animal

Advances in research on the prenatal development of skeletal muscle in animals in relation to the quality of muscle-based food. I. Regulation of myogenesis and environmental impact

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Skeletal muscle development in vertebrates – also termed myogenesis – is a highly integrated process. Evidence to date indicates that the processes are very similar across mammals, poultry and fish, although the timings of the various steps differ considerably. Myogenesis is regulated by the myogenic regulatory factors and consists of two to three distinct phases when different fibre populations appear. The critical times when myogenesis is prone to hormonal or environmental influences depend largely on the developmental stage. One of the main mechanisms for both genetic and environmental effects on muscle fibre development is via the direct action of the growth hormone–insulin-like growth factor (GH–IGF) axis. In mammals and poultry, postnatal growth and function of muscles relate mainly to the hypertrophy of the fibres formed during myogenesis and to their fibre-type composition in terms of metabolic and contractile properties, whereas in fish hyperplasia still plays a major role. Candidate genes that are important in skeletal muscle development, for instance, encode for IGFs and IGF-binding proteins, myosin heavy chain isoforms, troponin T, myosin light chain and others have been identified. In mammals, nutritional supply in utero *affects myogenesis and the GH–IGF axis may have an indirect action through the partitioning of nutrients towards the gravid uterus. Impaired myogenesis resulting in low skeletal myofibre numbers is considered one of the main reasons for negative long-term consequences of intrauterine growth retardation. Severe undernutrition* in utero *due to natural variation in litter or twin-bearing species or insufficient maternal nutrient supply may impair myogenesis and adversely affect carcass quality later in terms of reduced lean and increased fat deposition in the progeny. On the other hand, increases in maternal feed intake above standard requirement seem to have no beneficial effects on the growth of the progeny with myogenesis not or only slightly affected. Initial studies on low and high maternal protein feeding are published. Although there are only a few studies, first results also reveal an influence of nutrition on skeletal muscle development in fish and poultry. Finally, environmental temperature has been identified as a critical factor for growth and development of skeletal muscle in both fish and poultry.*

Keywords: farm animal, fish, skeletal muscle, animal performance, environmental effects

Implications

Skeletal muscle development in different animal species has been an important topic of scientific research for many years. The aim of this review is to provide recent knowledge on the regulation of prenatal muscle growth and its modification by environmental factors in a variety of species, such as pig, sheep, cattle, poultry and fish, and to show the consequences for later growth, carcass quality and meat/flesh quality, which are of great economic importance in animal production.

Introduction

There is increasing evidence that influences on prenatal and early postnatal development of skeletal muscle can result in

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long-term effects on postnatal growth and physiological function both in animals and in humans. In farm animals, these long-term effects of developmental origin have an impact on economically important traits such as vitality, growth performance, body composition and meat quality. However, the ways in which genotype, genome and physiology contribute to this interaction remains uncertain. Prenatal growth is determined by the genotype of the conceptus, and also depends on the maternal uterine or *in ovo* milieu of hormones, nutrients and growth factors. Understanding mechanisms that control prenatal development and growth are critical to define strategies to reduce the incidence of developmental disorders and their long-term consequences.

In order to intensify research in this field and to stimulate scientific discussion on the developmental origin of farm animal performance, a European network, COST action 925 'The importance of prenatal events for postnatal muscle growth in relation to the quality of muscle based foods' was established. This European Union-supported COST action (2004 to 2008) brought together scientists from 20 European countries and promoted the mutual exchange of scientific knowledge and resulted in a series of collaborative research projects. Moreover, training of young scientists in this research area was a priority and training grants were available for research visits to participating institutions of the member states.

This review will focus on the main outcomes of research based on the scientific results obtained from experiments with mammals, poultry and fish over 4 years (2004 to 2008) by participants of the COST 925 action. These include prenatal regulatory mechanisms of skeletal muscle development, genetic and environmental impact on muscle development and its consequences for animal performance and meat quality as well as advances and standardisation of research methodologies in this area. Moreover, this review will identify the main gaps and open questions in this field of research. The present part 1 of the review focuses on the regulation of myogenesis and the impact of environment on muscle development and related changes in animal performance (for part 2, see Rehfeldt *et al.*, 2011).

