produced by dorsal neural tubes outside the ectoderm. The upregulation and downregulation of (Wnt)/β-catenin cascade signaling control myogenesis and adipogenesis, respectively. PKA stimulates proliferation by promoting the expression of myogenic factors, including MYF5, MYOD, and PAX3, and suppressing the activity of MEF2 via phosphorylation. Cyclin-dependent kinases 2 and 4 (CDK2, 4) control cell-cycle progression via the phosphorylation of retinoblastoma protein (Rb), which prevents Rb from binding the E2 factor (E2F), thereby allowing continued expression of cell-cycle-related genes. In addition, phosphorylated Rb cannot bind MYOD, which triggers S phase entry, allowing for the suppression of differentiation by CDK2 and CDK4. Extracellular signal-regulated kinase (ERK) activation depends on the availability of growth factors (GFs), including fibroblast growth factor (FGF) and insulin-like growth factor (IGF). In early myogenesis, ERK1/2 activation is crucial for myoblast proliferation and the suppression of myoblast differentiation; in late myogenesis, it is required for proper myocyte fusion. Akt1 also supports proliferation by phosphorylating FOXO1, which suppresses the expression of genes associated with cell-cycle exit, including p27. p38α has been shown to be important for the differentiation of many cell types. In myogenesis, it causes myogenic precursor cells to exit the cell cycle via the phosphorylation of MEF2 and E47. All of these factors together, in association with MYOD
and phosphorylated RNA polymerase II, activated by CDK9, trigger differentiation. Many studies have demonstrated the role of Akt activity in the stimulation of differentiation and hypertrophy in culture and in vivo [34–37]. Specifically, Akt1 seems to be crucial for myoblast proliferation but not necessary for differentiation; it inhibits differentiation when its involvement occurs alone [38,39]. Elevation of the Akt2 level is indispensable for differentiation [38], but Akt2 activation is not necessary for proliferation. The inactivation of GSK3β in response to the Akt level also contributes to differentiation; activated GSK3β suppresses myoblast differentiation and fusion [40–42] via the phosphorylation of NFATC3 and β-catenin. Akt is also responsible for the maintenance of GSK3β inactivation via its phosphorylation during hypertrophy [42,43]. The mammalian target of rapamycin (mTOR) is required for differentiation and hypertrophy [44], but its kinase activity is just demanded for hypertrophy [45,46]. mTOR and its substrate S6K, whose involvement is crucial during hypertrophy, induce protein synthesis by commencing cap-dependent transfer [44]. The mammalian target of rapamycin (mTOR) is required for differentiation; it inhibits differentiation when its involvement occurs alone [38,39]. Elevation of the Akt2 level is indispensable for differentiation [38], but Akt2 activation is not necessary for proliferation. The inactivation of GSK3β in response to the Akt level also contributes to differentiation; activated GSK3β suppresses myoblast differentiation and fusion [40–42] via the phosphorylation of NFATC3 and β-catenin. Akt is also responsible for the maintenance of GSK3β inactivation via its phosphorylation during hypertrophy [42,43]. The mammalian target of rapamycin (mTOR) is required for differentiation and hypertrophy [44], but its kinase activity is just demanded for hypertrophy [45,46]. mTOR and its substrate S6K, whose involvement is crucial during hypertrophy, induce protein synthesis by commencing cap-dependent transfer [44]. mTOR also upregulates microRNA-1 (miR-1), suppressing HDAC4 expression and upregulating important myogenic genes, such as the profusion protein follistatin [47]. Figure 1 illustrates the involvement of myogenic transcription factors and protein kinases in the regulation of different stages of myogenesis.

Figure 1. The involvement of myogenic transcription factors and protein kinases in the regulation of different stages of myogenesis. Embryonic precursors or quiescent satellite cells proliferate and construct myoblasts. Myoblasts then undergo differentiation to form myocytes. Finally, multinucleated myotubes are formed as a result of fusion of myocytes. The upper and lower sections of the figure illustrate transcription factors and protein kinases required for myogenesis, respectively (modified from [13]).

3. Adipogenesis and Participating Transcription Factors

The fundamental components of skeletal muscle are myocytes, adipocytes, and fibroblasts. Adipocytes are derived from adipogenic progenitors [48,49], produced mainly in
the fetal period. The transcriptional factors that control adipogenesis include C/EBP and members of the PPAR family. PPARα, γ, and δ/β are nuclear hormone receptor-regulating genes associated with lipid metabolism [50]. PPARα, which is expressed abundantly in striated muscle, has been recognized as a mediator that stimulates peroxisomal proliferation in rodent livers [50]. Its activation enhances fatty acid β-oxidation in muscle and leads to body weight reduction [51]. Relative to PPARα, PPARγ is expressed more strongly in adipose tissues [50], stimulating adipocyte differentiation [52,53]. PPARγ is expressed abundantly in skeletal muscle, heart, and adipose tissue. Its active form enhances fatty acid oxidation in adipose tissue and muscle [54] and is upregulated in skeletal muscle during starvation [55]. During early adipogenesis, C/EBPα is stimulated and binds to the PPARγ promoter, stimulating its expression [56]. C/EBPα and PPARγ each induce the other’s expression in a self-reinforcing regulatory loop [7] (Figure 2) and are required for terminal adipocyte differentiation via the stimulation of genes such as adipocyte protein 2 (AP2), lipoprotein lipase (LPL), cluster of differentiation 36 (CD36), and glucose transporter type 4 (GLUT4) [57]. In bovine fetuses, myogenesis was found to be spoiled by proliferative preadipocyte-conditioned media, as demonstrated by the reduction of the fusion index, and enhanced by an adipocyte-conditioned medium, as demonstrated by the expansion of the myotube area [58]. Such crosstalk is regulated partly by adipokines, including leptin [59].

