The Genetic Background of the Muscle Development of the Rabbit

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Summary

Selection programs of hybrid rabbits and meat specific breeds are based on growing the amount of valuable meat parts of the carcass, making more profit to the breeder and extra amount of protein for customers. In this point of view, it is essential to know the process of muscle development from embryonic to the postnatal phase, and the regulatory genes which are able to determine muscle growth. This review briefly summarizes the prenatal development of the muscle tissue, regarding myogenic regulating factors and the upstream regulation of myogenesis. In addition, there are some significant components of the postnatal phase which are not negligible in terms of muscle development. It is crucial to see the whole process and the latest steps of molecular genetics helping to increase the selection progress.

Key words

genetic regulation, muscle growth, myogenesis, rabbit selection

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Introduction

Animal breeding concentrates on evolving the quality of certain products such as lean meat in case of the rabbit. While breeding programmes mainly focus on developing traits in the breeding goal, there are numerous levels of selection pressure applied for the tissues (bone, fat or muscle), resulting in different body types or meat-bone ratio. There is also a great variation of body size from dwarf rabbits to giant lines However, in meat production, medium-sized lines are the most preferred ones due to their growth rate and prolificacy.

The diversity of breeds also has different outcomes in meat quality and carcass yield. There are studies focusing on the slaughter weight of the rabbit, measured in different breeds and age groups (Perrier and Ouhayoun, 1990, Lukefahr et al., 1982, Lukefahr et al., 1983) determining the optimal slaughter age for concrete markets. Primarily the muscle tissue gives most part of the carcass weight regulated by ubiquitous factors (b/HLH proteins) and tissue-specific genes (MyoD gene family). These different genes can affect the cellular and biochemical composition of the muscle, expand fat and muscle tissue, thereby influencing muscle mass and meat quality.

In this study, we focused on the regulatory factors and genetic background of the muscle development because the selection process has to concentrate on the skeletal muscle tissue for lean meat production.

Prenatal development

During prenatal development, the genetic information codes tissue-specific proteins, which mean myotubes express a large set of genes (skeletal actin, myosin, troponin, tropomyosin etc.) of the neuromuscular junction and the sarcomere. Polypeptide-involved gene-expression induces muscle metabolism and myotubes express a common gene set with somatotrophs encoding the required proteins for metabolic transport, DNA replication and repair, creating the structure of the Golgi-apparate and the endoplasmic reticulum (Holtzer et al., 1969).

In the first stages of the embryo, myogenic precursor cells create the basis of myoblasts. The precursor cells originate from the epithelial spheres along the cranial-caudal axis of the embryo which derive from the paraxial mesoderm giving rise to the notochord (Christ and Ordal, 1995, Palacios et al., 2006, Buckingham and Rigby, 2014). Signalling molecules from different domains are able to determine the somitogenesis and form the sclerotome (SC) and dermomyotome (DM) (Hernández et al., 2017). Somitogenesis contains gene expression involving the Notch and Wnt pathways (Wnt1, Wnt3a from the neural tube and Wnt6 and Wnt7a from the ectoderm surface) towards the caudal part of the paraxial mesoderm restricting cells to the mesenchymal state with the high concentration of Fgf and Wnt restricting cells to an undifferentiated state (Aulehla and Pourique, 2010). This signalling mechanism also regulates the periodic activity of the Notch pathway which controls the generation of the somites by cyclic genes (Hofmann et al., 2004). Later, dorsal somites differentiate to dermomyotomes as the final source of the precursor cells (Cossu et al., 1996). These mesodermal originated cells determine the proliferation and divide the myoblast pool (Rehfeldt et al., 2000).

Myogenic regulatory factors

The genetic regulation of the muscle was triggered by discovering the MyoD family of basic-helix-loop-helix (bHLH) in the 1980s. This contains MyoD (Davis et al., 1987), myogenin (Edmonson and Olson, 1989, Wright et al., 1989), MRF4/Myf-6, (Rhodes and Konieczny 1989, Braun et al., 1990, Miner and Wold., 1990) and Myf-5, (Braun et al., 1990) conserving a protein domain and trans-activate the muscle-specific gene expression by interacting the E-box (consensus nucleotide motif) (Lassar et al., 1989, Murre et al., 1989). Most of the skeletal muscles contain E-boxes, although, in some cases, the bHLH proteins act as an intermediary regulator of muscle-specific gene transcription. One of these is myocyte enhancer factor (MEF), having two protein variants MEF2Cα1 and MEF2Cα2 which positively control the myogenic differentiation and enhance the proliferation of primary myoblasts and regeneration in a muscle-injury model in an overexpressed state (Baruffaldi et al., 2017).