Regulatory mechanisms of skeletal muscle development (myogenesis) and growth

Myogenesis and myogenic regulatory factors (MRFs)
The process whereby the skeletal muscle lineage is determined and develops into the mature muscle fibre is termed myogenesis. Evidence to date indicates that the processes are very similar across mammals, poultry and fish, although the timings for the various steps differ considerably. Myogenesis is regulated by a group of muscle-specific transcription factors, collectively known as the muscle regulatory factors or MRFs, and they appear to have the same functions across the various species. There are four MRFs (myf-5, myoD, myogenin and MRF4). Myf-5 and myoD are required for the commitment to the muscle cell type, whereas myogenin and MRF4 are important for inducing differentiation and formation of muscle

fibres (see reviews by Te Pas and Soumillion, 2001; Brameld *et al.*, 2003; Rehfeldt *et al.*, 2004a; Stickland *et al.*, 2004; Johnston, 2006; Chang, 2007; Brameld and Daniel, 2008).

Distinct phases of myofibre formation
There are two or three distinct phases of muscle fibre formation in mammals, poultry and fish, although the terminology used differs. Skeletal trunk muscle development, in mammals and poultry embryo, occurs in two major phases. In the first phase, a primary myotome is formed from cells originating from the four epithelial borders of the dermomyotome. In the second phase, the central region of the dermomyotome undergoes an epithelial to mesenchymal transition and releases pax3/7-positive cells into the primary myotome. These cells evolve into embryonic myoblasts (which give rise to primary fibres) or foetal myoblasts (which give rise to secondary fibres) or satellite cells (which contribute to further growth and repair of the myotome). On the other hand, limb muscles originate from muscle progenitors that delaminate from the ventrolateral border of the dermomyotome. For more details see, for example, the reviews by Biressi *et al.* (2007), Buckingham and Vincent (2009) and Relaix and Marcelle (2009). In mammals and poultry, primary fibres form first, followed by the secondary fibres that develop around these primaries (Maltin *et al.*, 2001; Picard *et al.*, 2002). In large mammals (e.g. sheep and pigs), tertiary fibres have also been described developing between the secondaries (Lefaucheur *et al.*, 1995), although this is hotly debated at times. In mammals, formation of new muscle fibres takes place *in utero*, with the numbers of muscle fibres within each muscle thought to be set around the time of birth (see reviews by Maltin *et al.*, 2001; Picard *et al.*, 2002; Brameld *et al.*, 2003; Chang, 2007; Brameld and Daniel, 2008). However, rats and mice are an exception as muscle fibre formation in some muscles continues during the early neonatal period (Rehfeldt *et al.*, 1987; Wilson *et al.*, 1988). Determination of the total number of fibres within a muscle is technically difficult, particularly in adult muscles of irregular shape from large mammals. It is therefore questionable how much formation of new fibres takes place in postnatal life, but the majority of fibres in most mammals appear to develop *in utero* (Rehfeldt *et al.*, 2004a). Hence, postnatal growth of muscle fibres in mammals mainly involves increases in fibre size (hypertrophy) rather than numbers of fibres. A population of myogenic cells, termed satellite cells, has been identified in muscle of mammals and poultry, particularly during neonatal and postnatal stages of development. In bovine and sheep foetuses, satellite cells are detected adjacent to the myofibres as early as 2 months and 85 days, respectively (Russell and Oteruelo, 1981; Greenwood *et al.*, 1999). Satellite cells proliferate and fuse with existing fibres, thereby increasing DNA content and protein synthetic capacity resulting in muscle fibre hypertrophy.

The development of muscle in chicken resembles that of mammals and the total number of muscle fibres (TNF) does not vary after hatching (Smith, 1963; Gollnick *et al.*, 1983). The muscle fibres then grow by hypertrophy, both in length and diameter, a phenomenon that involves satellite cells,

myogenic precursors present at the periphery of fibres. Satellite cells appear during late chicken embryogenesis between 13 and 16 days *in ovo* (Feldman and Stockdale, 1992; Hartley *et al.*, 1992). Satellite cells are able to multiply and fuse with fibres providing them with new nuclei for protein anabolism and this phenomenon accounts for more than 98% of the final DNA content of chicken muscle (Moss, 1968).