4. The Role of GFs in Skeletal Muscle Growth

Diverse types of GFs affect the differentiation and proliferation of skeletal muscle growth. Hepatocyte growth factor (HGF) induces the proliferation and migration of myogenic cells [60] and was found to increase the surface elasticity of bovine satellite cells in vitro [61]. FGF2 was found to promote the proliferation of muscle precursor cells, including satellite cells and myoblasts, and to suppress cell differentiation in chickens [62]. Thus, the proper construction of muscle fibers in the embryonic period requires FGF2 expression. However, this factor also inhibits myogenesis by suppressing myogenin transcription, which is required for proper myotube formation [63]. IGFs regulate and promote cell proliferation, differentiation, and hypertrophy and protein synthesis during myogenesis [13,64].

Transforming growth factor (TGF)-β and myostatin (GDF-8) have the opposite effect on differentiation [65]; thus, their expression must be limited in farm animals bred for meat. In chicken muscle, the expression of IGF-1 mRNA decreased during embryogenesis, increased after hatching, and decreased again after day 7 post-hatching, and was much greater in embryonic muscle than in embryonic liver [66]. In porcine satellite cells, IGF-1
and IGF-II were upregulated during differentiation [67]. In fetal sheep, IGF-II mRNA was upregulated most at gestational day 85, demonstrating its importance during this period of differentiation and myogenic fiber formation in the leg [68]. A delay in IGF-II expression and mutation of the MSTN gene led to an increase in the number of muscle fibers in double-muscled (DM) cattle [69]. Growth hormone (GH) is another important factor; a major mechanism that (genetically and environmentally) affects skeletal muscle development in farm animals involves the GH–IGF axis [10].

5. Candidate Genes Affecting Muscle Development in Cattle

Beef production has been improved dramatically, but researchers still struggle to find quantitative trait loci (QTLs) and candidate genes affecting meat production and growth in cattle. QTLs and candidate genes related to muscle development are distributed over several bovine chromosomes (BTA), such as BTA2, 3, 4, 6, 20, and 29 [70–74]. Genome-wide association studies (GWASs) performed with high-density single-nucleotide polymorphism (SNP) arrays are the main means of detecting genetic variants explaining variation in such economically important traits.

Using next-generation sequencing (NGS) with nearly 12 million imputed SNPs, we identified several important candidate genes influencing hindquarter muscle development in Chinese Simmental beef cattle [74]; they included IQUB, NDUFA5, and ASB15 in a ~322-kb area on BTA4, and LMOD2 and WASL about 50 kb upstream of ASB15. ASB15, a conserved gene that is usually expressed in hypertrophied skeletal muscles [75], was found to stimulate protein turnover and synthesis, thereby inducing muscle precursor cell differentiation and muscle cell development [75,76]. NDUFA5 upregulation has been observed in various tissues, including skeletal muscle [77], and is associated with marbling scores in Hanwoo cattle [78]. IQUB knockdown can suppress the expression of c-myc, which is involved in myoblast proliferation and differentiation [79]. LMOD2 was found to be involved in the regulation of the length of thin filaments in muscle, and thus in muscle development in cattle [80]. WASL was reported to affect the cytoskeleton, a sophisticated network that plays a role in muscle contraction [81]. Based on such compelling evidence, we hypothesized that the 280 kb region in which all of these genes are located strongly influenced muscle development on BTA4 in beef cattle [74]. Using imputed NGS dataset (Illumina Hiseq 2500), we identified myotrophin (MTPN) as a promising candidate gene affecting net meat weight [82]. This gene stimulated six markers that regulate muscle differentiation (MyoD, MyoG, MYH1, MYH2, MYH3, and MYH4), induced myotube hypertrophy by expanding myotube diameters, and reduced myoblast proliferation in flow cytometry and cell viability experiments [82]. MTPN has also been shown to affect muscle development in other species, such as pig [83]. MTPN and IGF-I have been shown to induce muscle cell hypertrophy by increasing myotube diameters in chickens [84]. Using the Illumina bovine SNP50 beadchip, Kim et al. [85] identified a marker of eye muscle area (EMA) on the DVL1 gene. Although the function of this gene in cattle is not known, research has shown that it is related to muscle development in humans and mice [86,87]. Thus, it was nominated as a candidate-gene-regulating muscle development in cattle [85]. qRT-PCR analysis showed that the expression of NCAPG, LCORL, and DCAF16 was upregulated in the fetal relative to the adult longissimus muscle in Chinese Qichuan beef cattle, reflecting the crucial roles of these genes in early bovine muscle growth [88]. NCAPG was also reported to be in linkage disequilibrium with the average daily gain (ADG) in cattle [89]. Candidate genes for muscle development and growth identified in Simmental beef cattle include MYH10 (associated with yearling weight), RLF (associated with ADG from birth to yearling), SQOR and ARHGAP3I (associated with body weight at the age of 18 months), and TBCB (associated with birth weight) [90]. TBCB was identified as a candidate gene affecting meat quality in pigs because it is associated with actin and cytoskeleton filament development [91]. RLF has also been reported to markedly enhance DNA methylation of factors associated with transcriptional regulation, which is indispensable for embryonic muscle growth [92]. Mutations in the myostatin gene were found to lead to muscularity...
in DM cattle, causing about 20% more hypertrophy and about 50% less fat accumulation compared with normal cattle [93]. Among adipose-specific genes, FABP4 is a promising candidate related to intermuscular fat accumulation [94]; many important differentiation-, hormone-, and fat-related regulatory factors have been identified in its promoter region. RA114 and ZNF423 have also been reported to be involved in adipogenesis in bovine muscle [95,96]. CDNA microarray examination of gene expression profiles in fetal bovine longissimus muscle led to the identification of FSTL1 and IGFBP5 as important genes related to muscle development [97]. These genes have also been shown to be associated with MYOD expression in a mouse model [98].