In the myogenic lineage, Myf-5 is the first regulatory gene activating in the epaxial and hypaxial domain. This process is followed by the Myf-4 gene expression contributing significantly to muscle cell differentiation. Braun et al. (1992) and Rudnicki et al. (1992) reported a Myf-5 knockout mouse which showed delayed myogenesis; later on, the knockout of Myf-5: MyoD was followed by a total lack of skeletal muscle (Rudnicki et al., 1993). MyoD as a transcription factor is the first determination gene to initiate the fibroblast-myoblast conversion (Davis et al., 1987).

Upstream regulation of myogenesis

In the skeletal muscle, Pax3 and Pax7 are the main, non-tissue specific upstream regulators (Bucingham and Relaix, 2007). The Pax family contains domain transcription factors which support tissue specification and the development of the organs in an embryonic stage. These genes are present in each vertebrate and according to Noll (1993), Pax3 and Pax7 originate from a common ancestral gene. During the maturation of the somite, both Pax genes activate Myf-5 and MyoD and move from the central region of dermomyotome to the myotome (Gros et al. 2005, Kassar-Duchossoy et al., 2005). Pax3 encodes a transcription factor that affects the early segmented somites and the presomitic mesoderm (Goulding et al., 1991) and gives rise to the hypaxial body (Tremblay et al., 1998) and limb muscles (Buckingham et al., 1999).

During this process, the number of Pax3 cells starts to increase and the central dermomyotome loses its epithelial structure. On the other hand, Pax7 takes part in the muscle development by establishing the satellite cell pool and forming the secondary myofibres (Maqbool and Jagla, 2007). These first waves are able to determine the shape of the muscles (Baumeister et al., 1997). However, mutations in Pax3/Pax7 can also occur where cells fail to enter the myogenic program, leading to a serious skeletal muscle loss (Relaix et al., 2005). In addition, the total absence of Pax3 lineage is embryonically lethal, as proved by Hutchenson et al. (2009) while the ablation of Pax7 expressing cells only causes fewer myofibres and smaller muscles (Seale et al., 2000, Hutcheson et al., 2009.)

The apex of the regulatory cascade is the Sine Oculis–Related Homeobox family with Six1 and Six4 homeoproteins. These are

co-expressed in the muscle-cell lineage and directly control Pax3 along with the hypaxial myogenic progenitors during embryonic development (Grifone et al., 2005). Six1 and Six4 are distinguished by the presence of the two conservation domains; the six-type homeodomain binding to DNA and the amino-terminal Six-domain. This one is able to interact with the co-activators and the corepressors of the transcription (Kawakami et al., 2000, Tessmar et al., 2002, Zhu et al., 2002). Six proteins are also capable to translocate eyes-absent homologues (Eya1; Eya2) and act as cofactors to activate the Six-target genes; Pax3, MyoD, MRF4, and myogenin (Grifone et al., 2005). Among the Six-genes Six1, Six2, Six4 and Six5 are expressed in the embryonic stage. Besides, there is a synergism between these Six-proteins and MRFs, sharing the same MEF3 binding site and participating in muscle-gene activation with MyoD.

Micro-RNA regulation

At the post-transcriptional level, a class of non-coding RNAs (~22 nucleotides) are responsible for the regulation of muscle gene expression (Filipowitz et al., 2005). These microRNAs (miRNAs) are able to take control of multiple mRNAs at the same time by inhibiting or improving the translation of the mRNA bonding with the 3'-UTR of their regulatory target (Lee et al., 2007) and participating in cell proliferation, differentiation and myogenesis (Mendell et al., 2005). The numerous miRNAs in mammals are tissue-specific, so that in muscle tissues myomiR family is liable for gene expression. Among these miRNAs, MiR-206 is expressed specifically in skeletal muscles (Sempere et al., 2004). Overexpressing of MiR-206 blocks cell cycle progression in the C2C12 lineage and incorporates in myotube formation and in conclusion, inhibition on the MiR-206 expression produces the opposite of this process (Kim et al., 2006).

The proliferation of the satellite cells is also controlled by a micro-RNA, called Mir-133, repressing the Serum Response Factor (Chen et al., 2006). On the other hand, miRNAs upregulate the satellite cell development by inhibiting Pax7 translation, so MyoD is no longer inhibited and myotube formation can begin (Chen et al., 2010). At this point, Pax3 is also targeted by Mir-27 for the sake of the differentiation (Crist et al., 2009). In rabbits, secreted frizzled-related protein 2 (SFRP2) mRNA was studied by Levin et al. (2001) and proved that SFRP2 is widely expressed in the rabbit embryo and falls off after birth. However, it could be detected within one day of muscle damage. As a consequence, this protein works as a Wnt antagonist and has a role in satellite cell activation.