Muscle fibre production in fish occurs in three distinct phases (i) embryonic (Rowlerson and Veggetti, 2001), (ii) late embryo to early larval stages (stratified hyperplasia) and (iii) larval to adult stages, when new white fibres are formed around larger diameter fibres, giving the muscle a mosaic appearance (mosaic hyperplasia; Rescan, 2008). During the embryonic phase, the formation of the primary myotome starts with the differentiation of a superficial layer of slow muscle fibres (or adaxial cells) from the most medial paraxial mesoderm cells. Subsequently, and shortly after segmentation, the deep fast muscle fibres differentiate from posterior somite cells. Anterior cells of the somite then migrate to the lateral surface of the primary myotome and contribute muscle progenitor cells for primary myotome expansion/growth (reviewed in Stellabotte and Devoto, 2007). In contrast to mammals and poultry, fish muscle can continue growing throughout life if the food supply is not limiting (Weatherley and Gill, 1987). Moreover, throughout the life cycle of fish, both hyperplastic and hypertrophic processes contribute to fish muscle growth, controlled by intrinsic and extrinsic regulatory factors (Carpenè *et al.*, 1982; Stickland, 1983; Kiessling *et al.*, 1990; Fauconneau *et al.*, 1997; Campinho *et al.*, 2006; Silva *et al.*, 2009a and 2009b). The proliferation of myogenic progenitor cells (stem cells and their progeny) in fish muscle is thought to be the reason why hyperplasia is possible throughout the life cycle (Johnston *et al.*, 2004). These cells may be analogous to the satellite cells described earlier in the muscle of postnatal mammals and poultry, although their functions appear to be quite different. Mosaic hyperplasia is the main mechanism for expanding white fibre number in the juvenile and adult stages of the majority of species, continuing until approximately 40% of the maximum fish length (Weatherley *et al.*, 1988). There is evidence that the relative contribution of increases in fibre number and area to total muscle growth in fish is related both to the growth rate and final size attained by each species (Weatherley *et al.*, 1988).

Critical timings and mechanisms
The timings for the appearance of the different fibre populations vary enormously, but it is becoming clear that the effects of environmental factors on numbers of muscle fibres formed is dependent on the stage of myogenesis at which exposure takes place. Importantly, the critical period for environmental effects appears to be during muscle cell proliferation, immediately before differentiation and fibre formation (Brameld and Daniel, 2008). Hence, factors that stimulate myoblast proliferation and/or delay differentiation appear to increase the numbers of muscle fibres, whereas factors that inhibit myoblast proliferation and/or induce early differentiation appear to decrease the numbers of muscle fibres. Some of the discrepancies between studies published to date may relate to differences in the timing of interventions relative to the timing of fibre formation in the species of interest. Indeed, different muscles within the same species may also develop at slightly different times. One possible common factor within all these studies would be changes in energy metabolism and availability for growth processes, particularly cell proliferation. The partitioning of energy to the gravid uterus is complex but involves the indirect action of the growth hormone–insulin like growth factor (GH–IGF) axis (Bauer *et al.*, 1998; Gluckman and Pinal, 2003; Rehfeldt *et al.*, 2004b).

It is widely agreed that one of the main mechanisms for both environmental and genetic effects on muscle fibre development in mammals, poultry and fish is via effects on the GH–IGF axis. The IGFs (IGF-I and IGF-II) are potent mitogens for most cell types, including myoblasts, but they also stimulate muscle cell differentiation by inducing expression of one of the MRFs, myogenin (see Florini *et al.*, 1996; Oksbjerg *et al.*, 2004; Codina *et al.*, 2008). Indeed, spontaneous differentiation in cultured muscle cell lines can be inhibited by blocking local IGF-II production/action (see Florini *et al.*, 1996), and the increased number of muscle fibres observed in double-muscled cattle is associated with a delay in both differentiation and local IGF-II expression (Gerrard and Grant, 1994), as well as mutations in the *myostatin* gene (see reviews by Maltin *et al.*, 2001; Picard *et al.*, 2002; Brameld *et al.*, 2003; Brameld and Daniel, 2008). However, a number of other hormones, growth factors (e.g. myostatin) and nutrients have also been shown to regulate myoblast proliferation and differentiation directly and therefore are also likely to play a role (see reviews by Maltin *et al.*, 2001; Picard *et al.*, 2002; Brameld *et al.*, 2003; Brameld and Daniel, 2008) including antioxidants (Orzechowski *et al.*, 2005), soya-derived isoflavones (Mau *et al.*, 2008a) and unsaturated fatty acids (Hurley *et al.*, 2006; see also 'Environmental impact on skeletal muscle development and consequences for animal growth, carcass and meat quality').