The identification of candidate genes associated with growth is also important because these genes are potentially related to muscle development. BTA14 harbors several crucial candidate genes associated with growth, including RPL39, PLAG1, RGS20, FAM110B, TOX, RP1, TCEA1, UBXN2B, and MRPL15 [99]. Using a high-density SNP array, Zhang et al. [100] showed that the PLAG1–OXRI region on BTA14 is a candidate region affecting meat yield from Wagyu cattle. OXRI has also been reported to regulate muscle development [101]. Its expression is regulated by the FABP5 gene through the PPARG node. A GWAS led to the recognition of RAB28, BTG1, and SMN1 as candidate genes for muscle development in Brahman cattle [102]. RAB28 is involved in the proliferation of endothelial and smooth muscle cells [103]. BTG1 seems to be involved in myogenic induction [104,105], and it regulates myoblast differentiation. SMN1, located on BTA20:8Mb, is associated with murine skeletal muscle growth [106]. Overall, the identification of candidate genes related to muscle development can be very beneficial for the beef industry, as it provides opportunities for the enhancement of meat production.

6. Candidate Genes Affecting Muscle Development in Sheep

An important goal of sheep breeders is to gain an understanding of the regulation of muscle growth and development, with the ultimate aim of increasing muscle growth. Recently, much research has focused on economically important traits and candidate genes influencing meat production from sheep, particularly those related to muscle development.

