THE MYOD GENE FAMILY AND MEAT PRODUCTION - A REVIEW

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SUMMARY

The biological basis for meat production in livestock animals is localized in the muscles, where lean meat production is under genetic control of tissue-specific and more ubiquitously operating genes. An important parameter for meat production is the embryonic formation of muscle tissue, or myogenesis. This process is under control of the MyoD gene family. The intention of this review is to place the discussion about the MyoD genes, which regulate the embryonic muscle tissue formation, in the field of meat production of livestock.

Introduction

Production is biologically realized in defined tissues of the animal, e.g. muscle tissue for lean meat production. Muscles are complex tissues composed of a number of different cell types, e.g. myocytes consisting of myofibers and satellite cells, intramuscular adipocytes, fibroblasts, endothelial cells, neurocytes, etc., of which myocytes are the most predominant cell type. Händel and Stickland (1984, 1988) showed that the number of myofibers present at birth determined the maximal lean meat growth capacity of pigs. Double muscled cattle show a higher number of prenatally developed myofibers than other cattle (Hanset et al., 1982; Swatland and Kiefer, 1974), which suggests lean meat production capacity to be determined by the embryonic development of myocyte number.

Muscle tissue formation, or myogenesis, is a complex, multistep process that chronologically involves (1) progenitor cell determination to the myogenic lineage, (2) migration of myogenic stem cells (myoblasts) to appropriate locations in the early embryo, (3) proliferation of myoblasts and nonmyogenic muscle-tissue cells, (4) terminal myocyte differentiation (i.e. fusion of myoblasts) and expression and organization of specific gene products active only in terminally differentiated muscle cells called sarcomerogenesis, and (5) maintenance of the terminal differentiated state and modulation of myofibers in various myofiber types in response to age and physiological cues (Edgerton and Roy, 1991; Funk et al., 1991; Gunning and Hardeman, 1991; Olson 1992).

Within the muscle, tissue-specific genes and ubiquitous genes are acting to regulate processes synthesizing lean meat and fat. Since these genes influence both cellular and biochemical composition of the tissue, they can be involved in regulating both product quantity and product quality. Therefore, it could be interesting to know these genes in detail, i.e., (1) to identify the genes, (2) to determine their structure, (3) to unravel their action mechanism, and (4) to determine genetic variation in their DNA sequence for breeding purposes. Furthermore, knowledge of the regulatory genes would also gain insight in the processes underlying production traits, and probably give some indication for the basis of production related diseases.

This paper focusses on some aspects of the genetic mechanisms underlying the development and growth of muscle tissue. Existing knowledge of the MyoD genes influencing embryonic muscle cell development will be evaluated shortly. For more comprehensive reviews on the regulation of muscle differentiation, the reader is referred to several recent reviews (Buckingham, 1992, Funk et al., 1991; Olson, 1990; Tapscott and Weintraub, 1991; Weintraub et al., 1991; Young and Brown, 1990). This paper will place the discussion in the framework of meat production of livestock.

Genetic control of muscle tissue development

The MyoD gene family which describes a mechanism for the genetic regulation of the myogenesis (fig. 1) consists of four members in vertebrates: MyoD (also called myf-3), myogenin (myf-4), MRF4 (myf-6, herculin) and myf-5. A number of recent reviews summarizes in detail the existing knowledge of the structure of the genes, the MyoD-myogenesis-model and the activation of muscle tissue-specific genes by the MyoD genes (for

reviews see above). Here, only the most relevant characteristics of the MyoD-myogenesis-pathway to explain muscle development with respect to lean meat production are summarized. Much information on the action of the MyoD gene-family is known from in vitro studies. Here, the model as identified in mammalian embryos will be described.

MyoD gene products and myogenesis

MyoD proteins are expressed specifically in muscle tissue where they act as tissue-specific transcription factors. In vitro, they are active after formation of dimer-complexes with proteins of the ubiquitously expressed E2A gene. The complex binds to specific transcription regulatory sequences of muscle-specific genes called enhancer regions in the promoters, thereby activating expression of the tissue- and developmental stage-specific genes (reviewed in Weintraub et al., 1991; Olson, 1990).

The first MyoD gene to be activated is the myf-5 gene which is activated in the early embryo. The gene is expressed at the appropriate time and position within the embryo to suggest its direct involvement in the initial muscle cell determination event.

Once activated, each member of the MyoD gene family can both positively autoregulate its own expression and regulate the expression of other MyoD genes, thereby continuing the differentiation pathway. Thus, once the pathway is activated, myogenesis continues until terminal differentiation is established.