Postnatal muscle growth

The number of the muscle fibres is mainly determined by genetic factors and it differs between species (Hall et al., 2004) and sexes (Seidemen and Crouse, 1986) controlled by a special biochemical regulation system. Muscle differentiation yields the largest tissue mass in the organism committing approximately ~10^{12} nuclei to the expression of muscle-specific genes.

Skeletal muscle involves muscle fibres from two distinct populations. Primary myofibres provide the framework of secondary fibres and they are formed during the initial stages of myoblast (Wigmore and Evans, 2002). The other population was firstly described by Moss and LeBlond (1971), called satellite cells, which are able to divide the myonuclei during postnatal growth. After birth, the total number of muscle fibres reported remaining unchanged in mammalian species. On the other hand, it is possible to increase the fibre number later as a result of maturation (Ontell and Kozeka 1984). This process makes the proliferation of mononucleated myogenic cells turn multinucleated (Reznik, 1976). However, it is assumed that a subpopulation of myoblasts is not assimilating in the development of the syncytia, in turn, it associates in the exterior of all developing fibres (Feldman and Stockdale, 1992). These stem cells also have the ability to cell renewal by the Pax7, thereby ensuring the muscle, growth and repair (Kuang et al., 2007). Examining the satellite cell differentiation in rabbits Barjot et al., (1995) discovered that they differ according to their muscle type origin and slow-twitch and the fast-twitch originated satellite cells show different phenotypic properties. As Table 1. shows, many genetic markers can affect satellite cells, proliferating and differentiating myoblasts from distant anatomical locations.

Table 1. Myogenic markers (Dumount and Rudnicki 2015)

Markers	Sat	Pro	Diff
Pax7	+	+	-
Calcitonin receptor	+	-	-
CD34	+	+/-	-
Caveolin-1	+	+/-	-
Cxcr4	+	+	-
Mcad	+	+	-
c-Met	+	+	-
Itga7 and Itgb1	+	+	+
Vcam1	+	+	+
Ncam1	+	+	+
Syndecan ¾	+	+	+
MyoD	-	+	+/-
Desmin	-	+	+
MyoG	-	-	+
MyHC	-	-	+

Sat: Quiescent satellite cells; Pro: Proliferating myoblasts; Diff: Differentiating myoblasts

Postnatal muscle composition

Muscle fibre type also can change during the maturation and the development of the skeletal muscle and affect meat quality. One of the major contracting proteins is the myosin heavy chain (MyHC) containing a total of 11 isoforms revealing the existence of "pure" and "hybrid" muscle fibre types depending on the number of the enclosed isoforms, accompanied by several proteins which

are capable of determining the functional properties (Staron and Pette, 1986). The genome includes at least 19 classes for the MyHC gene superfamily comprising isogenes (Sellers et al., 1997). The phenotypic expression of these genes can be activated by thyroid hormone (Lompre et al. 1984, Izumo et al. 1986) passive stretch (Goldspink et al., 1992, Russell and Dix, 1992) and physical activity like electric stimulation (Pette and Vrbova, 1992). In addition, skeletal muscle fibres from different anatomical origin express a various set of genes adapting them to their required contractive activity. As an example, stretching and immobilising the fast contracting *m. tibialis anterior* of the rabbit results in a 30% muscle growth within 4 days (Goldspink et al., 1992). Later, Shiyu et al. (1997) reported that IGF gene expression also has a serious impact on muscle fibre length and the number of sarcomeres of the rabbit.

Another regulator gene is *Myostatin* (MSTN), which is responsible for the regulation of muscle fibre types and sizes in the rabbit, acting as a negative regulator to muscle growth (McPherron et al. 1997, Lee, 2004). It is a part of TGF-β superfamily, phylogenetically classified as a growth and differentiation factor (GDF) in the GDF8 subgroup (Lee and McPherron, 1999). In pro-domain form, it can affect the mature C-terminal ligand (Massagué, 1990), antagonize its biological activity resulting in increased muscle mass (Thies et al., 2001, Young et al., 2001) and eventuate fat loss even if the animal has been exogenously treated with it (Lin et al., 2002). The double-muscling (DM) was firstly described in cattle (McPherron, 1997) leading to a serious increase in muscle fibre number, while the size remained unchanged. Thus, the amount of muscle mass thrives almost with 20% (Shahin and Berg, 1985, Wegner et al., 2000). The MSTN gene of the rabbit is composed of two introns and three exons. Kuang et al., (2014) studied the effect of MSTN to the *m. longissimus dorsi* and *m. biceps femoris* in Californian White (CW) and German great line of ZIKA (GZ) rabbits, where GZ rabbits showed less growth inhibition from MSTN, which lead to 36% higher slaughter weight.