The most comprehensively studied QTLs in sheep are related to muscle hypertrophy. The paternal heterozygous callipyge mutation leads to skeletal muscle hypertrophy, especially in the hindquarters [107]. The callipyge variant is related to an SNpcLPG mutation in the intergenic region between DLK1 and GTL2 on ovine chromosome 18 (OAR18), which contains various paternally expressed genes, such as BEGAIN [108], DLK1 [109], PEG11 or RTL1 [110], and DIO3 [111]. It also contains several maternally expressed noncoding RNA genes, including antiPEG11 [110], GTL2 [112], MIRG [113], and MEG8 [110]. Dlk1 is a potent candidate gene with the potential to generate muscle hypertrophy in callipyge sheep; Dlk1 mRNA expression was increased markedly in the muscles of these sheep from day 120 in gestation day to 84 days after birth [107]. The rib-eye muscle (Carwell) locus, which is in close proximity to CLPG on OAR18, has been associated with muscular hypertrophy but only of the LDM; it has no effect on carcass fatness [114]. The Carwell phenotype has been reported to enhance the loin eye area by about 11% and LDM weight by about 7% [115]. In comparison with the callipyge phenotype, the Carwell phenotype has no impact on meat quality, including meat hardness and intramuscular fat content [116]. The MSTN gene, which encodes myostatin, plays an important role in muscle development in sheep. In Texel sheep (known for double muscling), a mutation on MSTN producing a novel binding site for mRNA molecules was found to lead to muscle hypertrophy [117]; this mutation was shown to affect the meat and fat contents in lamb carcasses [118]. Gan et al. [119] identified various mutations in several regions of this gene that correlated directly with the ADG and indirectly with the double-muscling phenotype and myostatin gene function. MSTN is also believed to be related to calpastatin (CAST) expression and lamb meat quality [120,121]. In turn, CAST gene function is associated with protein activity in muscle and the proportion of postmortem tenderization [121–123]. Nikmard et al. [124] reported that CAST is associated with muscle mass enhancement in sheep.
The MEF2B gene is a member of the myocyte enhancer factor-2 family, which also includes MEF2A, MEF2C, and MEF2D. MEF2B regulates muscle growth and development in sheep; PCR experiments have revealed variants in this gene that affect sheep growth and body weight [125,126]. GWASs led to the identification of several genes, including complex subunit 1 (MSL1), POL, and shisa family member 9 (SHISA 9), as candidate genes affecting the regulation of processes such as cell growth and muscle differentiation [125,127]. Zhang et al. [127] identified five variants in or near MEF2B, RFXANK, RIPK2, GRM1, POL, and UBR2 with roles in growth and meat production. They also reported the downregulation of TRAF6 in myoblasts, suggesting that this gene plays roles in myoblast proliferation and differentiation in sheep. Lamb carrying the FecB gene in a backcross population of Texel sheep exhibited a difference in meat color and greater dressing percentage and eye-muscle depth than did noncarriers [128]. Skeletal muscle transcriptome analysis revealed candidate genes affecting muscle development in Bandur sheep; genes of the Kelch superfamily (KLHL6, KLHL34, and KLHL40) were upregulated more than two-fold, and ANKR2D2 and KLH13 were found to be involved in muscle development [129]. Based on analysis of gene expression profiles in ovine skeletal muscle from five Spanish meat breeds, candidate genes related to muscle contraction, including actin α1 (ACTA1), myosin light chain phosphorylatable fast skeletal muscle (MYLF), myosin heavy chains 2 (MYH2) and 7 (MYH7), tropomyosin 2 (TPM2), and titin (TTN), were identified [130]. Fan et al. [131] employed whole-genome bisulfite sequencing to examine genome-wide DNA methylation profiles in Hu sheep and identified many important differentially methylated genes associated with muscle growth and metabolism (Figure 3). Based on network analysis, they identified nine candidate genes (ADIPOQ, CCNA2, ITGA2, MYOG, MAPT, DIAPH1, NR4A1, DLK1, and COL1A2) that may be associated with muscle cell proliferation and differentiation and determined that their regulation across DNA methylation can control differential muscle development. In Icelandic sheep, Guðmundsdóttir [132] identified several candidate genes for muscle growth and development (CSF3R, ADAM17, GADD45B, GRID2, SPG11, DAB2, FREM3, GAB1, KLF13, AKAP6, PNN, DOCK1, and TRRAP) near the most closely associated SNPs. Flicek et al. [133] also reported many genes associated with muscle growth and development and muscle fiber development in sheep [USMG5 (Chr 13), IFRD1 (Chr 4), MSC (Chr 9), PPP2R3A (Chr 1), PTPX1 (Chr 5), TCF21 (Chr 8), CACNA1S (Chr 12), PITX2 (Chr 6), MYOG (Chr 12), and MYOD1 (Chr 15)]. A comprehensive analysis of genome-wide DNA methylation in the LDMs of Dorper × small-tailed Han and small-tailed Han sheep revealed candidate genes potentially associated with muscle production and growth (ACOX2, PPPARG2, NTN1, RIN2, MAPRE1, ACSL1, SH3PXD2B, ADAMTS2, MYOM1, ZDHHC13, TGFβ3, and RYR1) [134]. Various mutations in the leptin gene associated with muscle growth, meat quality, and carcass fat content have been identified in sheep [135,136]. The FABP4 gene has an important effect on meat quality in sheep, as it does in cattle; polymorphism of this gene affects the marbling, shear force, and intramuscular fat content of the LMD [116]. In addition, FABP4 allele A promotes lamb meat tenderness [137].
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cattle; polymorphism of this gene affects the marbling, shear force, and intramuscular fat content of the LMD [116]. In addition, FABP4 allele A promotes lamb meat tenderness [137].

Figure 3. The network of differentially methylated genes associated with muscle development in sheep. Darker lines indicate higher confidence levels [131].

7. Candidate Genes Affecting Muscle Development in Pigs

Many researchers have examined pig muscle characteristics (e.g., growth and development) in efforts to improve quantity and quality of pig meat and pig growth rates. The identification of additional candidate genes would aid understanding of the mechanisms underlying pig muscle growth, benefitting breeders and consumers and contributing to the improvement of efficiency in the pork industry.

Gene expression changes dramatically throughout the pig life cycle, particularly during prenatal growth and in the first stages of postnatal growth [138,139]. For example, ACTC1, DLK1, COMP, ARHGAP36, FGF21, TNN, IBSP, and ATP6V0D2, which are related to the development of various tissues, including muscle, are markedly upregulated in newborn piglets [27]. In addition, the RETN gene, which is associated with lipogenesis and thus
meat quality, was found to be upregulated at birth [27]. Ayuso et al. [27] identified several candidate genes that might regulate muscle growth and development in IB and IB × DU pigs (MEFs, SIM1, TCF7L2 or FOXO1, KLF1 or IRF2, MYH10, FVALB, CTNNB, MYOG, and SOX4). Comparison of the muscle transcriptomes of piglet [140] and weaning [141] IB and IB × DU pigs revealed that MYH10 is upregulated in IB × DU pigs, proving its association with muscle development. Ayuso et al. [27] also identified candidate genes associated with protein degradation and turnover and thus related to muscle development (CTSF, ADAMTS8 or CELA2, HSPS1, HSPA4L, ELANE, MMP9, FBX032, and DNAJA1). Among 83 genes found to be upregulated in LDM in their research, ZIC1 and MMP13 control myogenesis and myostatin signaling [142–145]. Using Solexa/Illumina’s genome analyzer in Lantang (LT, obese) and Landrace (LR, lean) pig breeds, Zhao et al. [158] identified 595 differentially expressed myogenesis genes (Figure 4). Moreover, they identified that IKK, ACVR1, GSK3B, STMN1, and ITGA might cause more muscle fibers in LR compared to LT. In comparison with LR, LT showed higher expression of several important inhibitors of myogenesis including HMOX1, NOTCH2, CTNNB1, ID1, ID2, SMAD4, GPC3, MSTN, and CABIN1, which might lead to slowing down the process of muscle differentiation in LT than in LR.