Determinated cells (called myoblasts) are able to migrate and proliferate (for a review see Olson, 1990, 1992). Irreversible terminal differentiation is induced by fusion of the myoblast into multinucleated myofibers. The fusion is induced by the activation of myogenin (myf-4) and MyoD (myf-3) genes in myoblasts (Olson, 1990).

Knock out mice carrying either an inactivated myf-5 or myf-3 gene show normal muscle development (Braun et al., 1992; Rudnicki et al., 1992), suggesting either plasticity of the myogenic pathway or the existence of alternative myogenic pathways. On the other hand, myf-3 and myf-5 double mutant transgenic mice are not viable which is also the case for myf-4 negative mutant transgenic mice. In both cases normal muscle development was lacking (Arnold et al., 1993; Hasty et al., 1993; Nabeshima et al., 1993) suggesting that the genes of the MyoD gene family play a central role in myogenesis.

The fourth MyoD-gene, myf-6, is activated transiently during early myogenesis and is activated constitutively postnatal when differentiation is already completed. It has been suggested that myf-6 acts primarily on maintenance of the differentiated state of the myofibers (Funk et al., 1991). Probably myf-6 protein is also involved in fusion of satellite cells with myofibers during hypertrophic growth.

Regulation of the expression of MyoD genes

A number of other gene products, such as specific hormones, growth factors and proto-oncogenes are known to modulate myoblast proliferation and differentiation by modulating the expression of one or more of the MyoD genes (for reviews see Florini, 1985; Florini et al., 1991; Hesketh and Whitelaw, 1992; Magri et al., 1991; Olson et al., 1991). This strengthens the idea that the MyoD gene family plays a central role in the development of muscle tissue by controlling the switch from proliferation to differentiation and directing the myogenesis pathway. Terminal differentiation is associated with irreversible withdrawal of the myoblasts from the cell cycle. Tight control between proliferation and differentiation is necessary, since this directly determines the number of cells available for tissue formation (Olson, 1992). Since the MyoD gene family appears to function as a regulatory on/off switch at the decision point, control of the endpoint of proliferation and the onset of differentiation can occur through regulation of the activity of MyoD genes.

Discussion and Conclusions

The number of myofibers is prenatally determined, the maximal number of myofibers available for meat production is formed during embryonic myogenesis. Furthermore, a direct relationship between maximal lean meat growth capacity and myofiber number has been shown in pigs and cattle. So the action of the MyoD genes in myogenesis probably is the most prominent genetic factor for meat production.

The investigation of the interactions between the MyoD genes controlling muscle tissue formation and genes controlling muscle hypertrophic growth capacity would also be fruitfull because the results from such studies could indicate the mechanisms and physiological borders of meat deposition in livestock animals. Detailed knowledge of such mechanisms could induce a more balanced improvement of meat production traits. For example, the breeding strategy could be focussed on prenatal hyperplastic growth and postnatal

hypertrophic growth of meat tissue so that animals could be selected with high genetic capacity for lean meat deposition without having birth problems.

In order to understand muscle tissue better genes may be important which are active especially in the terminally differentiated state of the myofibers. These genes can be relevant for tissue physiology, structure and properties, and thus for meat quality. It may also be interesting to investigate the modulation of the terminally differentiated state of myofibers, expressing fibertype-specific isoforms of muscle-specific proteins and fibertype-specific genes (review: Gunning and Hardeman, 1991). The pathways specifying the myofibertypes are complex and poorly understood while regulatory genes (QTLs) are unknown. MyoD genes might be involved since different myofiber types in adult rat muscles show low, but different expression of the myf-3 and myf-4 genes (Hughes et al., 1993). However, the possible relationship between the MyoD genes and the processes regulating the formation of the different muscle fibertypes still needs to be evaluated. To know the genes controlling myofibertype specification can be important since each myofibertype may influence meat quality parameters like colour and water binding capacity differently. Finally, to understand meat quality traits better it may be interesting to investigate the other cell types in muscle tissue too, e.g. intramuscular adipocyte development and their metabolism.

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Figure 1

The myf-5 gene is activated in mesoderm cells in the early embryo resulting in determination of the cells to the myogenic cell lineage. The transiently activated myf-6 gene may participate in this process. The action of myf-3 and myf-4 induces terminal myogenic differentiation in the cells. Myf-6 is activated again in terminally differentiated cells, suggesting its involvement in maintenance of the differentiated state.