Molecular genetics serving the selection process

Microsatellite analysis

Microsatellite markers are widely used in animal breeding. Fontanesi et al. (2008) applied DNA markers to identify the genetic variability of the growth hormone (GH) and MSTN to the production traits of rabbits. While GH showed no mutations on the sequenced regions, the polymorphism on MSTN (C>T on intron 2) can be used as a gene marker to the production traits according to its allele distribution. Linkage and quantitative trait loci (QTL) mapping of the rabbit genome to carcass traits was described by Sternstein et al. (2015) identifying the major QTL on chromosome 7 responsible for carcass weight.

SNP markers

Single nucleotide polymorphisms (SNPs) were also detected by several authors, affecting the skeletal muscle development of the rabbit. Qiao et al. (2014) found an SNP on the 476th locus of the 5'-regulatory region which had a significant effect on liver weight, carcass weight, and the weight of the forelegs. Fontanesi et al. (2011) found four SNPs in the MSTN gene of the rabbit representing differences between breeds in conformation and muscle mass. Sternstein et al. (2014) reported a strong association between one SNP (c. 373+234G>A), and 9 carcass composition traits. (hot carcass weight, reference carcass weight, dressing out percentage, fore-intermediate and hind carcass weight, meat weight for the fore and intermediate part and bone weight for the intermediate part). According to Abdel-Kafy et al. (2016) the „G" allele of MSTN at the *194A>G SNP had positive effects to the growth performance and the carcass traits. On the other hand, it did not produce any negative effects on reproductive traits, such as number of services per conception and the kindling interval.

SNP markers are also widely used for the genotyping of the meat quality traits. In this case, Calpastatin gene (CAST) and Myopalladin gene (MYPN) can be used (Wang et al., 2016, Wang et al., 2017), due to their allele frequency to the selection process. An SNP on the CAST gene (11th chromosome, g.16441502 C > T located at 67 bp in intron 3) determined the yellowness and the intramuscular fat content of the *m. longissimus dorsi* and *m. biceps femoris* while a (g.18497416 G > A) was found at 229 bp in exon 13 of chromosome 18 showing strong correlations with intramuscular fat content of the examined muscles.

CRISPR/Cas9

Genetically modified animal models are widely used in recent years. CRISPR/Cas9 gene editing technology generated gene-targeted animal models in sheep (Crispo et al., 2015), mice (Horii et al., 2014) and pigs (Wang et al., 2015). Rabbits were firstly used by Qingyan et al. (2016) creating successfully MSTN KO rabbits, where skeletal muscle hypertrophy and hyperplasia along with increased body weight was observed and inherited to the F1 generation.

Conclusions

The genetic basis of the carcass traits is determined by multiple loci. Laboratory studies can provide a range of insights into the genetic background of these phenotypic traits. However, many genes and SNPs are still unknown. The improving knowledge and technology may solve this problem and hopefully help in making selection decisions for lean meat production in the future.

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References

Abdel-Kafy E.M., Darwish S.F., Elkhisin D. (2016). Correlating single nucleotide polymorphisms in the myostatin gene with performance traits in rabbits. World Rabbit Sci 24: 213-221. doi: https://doi.org/10.4995/wrs.2016.4026

Aulehla, A., Pourquié, O. (2010). Signaling gradients during paraxial mesoderm development. Cold Spring Harbor perspectives in biology 2 (2): a000869. doi: 10.1101/cshperspect.a000869

Baumeister A, Arber S, Caroni P (1997). Accumulation of muscle ankyrin repeat protein transcript reveals local activation of primary myotube endcompartments during muscle morphogenesis. J Cell Biol 139: 1231–1242

Barjot C., Cotten M. L., Goblet C, Whalen R. G, Bacou F. (1995). Expression of myosin heavy chain and of myogenic regulatory factor

genes in fast or slow rabbit muscle satellite cell cultures. J Muscle Res Cell Motil 16 (6): 619–628

Baruffaldi F., Montarras D., Basile V., De Feo L., Badody S., Ganassi M., Battini R., Nicoletti C., Imbriano C., Musaró A., Molinari S. (2017). Dynamic Phosphorylation of the Myocyte Enhancer Factor 2Cα1 Splice Variant Promotes Skeletal Muscle Regeneration and Hypertrophy. Stem Cells. 35 (3): 725-738. doi: https://doi.org/10.1002/stem.2495

Braun, T., E. Bober, B. Winter, N. Rosenthal, and H. H. Arnold. (1990). Myf-6, a new member of the human gene family of myogenic determination factors: evidence for a gene cluster on chromosome 12. EMBO (Eur. Mol. Biol. Organ.). J 9:821-831

Braun T., Bober E., H.-H. Arnold. (1992). Inhibition of muscle differentiation by the adenovirus E1a protein: repression of the transcriptional activating function of the HLH protein Myf-5 Genes Dev 6: 888-902

Buckingham M., Tajbakhsh S. (1999). 41 - Myogenic Cell Specification during Somitogenesis, In: Cell Lineage and Fate Determination, (Sally A. Moody ed.) Academic Press, pp. 617-633