Genes related to an increased number of muscle fibers and the regulation of late myogenesis (STMN1, ACVR1, GSK3B, IKK, and ITGA) were identified in the Landrace breed [146]. In an RNA-sequencing analysis focusing on myogenesis phases in 40-, 55-, 63-, 70-, and 90-day Tongcheng and Yorkshire pig fetuses, Liu et al. [147] identified candidate genes associated with muscle growth and responsible for developmental differences between the breeds (PPP1CC, EP300, MYO9A, PTEN, CDK14, and IRS1). The Akirin2 gene has been reported to be a promising candidate gene affecting porcine muscle satellite cell proliferation and differentiation, acting via the ERK1/2 and NFATc1 signaling pathways [148]. The LEF1 gene, which is associated with the Wnt signaling pathway, plays an indispensable role in muscle fiber development by regulating the expression of MRFs such as MYF5 and MYOD. Reis et al. [149] recognized LEF1 as a promising candidate gene whose differential expression affects muscle mass; they observed greater expression of this gene in 3-week-old and 40-day-old fetuses of Duroc × Landrace × Large White cross pigs than in Piou pigs, associated with somite construction and proliferation and myoblast fusion. Notch genes (Notch1–4) have different expression patterns during prenatal and postnatal tissue development in mammals. Notch1, but not Notch2 or Notch3, plays a key role in porcine satellite cell function, regulating the expression of the HES5 gene, which controls MYOD and MYOG expression. Notch1 also controls GSK3β-3 gene expression, which has an important role in the Wnt signaling pathway [146,150]. Li et al. [151] examined the systematic correlation between obesity and DNA methylation and generated gene expression maps for muscle and adipose tissue. They identified favorable expression of ACE, PRKAR1A, PRKCQ, and GHSR in muscles; these genes stimulate the release of growth hormone and increase lean mass in obese pigs [152]. In Berkshire pigs, the hydroxysteroid 17-beta dehydrogenase 4 gene may influence muscle development, and it has been found to play a key role during early myogenesis, when its mRNA expression is substantially elevated [153]. Some genetic mutations have major impacts on muscle fiber number and size in pigs; many are related to muscle hypertrophy and in some situations affect meat quality [154]. A mutation in the RYR1 gene causes lean muscle growth and muscle hypertrophy in heterozygous pigs [132]. Mutations in the IGF2 and PRKAG3 genes result in enhanced muscle mass in pigs [155]. Analysis of the LDM transcriptomes from Iberian pigs with divergent intramuscular fat content led to the identification of several candidate genes related to skeletal muscle development (FOSB, FOS, CHAC1, ATF3, PPP1R15A, JUNB, DUSP1, PPP1R1B, NR4A2, CYRS1, EGR1, EGR2, EG3, and POL2F1) [156]. Moreover, Muñoz et al. [156] established 18 gene networks; network 1 contained many genes associated with skeletal and muscular system development (ACTC1, ASB10, AHSP, ARHGEF4, ARHGEF6, DMD, JUNB, LMO7, MYL12A, RPM, SDR16C5, SIRT3, and UCK2). Analyses of regulatory impact factors led to the identification of genes associated with adipogenesis (ARID5B, CREB1, VDR, ATF6, and
SP1) and myogenesis (KLF11 and MYF6) [156]. In an analysis of the pig LDM transcriptome, Lobjois et al. [157] identified candidate genes in different functional networks: cell proliferation and myogenic differentiation (AK1, BAG3, BNIP3, CDC34, CKM, COL1A2, CSN2B, DES, FKBP8, GSN, HSP90AA1, IGF2, SET, TNNC2, and TNNT3), and energy metabolism and muscle development (COX8, DYSF, EEF2, IPO13, MYOZ1, NEB, TPM1, TTN, H19, NOP17, and RPL13A). MYH7, MYL1, and MYL3, associated with muscle development, were also identified via transcriptome analysis in pig. Using RNA sequencing in combination with other livestock genomics research, Guo et al. [158] mentioned SFRP2, KDM6A, and OGT as candidate genes associated with pig growth traits. SFRP2 has been shown to play key roles in muscle development and muscle satellite cell proliferation and differentiation in mice [159,160], and to affect skeletal muscle development during embryogenesis in pigs [158]. RNA sequencing led to the identification of ASB2, MSTN, ANKRD1, and ANKRD2 as functional candidate genes associated with skeletal muscle development in Wei and Yorkshire pigs [161]. MSTN expression was found to be lesser in Wei pigs than in Yorkshire pigs, suggesting that this gene inhibits muscle growth less in the former breed [161]. ASB2, which has a negative regulatory effect on muscle mass [162], was also found to not be conductive to muscle growth in Wei pigs [161]. ANKRD1 and ANKRD2 belong to the muscle ankyrin repeat protein family and are known to regulate skeletal muscle cell differentiation [163]. To elucidate the genetic background affecting meat content, Ropka-Molik et al. [164] used microRNA expression profiles to identify DEGs that were upregulated and downregulated in pigs with greater muscle mass. They identified the SOX2, SIRT1, KLF4, PAX6, and transforming growth factor-beta genes as candidates likely associated with muscle mass, and found that SETD2, which encodes a histone methyltransferase, had modified transcript levels determined by loin mass. This gene is associated with epigenetic mechanisms controlling myoblast proliferation and differentiation, and its silencing results in cell-cycle arrest [165]. Taken together, the functions of this gene are crucial for muscle development and growth in pigs. In addition, the TBX2 gene, which encodes the T-box transcription factor, is upregulated in pigs with greater muscle mass (Figure 5). TBX2 controls the cell cycle in skeletal muscle through interaction with MYOD and cell-cycle regulators, including p21 and p14 [166].
Figure 4. The interaction network of differentially expressed genes (DEGs) regulating myogenesis in Landrace (LR) (a) and Lantang (LT) (b) pig breeds. Yellow and blue dots represent DE and non-DE genes, respectively. Straight lines represent interaction association between genes. Solid and dashed lines represent direct and indirect interaction, respectively. Value and diameter of lines represent the interaction size [138].
Figure 5. Upregulation of differentially expressed genes in the muscle of pigs with greater-than-normal muscle mass. Identified genes were colored and marked in grey; line shape represents anticipated mode of action. Lines colored represent anticipated mode of action (red shows interactions that were experimentally identified; blue shows interactions from selected databases; black shows coexpression; green shows text-mining relations and interactions contingent on appropriate researches stating a transfer from different organisms; and yellow shows transcriptional adjustment [164].