Skeletal muscle growth, plasticity and function
The biological characteristics of the muscle and the way in which it grows are major factors influencing overall growth capacity, as well as the quality of the farmed product in mammals, poultry and fish (Johnston, 1999 and 2001; Chang, 2007). Although growth rate and growth potential are undoubtedly heritable characteristics, growth of all species is dependent upon environmental factors, such as ambient temperature and food availability, both in the determination of growth *per se* and in the expression of morphological characteristics (Leatherland, 1994). Growth and function of muscles relate to their fibre-type composition, particularly in terms of contractile speed (slow *v.* fast) and metabolism (oxidative *v.* glycolytic). In mammals at least, the majority of primary fibres appear to initially become slow oxidative (type I) muscle fibres, whereas the majority of secondary and tertiary fibres appear to initially become faster fibre types

(types IIA, IIX and IIB, see Picard *et al.*, 2002). Fibre-type transformations occur during neo- and postnatal development in mammals and are regulated by a variety of factors including innervation, exercise and thyroid hormones (THs; Chang, 2007). Importantly, faster fibre types (IIX and IIB) tend to have larger diameters, and are therefore important for growth, but are associated with a whiter colour, reduced lipid content and increased toughness, which are important organoleptic properties of meat. Similarly, the distinctive phases of muscle development in fish are underpinned by molecular changes that probably better adapt muscle function to changing physiological requirements during development (Chauvigné *et al.*, 2006; Campinho *et al.*, 2007; Rescan, 2008). The red and white muscle fibres in fish are arranged in discrete anatomical regions (Bone, 1978; Mascarello *et al.*, 1995; Moutou *et al.*, 2005; Silva *et al.*, 2008) largely located in the hypaxial and epaxial muscles along the length of the body and represent 40% to 60% of body mass. Moreover, as fish are poikilotherms and do not regulate body temperature, changes in environmental temperature can have a profound impact on the rate of myogenesis, composition of sub-cellular organelles, patterns of gene expression and the number and size distribution of muscle fibres (reviewed by Johnston, 2006). During the embryonic and larval stages, fish muscle plasticity in response to the environment is usually irreversible due to the rapid pace of ontogenetic change with potential consequences for larval survival as well as long-lasting effects on white muscle cellularity, including the duration and intensity of myotube formation in adult stages.

Candidate gene expression related to muscle development and growth

Expression of specific genes involved in myogenesis studied *in vitro* or *in vivo* may highlight important aspects of its regulation at the molecular level. Studies on the temporal expression of important genes during myogenesis could also provide insight in defining critical windows prone to nutritional or other manipulations (see 'Environmental impact on skeletal muscle development and consequences for animal growth, carcass and meat quality'). Future aquaculture and animal production systems may benefit from results enabling monitoring of skeletal muscle development of species.

Using the murine C_2C_{12} satellite cell line Kwiecinska *et al.* (2005) showed that MAP kinase p38 (SAPK) is crucial and essential to initiate myogenesis. It is suggested that the auto- and/or paracrine mechanism decisive for myogenesis leads to the activation of p38 MAPK with subsequent genomic effect. NF-κB induction points to the cytokines that improve cell viability, whereas elevated Bcl-2 protein prevents intrinsic apoptosis. Pawlikowska *et al.* (2006) showed that mitochondria are essential for insulin-mediated myogenesis. The mitofusin-2 protein derived from the hyperplasia suppressor gene (*hsg*) mediates this role of mitochondria by interacting with the RAS protein in C_2C_{12} cells (Pawlikowska *et al.*, 2007a). Metabolic programming of muscles also proved to be sensitive to cachexia (Pawlikowska *et al.*, 2007b), further supporting the role of energy metabolism in

myogenesis. Furthermore, IGF-I increased proliferation of C_2C_{12} cells and simultaneous addition of IGF binding protein (IGFBP)-2 and -3 inhibited this effect probably due to IGF-I sequestering (Oksbjerg *et al.*, 2006).