Buckingham M., Relaix F. (2007). The role of Pax genes in the development of tissues and organs: Pax3 and Pax7 regulate muscle progenitor cell functions. Annu Rev Cell Dev Biol 23: 645-673. DOI: 10.1146/annurev.cellbio.23.090506.123438

Buckingham M., Rigby P. W., (2014). Gene regulatory networks and transcriptional mechanisms that control myogenesis. Dev Cell 28: 225–238. doi: 10.1016/j.devcel.2013.12.020

Chen J. F., Mandel E. M., Thomson J. M., Wu Q., Callis T. E., Hammond S.M, Conlon F. L., Wang D. Z. (2006). The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation Nature Genetics, 38: 228-233. doi: 10.1038/ng1725

Chen J.F., Tao Y, Li J, Deng Z, Yan Z, Xiao X, Wang D. Z. (2010). MicroRNA-1 and microRNA-206 regulate skeletal muscle satellite cell proliferation and differentiation by repressing Pax7. Journal of Cell Biology, 190: 867-879. doi: 10.1083/jcb.200911036

Christ B., Ordahl C.P., (1995). Early stages of chick somite development, Anat Embryol 191: 381–396

Crist C. G., Montarras D., G. Pallafacchina G. Rocancourt D., Cumano A., Conway S. J., Buckingham M. (2009). Muscle stem cell behaviour is modified by microRNA-27 regulation of Pax3 expression. Proceedings of the National Academy of Sciences of the United States of America, 106. 13383-13387

Crispo, M., Mulet A. P., Tesson L., Barrera N., Cuadro F., dos Santos-Neto P., C., Nguyen T. H., Crénéguy A., Brusselle L., Anegón I., Menchaca A. (2015). Efficient generation of myostatin knock-out sheep using CRISPR/Cas9 technology and microinjection into zygotes. PLoS One 10 (8): e0136690. doi: 10.1371/journal.pone.0136690

Cossu G., Tajbakhsh S., Buckingham M., How is myogenesis initiated in the embryo? (1996). Trends Genet 12: 218–223

Davis L. R., Weintraub H., Lassar A. B. (1987). Expression of a single transfected cDNA converts fibroblasts to myoblasts. Cell. 51 (6): 987-1000

Dumont N., Rudnicki M. A., (2015). Characterizing Satellite Cells and Myogenic Progenitors During Skeletal Muscle Regeneration. Methods in Molecular Biology 1560: 179-188

Feldman J. L., Stockdale F.E. (1992). Temporal appearance of satellite cells during myogenesis. Dev. Biol. 153 (2): 217-226

Filipowicz W. Jaskiewicz L. Kolb F.A.Pillai R.S. (2005). Post-transcriptional gene silencing by siRNAs and miRNAs. Curr Opin Struct Biol .15: 331–341

Edmondson D. G., Olson E. N. (1989). A gene with homology to the myc similarity region of MyoD1 is expressed during myogenesis and is sufficient to activate the muscle differentiation program. Genes Dev 3 (5): 628-40

Fontanesi L., Tazzoli M., Scotti E., Russo V. (2008). Analysis of candidate genes for meat production traits in domestic rabbit breeds. Proceedings of the 9th World Rabbit Congress, Verona, Italy, 10-13 June 2008 pp.79-84

Fontanesi L., Scotti E., Fabretti A., Fornasini D., Picconi A., Russo V. (2011). Identification of polymorphisms in the rabbit (Oryctolagus cuniculus) myostatin (MSTN) gene and association analysis with finishing weight in a commercial rabbit population. Anim Genetics. 42: (3). 339. doi: 10.1111/j.1365-2052.2010.02163.x.

Goulding M. D., Chalepakis G., Deutsch U., Erselius JR, Gruss P. (1991). Pax3, a novel murine DNA binding protein expressed during early neurogenesis. EMBO J 10: 1135–1147

Goldspink, G., Scutt, A., Loughna, P., Wells, D., Jaenicke, T. and Gerlach, G. F. (1992). Gene expression in skeletal muscle in response to mechanical signals. American Journal of Physiology 262: 326–363

Grifone R, Demignon J, Houbron C, Souil E, Niro C, Seller MJ, Hamard G, Maire P. (2005). Six1 and Six4 homeoproteins are required for Pax3 and Mrf expression during myogenesis in the mouse embryo. Development 132: 2235–2249

Gros, J., Manceau, M., Thome, V., and Marcelle, C. (2005). A common somitic origin for embryonic muscle progenitors and satellite cells. Nature 435: 954–958