8. Candidate Genes Affecting Muscle Development in Chickens

The consistently increasing demand for poultry meat has stimulated breeding of chickens with greater production value [167]. Controlled selection is performed to enhance the growth rate, feed efficiency, and carcass meat content of chicken [168]. Chicken muscularity and muscle growth are economically important characteristics with substantial agricultural implications. Thus, selection for chickens with increased muscle mass and acceptable meat quality is important to achieve consumer satisfaction. An understanding of the mechanisms underlying muscle development and growth and the identification of related candidate genes are key for efficient selection for poultry production.

Chickens bred for meat (broilers) and egg production (layers) are used in the best-known models for the investigation of the mechanisms underlying the regulation of the myogenesis rate and muscle development. In past decades, selection has focused primarily on the improvement of the broiler growth rate and muscle mass. Zheng et al. [169] examined gene expression differences in muscle between layers and broilers by microarray hybridization, and identified several genes associated positively or negatively with growth rates (and thus likely involved in muscle growth and development). They determined that the slow growth rate of layers relative to that of broilers was related to the higher expression levels of slow-type muscle-related genes (MB, MYH7B, TNNI1, MYL3, and MYL2B) and identified DEGs associated with satellite cell proliferation and differentiation, as well as muscle hypertrophy (MUSTN1, FHL2, FGFR2, HS6ST2, and CSRP3; Table 1). CSRP3 was reported to be downregulated in humans with pathogenic cardiac hypertrophy [170].
expression in muscle precursor cells stimulated myoblast differentiation in mice [171], and it may control muscle growth and hypertrophy via the regulation of satellite cell proliferation and differentiation in chickens. The expression level of MUSN1, a candidate gene related to muscle development that is upregulated after exercise in hypertrophic muscle [172], was greater in broilers than in layers, suggesting that this gene is a key regulator of skeletal muscle hypertrophy [169]. Broiler chickens also have lower expression levels of FBXO22, FBXO30, UCHL1, RNF12, HERC4, RLD5, and HERC5 than do layers; these genes are associated with protein degradation and may be responsible for the greater muscle mass of broilers compared with layers [169]. Zheng et al. [169] also reported that DKK3 may be associated with muscle development in chickens, as it is expressed more in broilers than in layers, in accordance with the divergent muscle growth rates of the two chicken lines. DKK3 is known to suppress tumor growth by inhibiting cancer cell proliferation in human [173–175]. In another study, POMC, NMI, NPW, PMCH, GAL, and FOS were determined to be related to the broiler growth rate, as variable growth was attributed to their differential expression in the hypothalamus [176]. In a comprehensive study of DEGs that included principal component analysis, Nihashi et al. [177] identified 13 candidate genes potentially related to myoblast proliferation and differentiation in chickens (CDKN2B, ACTC1, MYH15, TNN1, TNN2, TNNT2, CCK, CXCL14, MKD, PENK, CSRP2, MFAP5, and UCHL1). These genes play crucial roles in muscle cell differentiation in chickens. CXCL14 knockout stimulates myogenic differentiation through the suppression of the myoblast cell cycle in mice [178]. CSRP3 induces myoblast differentiation [179] and CSRP2 is associated with the differentiation of smooth muscle cells in chicken [180]. The CSRP2 expression level was high across differentiation in WL and UKC myogenic cells in chickens [177]. MFAP5 tended to be more upregulated in WL than in UKC myogenic cells, indicating that it inhibits myotube formation in chickens. The level of BMP4 expression in the hindlimbs of UKC broilers and WL layers was found to be highest at Hamburger–Hamilton (HH) stage 31–34 (E7–8) [181], suggesting that enhanced BMP4 expression has a breed-dependent effect on myofiber formation. Using RNA sequencing, Xue et al. [182] analyzed the transcriptomes of Jinghai Yellow chicken muscle tissues in different early developmental phases. Their functional analyses resulted in the identification of DEGs related mainly to muscle development and growth (GH, IGF2BP2, IGFBP3, CEBBP, FGF2, and IGFBP5); in total, 44 candidate genes (including FN1, MYH10, MAPK9, FGF2, CFL2, IRS1, PHKA1, FGF16, PHKG1 and PHKB) were related to differences in growth among developmental stages. They also identified genes associated with muscle differentiation and development (MYOD1, MYLK2, SMYD1, B7G2, ANKR2D, PPP3CA, GPX1, TCF15, KHL40, and CRYAB). CEBBP is known to suppress myogenesis and activate adipogenesis [183,184] and to control several genes in response to GH [185].