Theil *et al.* (2006) showed that IGF-I, IGF-II and type I IGF-receptor were upregulated in porcine satellite cells during differentiation. IGFBP-5 expression was greatly elevated as cells were grown to near confluence supporting the role of IGFBP-5 in inhibiting the mitogenic effects of IGF-I but stimulating its myogenic effect. Myostatin was also upregulated during myogenesis supporting its inhibitory role in controlling proliferation and differentiation. Exogenous insulin stimulated cell differentiation by upregulating IGFBP-5 and downregulating myostatin, whereas myogenin expression was increased. In a study with large and small littermate pigs *in utero*, Karunaratne *et al.* (2007) found elevated levels of IGFBP-5 in the small littermate and suggested this protein to be involved in the shift from muscle to connective tissue in developing muscles. Comparing proliferating with differentiating porcine satellite cell cultures under serum-free conditions Kalbe *et al.* (2008) observed a slight decrease in IGF-I and increases in IGF-II and epidermal growth factor (EGF) mRNA expression in differentiating cultures, whereas IGF receptor-1 expression tended to be upregulated. Fahey *et al.* (2005a) hypothesised that the period of proliferation immediately before fibre formation would be crucial. In foetal sheep they noted a peak for myogenin and IGF-II mRNA expression on day 85 of gestation, which indicated that differentiation and formation of the majority of muscle fibres in the leg were occurring at this time.

In cattle, proteomic analysis of muscle at five key gestational stages revealed that the abundance of 245 proteins changed with myogenesis. Mainly, three categories of proteins were displayed: contractile proteins (many isoforms of myosin heavy chain (MyHC) and troponin T (TnT)), cytoskeletal proteins (desmin, actin, HSP27) and proteins involved in cell cycle regulation and/or in the control of the proliferation/apoptosis balance. This last group of about 25 proteins, including PAK2, PARK7, SNX6, desmin, galectin 1 and others, could lead to the identification of a potential marker of the TNF (Chaze *et al.*, 2008), which is one of the most important traits that control muscle mass. In cattle, TNF is fixed from 180 dpc onwards. This is supported by proteomic data indicating a reduction in cell proliferation (Chaze *et al.*, 2008). Thus, stathmin, which plays an important role in cell cycle regulation, showed decreased expression from 180 dpc onwards. Septin proteins (septin 2 and 11 isoforms) involved in cytoskeletal organisation, scaffolding and division plane had a stable expression up to 180 dpc, confirming intense cell division until this stage, and declined thereafter. In parallel, annexin A1, which has an anti-proliferative function via the activation of ERK pathways, showed increased abundance from 180 dcp onwards. Increased maturation is reflected by significant changes in the profiles of protein isoforms belonging to metabolic and contractile pathways. Thus, proteins of the aldehyde dehydrogenase family involved in the metabolism of amino acids, carbohydrates and lipids, dihydrolipoyl dehydrogenase, involved in pyruvate metabolism, as well as enolase, lactate dehydrogenase (LDH)

and isocitrate dehydrogenase (ICDH), all enzymes involved in carbohydrate metabolism, showed increased abundance from 180 dpc onwards. Similar results were found for proteins of the contractile apparatus. Abundance of different isoforms of myosin light chains 1 and 2, α-cardiac actin, fast TnT (fTnT), myosin-binding protein and adult forms of MyHC increased during the later stages of foetal life (Chaze *et al.*, 2009). Proteomic analysis of cattle with high muscle growth potential (double-muscled with mutation in *myostatin* gene or selected on this criteria) revealed some proteins related to muscle mass (Picard *et al.*, 2005). For example, the ratio of fTnT from exon 16 to fTnT from exon 17 was found to be a good marker of muscle mass development.

In chicken and turkey embryos, neuromuscular stimulation influenced the IGF axis gene expression in a muscle fibre type-dependent manner. Fibre number and oxidative capacity were also increased in the *Musculus semitendinosus* (ST) of the stimulated chicks before hatching (Heywood *et al.*, 2005). Neuromuscular stimulation caused muscle phenotype-dependent changes in the expression of the IGFs and their binding proteins in developing slow and fast muscle of chicken embryos (McEntee *et al.*, 2006). In addition, in chicken *Musculus pectoralis* the mRNA expression of the *PTEN* gene, an inhibitor of cell signalling, increased with age, whereas the protein levels of PTEN and its activity were considerably decreased between E18 and d43 stages, suggesting its involvement in myogenesis (Vaudin *et al.*, 2006).