Hall M. N., Raff M., Thomas G., (2004). Cell Growth: Control of Cell Size. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Hernández-Hernández J. M., García-González E. G., Brun C. E., Rudnicki M. A. (2017). The myogenic regulatory factors, determinants of muscle development, cell identity and regeneration. Seminars in Cell & Developmental Biology 7: 10–18. doi: 10.1016/j.semcdb.2017.11.010

Horii, T., Arai Y., Yamazaki M., Morita S., Kimura M., Itoh M., Abe Y., Hatada I., (2014). Validation of microinjection methods for generating knockout mice by CRISPR/Cas-mediated genome engineering. Sci Rep 4: 4513, doi: 10.1038/srep04513

Hofmann M, Schuster-Gossler K, Watabe-Rudolph M, Aulehla A, Herrmann BG, Gossler A. (2004). WNT signalling, in synergy with T/TBX6, controls Notch signalling by regulating Dll1 expression in the presomitic mesoderm of mouse embryos. Genes Dev 18: 2712–2717

Holtzer, H.; Bischoff, R.; Chacko, S. (1969). In: Cellular Recognition (Smith, R.T.; Good, R.A., eds.) p 19. Appleton, New York.

Hutchenson D. A., Zhao J., Merrel A., Haldar M., Kardon G. (2009). Embryonic and fetal limb myogenic cells are derived from developmentally distinct progenitors and have different requirements for beta-catenin. Genes Dev 15. 23 (8): 997-1013. doi: 10.1101/gad.1769009

Izumo S., Nadal-Ginard B., Mahdavi V. (1986). All members of the MHC multigene family respond to thyroid hormone in a highly tissue-specific manner. Science. 231 (4738): 597-600

Kassar-Duchossoy, L., Giacone, E., Gayraud-Morel, B., Jory, A., Gomes, D., and Tajbakhsh, S. (2005). Pax3/Pax7 mark a novel population of primitive myogenic cells during development. Genes & Dev. 19: 1426–1431

Kawakami K, Sato S, Ozaki H, Ikeda K. (2000). Six family genes—structure and function as transcription factors and their roles in development. Bioessays 22: 616–626

Kim H .K., Lee Y. S., Sivaprasad U., Malhotra A., Dutta A. (2006). Muscle-specific microRNA miR-206 promotes muscle differentiation. J Cell Biol. 174: 677-687

Koishi, K., Zhang, M., Mclennan, I. S. and Harris, A. J. (1995). MyoD protein accumulates in satellite cells and is neurally regulated in regenerating myotubes and skeletal muscle fibres. Dev. Dynam. 202, 244-254

Kuang S., Kuroda K., Le Grand F., Rudnicki M. A. (2007). Asymmetric self-renewal and commitment of satellite stem cells in muscle. Cell 129 (5): 999–1010

Kuang L., Xie X., Zhang X., Lei M., Li C., Ren Y., Zheng J., Guo Z., Zhang C., Yang C., Zheng Y., (2014). Expression Profiles of Myostatin, Myogenin, and Myosin Heavy Chain in Skeletal Muscles of Two Rabbit Breeds Differing in Growth Rate, Animal Biotechnology, 25 (4): 223-233, doi: 10.1080/10495398.2013.865639

Lassar AB, Buskin JN, Lockshon D, Davis RL, Apone S, Hauschka SD, Weintraub H. MyoD is a sequence-specific DNA binding protein requiring a region of myc homology to bind to the muscle creatine