GWASs have been used to identify gene loci and genomic regions related to muscle development more robustly and consistently than other approaches [186]. A GWAS led to the identification of five SNPs in 1.5 Mb of the KPNAA3-FOXO1A region on GGA1 as related to muscle growth in an F2 resource chicken population [187]. Two of these SNPs were determined to affect the ADG, and the gene closest to them was recognized as FOXO1A [187], a crucial transcription factor for skeletal muscle development [188–190]. Several SNPs on GGA4 have been related significantly to chicken growth [191,192], and genes located close to them, such as LIM domain-binding 2, ligand-dependent nuclear receptor corepressor-like protein 1, and microtubule-associated protein tau, are less upregulated in the breast muscle of slow-growing relative to fast-growing chickens, suggesting that they are associated with muscle development [192]. Another GWAS led to the recognition that a region on GGA3 was related to the breast muscle percentage and weight in chickens [193]. The GJA1 gene, located in this region, was identified as a candidate gene affecting muscle development, and its upregulation was found to be associated with increased breast muscle weight during development [193]. Several myogenic gene polymorphisms significantly related to muscle development (e.g., in IGF1R [194], IGFBP2 [195], IGF1 [196], GHR [197], PIT1 [198], GHSR [199], GHRL [200], MSTN [201], MEF2A [202], MYF5 [203], and PAX7 [204]) have
been identified in chickens. We also identified polymorphism of UCP gene associated with growth traits in Mazandaran indigenous chicken [205]. UCP2 gene is expressed hugely in several tissues such as adipose and skeletal muscle in human [206]. Although there is a lack of information regarding the association of UCP gene and muscle development in chicken, we hypothesized that this gene has potential to be associated with muscle growth in chicken.

Table 1. Genes associated with muscle growth in broiler and layer chickens.

| Gene Name                                      | Symbol         | 1D  | 2W  | 4W  | 6W  | 8W  |
|------------------------------------------------|----------------|-----|-----|-----|-----|-----|
| Slow-type myofiber protein genes               |                |     |     |     |     |     |
| Troponin I type 1 (skeletal, slow)             | TNN1           | −1.99| 1.05| −6.47| −1.05| 1.14|
| Myoglobin                                       | MB             | 1.04| −1.81| −10.04| −6.8| 1.17|
| Myosin, light chain 3, alkali; ventricular, skeletal, slow | MYL3         | −1.96| −1.04| −19.79| −1.41| −1.02|
| Myosin, heavy chain 7B, cardiac muscle, beta   | MYH7B          | −3.07| −1.01| −11.31| 1.1  | 1.36|
| Similar to myosin L2B regulatory light chain, cardiac muscle – chicken | LOC417506    | −1.27| 1.04| −58.02| −5.54| 1.34|
| Myosin basic protein                            | MBP            | 1.16| −1.81| −1.83| −3.67| −1.68|
| Similar to dynein light chain-2                | LOC417663      | −1.25| −2.13| −1.77| −1.28| −1.73|
| Satellite cell proliferation and muscle hypertrophy |               |     |     |     |     |     |
| Cysteine and glycine-rich protein 3 (cardiac LIM protein) | CSRP3        | −2.17| 1.01| −9.44| −16.72| −1.04|
| Four and a half LIM domains 2                   | FHL2           | −1.38| −8.19| −10.95| −7.65| −1.84|
| Similar to actin binding LIM protein family member 2 | LOC422866    | −1.08| −2.06| −1.78| −2.24| −2.56|
| Fibroblast growth factor receptor 2            | FGFR2          | −1.31| −2.28| −1.05| −1.6 | −1.87|
| Fibroblast growth factor 1 (acidic)             | FGF1           | −1.11| −2.45| −2.07| −2.75| −1.61|
| Heparan sulfate 6-O-sulfotransferase 2         | HS6ST2         | −3.07| −4.09| −1.51| −2.13| −3.1 |
| Musculoskeletal, embryonic nuclear protein 1    | MUSTN1         | −1.01| 2.94| 2.17 | 2.45 | 1.51 |
| Fibroblast growth factor 16                     | FGFR16         | −1.06| 2.86| 2.45 | 8.16 | 2.77 |
| Inner centromere protein antigens 135/155 kDa   | INCENP         | 2.02| 1.59| 2.15 | 1.39 | 1.3  |
| NudE nuclear distribution gene E homolog 1 (A. nidulans) | NDE1         | 1.49| 2.48| 2.68 | 1.91 | 1.23 |

* Comparison of expression values between muscle cells of broilers and layers, which normalized to a fold change of 1.0 and −1.0 in case of broilers having more and less mRNAs, respectively. D stands for day and W stands for week [169].