kinase enhancer. (1989) .Cell. 58(5): 823–831
Lee, S.-J., McPherron A. C., (1999). Myostatin and the control of skeletal muscle mass. Curr Op Genet Dev. 9: 604-607
Lee S.-J. (2004). Regulation of muscle mass by myostatin. Annu Rev Cell Dev Biol 20, 61–86
Lee C. T., Risom T., Strauss W. M. (2007). Evolutionary conservation of microRNA regulatory circuits: an examination of microRNA gene complexity and conserved microRNA-target interactions through metazoan phylogeny. DNA Cell Biol 26 (4): 209-18
Levin J. M., Boubaker el Andalousi R., Dainat J., Reyne Y., Bacou F. (2001). SFRP2 expression in rabbit myogenic progenitor cells and in adult skeletal muscles. Journal of Muscle Research & Cell Motility. 22 (4): 361-369
Lin J., Wu H., Tarr P. T., Zhang C. Y., Wu Z., Boss O., et al. (2002). Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. Nature 418, 797–801 Lompre A. M., Nadal-Ginard B., Mahdavi V. (1984). Expression of the cardiac ventricular alpha- and beta-myosin heavy chain genes is developmentally and hormonally regulated. Journal of Biological Chemistry 259: 6437–6446
Lukefahr S. D., Hohenboken W. D., Cheeke P. R, Patton N. M, Kennick W. H. (1982). Carcass and meat characteristics of Flemish Giant and New Zealand White purebred and Terminal-Cross rabbits Journal of Animal Science, 54 (1982), pp. 1169-1174
Lukefahr, S. D., Hohenboken, W. D., Cheeke, P. R. & Patton, N. M. (1983). Appraisal of nine genetic groups of rabbits for carcass and lean yield traits. J Anim Sci 57: 899-709
Maqbool T, Jagla K. (2007). Genetic control of muscle development: Learning from Drosophila. J Muscle Res Cell Motil 28: 397–407. doi: 10.1007/s10974-008-9133-1
Massagué, J. (1990). The transforming growth factor-β family. Annu Rev Cell Biol. 6: 597-641
McPherron, A. C., and Lee S. J. (1997). Double muscling in cattle due to mutations in the myostatin gene. Proc Natl Acad Sci. 94:12457-12461
Mendell J.T. (2005). MicroRNAs: critical regulators of development, cellular physiology and malignancy. Cell Cycle Georget Tex. 4:1179–1184
Miner, J. H., and B. Wold. (1990). Herculin, a fourth member of the myoD family of myogenic regulatory genes. Proc Natl Acad Sci. 87: 1089-1093
Moss F. P., Leblond C. P. (1971). Satellite cells as the source of nuclei in muscles of growing rats. Anat. Rec. 170 (4): 421-435
Murre C., McCaw P. S, Vaessin H., Caudy M., Jan L. Y, Jan Y. N, Cabrera C. V., Buskin J. N., Hauschka S. D., Lassar AB, et al. (1989). Interactions between heterologous helix-loop-helix proteins generate complexes that bind specifically to a common DNA sequence. Cell. 58 (3): 537–544
Noll M. (1993). Evolution and role of Pax genes. Curr Opin Genet Dev 3: 595–605
Ontell, M. and Kozeka, K. (1984). Organogenesis of the mouse extensor digitorum longus muscle: a quantitative study. American Journal of Anatomy 171: 149–161
Palacios D., Puri P. L., (2006). The epigenetic network regulating muscle development and regeneration, J Cell Physiol. 207 1–11
Perrier, G. & Ouhayoun, J. (1990). 5th Jour. Res. Cunic. December 1990, Comm. 41.
Pette D, Vrbova G. (1992). Adaptation of mammalian skeletal muscle fibres to chronic electrical stimulation [Review]. Reviews of Physiology, Biochemistry & Pharmacology 120: 115–202
Qiao X. B, Xu K. Y., Li B., Luan X., Xia T., Fan X. Z., (2014). Rabbit MSTN gene polymorphisms and genetic effect analysis. Genetics and molecular research.13 (2) : 2590-2597. doi: 10.4238/2014.April.8.1
Qingyan L. V., Yuan L., Deng J., Chen M., Wang Y., Zeng J., Li Z. (2016). Efficient Generation of *Myostatin* Gene Mutated Rabbit by CRISPR/Cas9. Sci Rep. 26; 6: 25029. doi: 10.1038/srep25029
Rehfeldt, C., Fiedler, I., Dietl, G. and Ender, K. (2000) Myogenesis and postnatal skeletal muscle cell growth as influenced by selection. Livestock Production Science 66 (2): 177–188
Relaix, F., Rocancourt, D., Mansouri, A., and Buckingham, M. (2005). A Pax3/Pax7-dependent population of skeletal muscle progenitor cells. Nature 435: 948–953
Reznik, M. 1976. Origin of the myogenic cell in the adult striated muscle of mammals. A review and a hypothesis. Differentiation 7, 65-73.
Rhodes S. J., Konieczny S. F. (1989). Identification of MRF4: A new member of the muscle regulatory factor gene family Genes Dev. 3: 2050-2061
Rudnicki MA, Braun T, Hinuma S, Jaenisch R (1992). Inactivation of MyoD in mice leads to up-regulation of the myogenic HLH gene Myf-5 and results in apparently normal muscle development. Cell 71: 383–390
Rudnicki, M. A., Schnegelsberg, P. N., Stead, R. H., Braun, T., Arnold, H. H. and Jaenisch, R. (1993). MyoD or Myf-5 is required for the formation of skeletal muscle. Cell 75: 1351-1359
Russell B, Dix DJ. (1992). Mechanisms for intracellular distribution of mRNA: *in situ* hybridization studies in muscle. American Journal of Physiology. 262: C1–8
Seideman, S. C., Crouse, J. D. (1986). The effects of sex condition, genotype and diet on bovine muscle fibre characteristics. Meat Science 17: 55–72
Seale, P., Sabourin, L. A., Girgis-Gabardo, A., Mansouri, A., Gruss, P., Rudnicki, M.A. (2000). Pax7 is required for the specification of myogenic satellite cells. Cell. 102: 777–786.
Sellers, J. R., Goodson, H.V. and Wang, F. 1997. A myosin family reunion. Journal of Muscle Research and Cell Motility 17: 7–22
Shahin K.A., Berg R.T. (1985). Growth patterns of muscle, fat, and bone, and carcass composition of double-muscled and normal cattle. Can J Anim Sci. 65: 279–293
Sempere L. F., Freemantle S., Pitha-Rowe I., Moss E., Dmitrowski E., Ambros V. (2004). Expression profiling of mammalian microRNAs uncovers a subset of brain-expressed microRNAs with possible roles in murine and human neuronal differentiation. Genome Biol. 5 (3): R13.
Shiyu Y., Alnaqueeb M., Simpson H., Goldsprink G. (1997). Changes in muscle fibre type, muscle mass and IGF-1 gene expression in rabbit skeletal muscle subjected to stretch. J. Anat.190, pp. 613-622
Smith, T. H., Block, N. E., Rhodes, S. J., Konieczny, S. F. and Miller, J. B. (1993). A unique pattern of expression of the four muscle regulatory factor proteins distinguishes somitic from embryonic, fetal and newborn mouse myogenic cells. Development 117: 1125-1133
Staron RS, Pette D (1986). Correlation between myofibrillar ATPase activity and myosin heavy chain composition in rabbit muscle fibres. Histochemistry 86:19–23
Sternstein, I., Reissmann, M., Maj, D., Bieniek, J., & Brockmann, G. A. (2014). A new single nucleotide polymorphism in the rabbit (Oryctolagus cuniculus) myostatin (MSTN) gene is associated with carcass composition traits. Animal Genetics. 45 (4): 596–599, doi:10.1111/age.12165
Sternstein I., Reismann M., Maj D., Bieniek J., Brockamnn G. (2015). A comprehensive linkage map and QTL map for carcass traits in a cross between Giant Grey and New Zealand White rabbits. BMC Genetics.16:16. doi: 10.1186/s12863-015-0168-1
Tessmar K, Loosli F, Wittbrodt J. (2002). A screen for co factors of Six3. Mech Dev 117: 103–113
Thies R. S., Chen T., Davies M V., Tomkinson N K, Pearson A. A., Shakey Q. A., Wolfman N. M, (2001). GDF-8 propeptide binds to GDF-8 and antagonizes biological activity by inhibiting GDF-8 receptor binding. Growth Factors 19: 251-259.
Tremblay, P., Dietrich S., Mericskay M., Schubert F. R., Li Z., Paulin D. (1998). A crucial role for Pax3 in the development of the hypaxial musculature and the long-range migration of muscle precursors. Dev Biol. 203: 49–-61
Wang J., Elzo M.A., Yan L., Chen S., Jia X., Zhang M., Lai S. (2016). A single nucleotid polymorphism in CAST gene is associated with meat quality traits in rabbits. Anim Sci Pap Rep. 34: 269-278