Using high-throughput sequencing and microarray experiments, scientists have identified numerous candidate genes associated with skeletal muscle development in chickens. RNA sequencing of skeletal muscle samples from white rock and Xinghua chickens revealed greater expression of FOXO3, which may suppress skeletal muscle development in the Xinghua breed; decreased FOXO3 expression may upregulate growth-related genes in DF-1 cells [207]. A comparison of DEGs between embryonic day 14 and week 7 in normal and sex-linked dwarf chickens led to the identification of numerous genes involved in the Wnt, insulin, MAPK, and PI3K-Akt pathways and associated with chicken muscle development. Integrative miRNA target prediction and network analysis led to the formation of regulatory (e.g., miRNA–mRNA) networks for skeletal muscle development [208].

Several miRNAs have been reported to have regulatory effects in different stages of muscle development. Integrative miRNA target prediction and network analysis led to the identification of many candidate genes and miRNA targets related to skeletal muscle development in chickens; for example, gga-miR-1a inhibits ACVR2B gene expression, and RECK is the target of gga-miR-200b [169]. In another study, let-7b was found to inhibit GHR gene expression and thus to play an important role in skeletal muscle development in chickens [209]. The miR-206 gene was also found to play a critical role in chicken muscle development, with a proven effect on chicken birth weight [210]. In vitro experiments showed that miR-203 inhibits myoblast proliferation and differentiation in chickens through the suppression of c-JUN and MEF2C, respectively [211]. c-JUN and E2F1 play crucial roles in the stimulation of myoblast proliferation in chickens via the control of their target genes [211,212].
9. Conclusions

Muscle development is a complex but consistent process that can be improved substantially in farm animals through selection and be further enhanced by identification of related candidate genes. During the past years, significant progress has been made for understanding the mechanisms of muscle growth and development, and thus, we decided to write a comprehensive review covering regulators and (candidate) genes crucial for muscle development and growth in farm animals. We have highlighted important regulators including transcription factors, myogenic kinome, and GFs, and investigated the role of them on different aspects of muscle growth. Moreover, the role of many important (candidate) genes such as MTPN, IQUB, NDUFA5, ASB15, LMOD2, and WASL (beef cattle), differentially methylated genes (sheep, chicken), and the interaction network of DEGs (pig) on muscle growth in farm animals were discussed. Identification of such important regulators and genes offers enormous help for marker-assisted selection, plays an important role toward the goal of increasing meat yields, and helps breeders to maximize meat quantity and quality. In addition, the gene sets mentioned have the potential to be generally beneficial to the applied study of mammalian muscle growth. However, the mechanisms underlying muscle development and growth in farm animals especially beef and sheep need further explorations.

Author Contributions: Writing—original draft preparation and writing—review and editing, F.B.; validation and supervision, M.M.; conceptualization and project administration, M.D.; conceptualization and writing—review and editing, W.G.; validation and writing—review and editing, J.J. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare that they have no competing interests.

Abbreviations

The following abbreviations are used in this manuscript: MSC: mesenchymal stem cell; MRF: myogenic regulatory factor; MEF2: myocyte enhancer factor 2; miR-1: microRNA-1; LWS: low-weight-select; HWS: high-weight-select; qRT-PCR: quantitative real-time reverse-transcription polymerase chain reaction; LDM: longissimus dorsi muscle; PKA: protein kinase; Rb: retinoblastoma protein; E2F: E2 factor; ERK: extracellular signal-regulated kinase; FGF: fibroblast growth factor; IGF: insulin-like growth factor; mTOR: mammalian target of rapamycin; HGF: hepatocyte growth factor; TGF: transforming growth factor; BTA: bovine chromosome; DM: double-muscled; QTL: quantitative trait loci; GWAS: genome-wide association studies; CAST: calpastatin; SHISA 9: Shisa family member 9; MSL1: complex subunit 1; CDK: cyclin-dependent kinases; SNP: Single nucleotide polymorphism; NGS: Next-generation sequencing; MTPN: Myotrophin; GDF-8: myostatin; EMA: eye muscle area; ADG: average daily gain; OAR: ovine chromosome; MYLPF: myosin light chain phosphorylatable fast skeletal muscle; MYH: myosin heavy chains; TPM2: tropomyosin 2; TTN: Titin; LT: Lantang; LR: Landrace; DEG: differentially expressed genes; HH: Hamburger–Hamilton; TNNI1: troponin I; MB: myoglobin; MYL3: myosin, light chain 3; MBP: myelin basic protein; CSRP3: cysteine and glycine-rich protein 3; FHL2: four and a half LIM domains 2; HS6ST2: heparan sulfate 6-O-sulfotransferase 2; MUSTN1: musculoskeletal, embryonic nuclear protein 1; FGF16: fibroblast growth factor 16; INCENP: inner centromere protein antigens 135/155 kDa; and NDE1: NudE nuclear distribution gene E homolog 1 (A. nidulans).
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