Wang, Y., Du Y., Shen B., Zhou X., Li J., Liu Y., Wang J., Zhou J., Hu B., Kang N., Gao J., Yu L., Huang X., Wei H. (2015). Efficient generation of gene-modified pigs via injection of a zygote with Cas9/sgRNA. Sci. Rep. 5: 8256, doi: 10.138/srep08256

Wang J., Shi Y., Mauricio A. E, Su Y, Jia X., Chen S., Lai S. (2017). Myopalladin gene polymorphism is associated with rabbit meat quality traits. Italian Journal of Animal Science 16 (3): 400-404. doi: 10.1080/1828051X.2017.1296333

Wegner, J., E. Albrecht, I. Fiedler, F. Teuscher, H.-J. Papstein and K. Ender. (2000). Growth- and breed-related changes of muscle fibre characteristics in cattle. J. Anim. Sci. 78:1485-1496

Wigmore, P.M. and Evans, D.J. (2002) Molecular and cellular mechanisms involved in the generation of fibre diversity during myogenesis. International Review of Cytology 216: 175–232

Wright W. E., Sassoon D. A., Lin V. K., 1989. Myogenin, a factor regulating myogenesis, has a domain homologous to myod Cell, 56, 607-617

Zimmers TA, Davies MV, Koniaris LG, Haynes P, Esquela AF, Tomkinson KN, McPherron AC, Wolfman NM, Lee SJ. (2002). Induction of cachexia in mice by systemically administered myostatin. Science 296: 1486–1488

Young P, Ehler E, Gautel M. (2001). Obscurin, a giant sarcomeric Rho guanine nucleotide exchange factor protein involved in sarcomere assembly. J Cell Biol. 154: 123–136

Zhu Z., Pipel Y., Church G. M. (2002). Computational identification of transcription factor binding sites via a transcription-factor-centric clustering (TFCC) algorithm. J Mol Biol. 19 318(1): 71-81.

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