Changes in MyHC isoforms and enzymes representative of mitochondrial activity or glucose metabolism have been studied in cattle. These studies indicated a disappearance of foetal myosin and a gradual increase in oxidative enzymes from day 180 of gestational age, whereas enzymes of glucose metabolism progressively increased throughout gestation (Cassar-Malek *et al.*, 2007). Picard and Cassar-Malek (2009) have demonstrated the expression of the IIb MyHC isoform in the ST and *Musculus longissimus thoracis* of a French beef breed, Blonde d'Aquitaine, for the first time. MyHC IIb was expressed at the mRNA level in the two muscles from the eleven young bulls studied (Picard and Cassar-Malek, 2009). Furthermore, the ST muscle exhibited higher proportions of MyHC I (slow oxidative isoform) and MyHC IIa (fast oxido-glycolytic isoform), a lower proportion of MyHC IIx (fast glycolytic isoform), higher cytochrome-c oxidase and β-hydroxyacyl-CoA dehydrogenase activities and a lower ratio of LDH/ICDH in cloned compared to control heifers at 8 months of age (Jurie *et al.*, 2009). Thus, young cloned heifers had slower muscle types associated with a more oxidative muscular metabolism than control heifers. From 12 months of age, significant differences were no longer observed between cloned and control heifers.

Rescan and co-workers used whole mount *in situ* hybridisation of rainbow trout with a large repertoire of somite-specific transcripts to describe the gene activations that underlie the somite patterning in teleost fish (Chauvigné *et al.*, 2005 and 2006; Rescan, 2005 and 2008). They showed that the *pax7*-positive external cell layer that provides myogenic cell for the growth of the embryonic myotome also exhibits features of dermogenic differentiation as indicated by the expression of *Dermo-1* (Dumont *et al.*, 2008) and collagen (Rescan *et al.*, 2005). These expression patterns support the view that the external cell layer in fish is homologous to the amniote dermomyotome as suggested by Devoto *et al.* (2006). It has also been shown that the *NLRR-1* gene, which encodes a cell adhesion molecule regulating morphogenesis, is specifically expressed in migrating slow muscle cells (Dumont *et al.*, 2007), whereas the genes for the helix–loop–helix proteins, *Id6a*, *Id6b*, *Id1* and *Id2* – which are specific myogenesis inhibitors – are specifically expressed in the ventral and dorsal domains of the developing fish somites (Rallière *et al.*, 2004).

Muscle development was also studied in teleost fish using the *TnT* and myosin light chain (*MLC*) genes as markers. Different isoforms mark different developmental stages and probably different developmental mechanisms as well as different muscle fibre types (Campinho *et al.*, 2005a, 2005b and 2007; Moutou *et al.*, 2005; Silva *et al.*, 2007a). In addition, these genes can be used as markers for the study of prenatal events with an effect on postnatal growth performance, for example, the axial musculature of the developing larvae of the Atlantic halibut is the largest and most rapidly growing tissue and during the transition from larval to adult muscle fibre types significant changes in fibre morphology and gene transcription occur. The change in myotome height correlates well with different larval halibut stages.

The mRNA expression of *fTnT* genes in the flatfish Atlantic halibut, which undergoes TH-driven metamorphosis leading to a dramatic change from a symmetrical larva to an asymmetrical juvenile and the roundfish sea bream, was studied throughout development and in adult tissue. Three alternative spliced forms of *fTnT* were identified. In both species, the isoforms appear to be stage-specific and correspond in sea bream to embryonic- (*efTnTsb*), larval- (*LfTnTsb*) and adult (*afTnTsb*)-specific isoforms, whereas in halibut they correspond to embryonic/larval (*efTnThh*) and juvenile/adult (*fTnThh-1 and -2*) isoforms. In the sea bream, each isoform is characteristic of the principal developmental stages and the embryonic acidic isoform (*efTnTsb*) is downregulated immediately after hatching and is replaced by a larval isoform, *LfTnTsb*. In contrast, in pre-metamorphic halibut larvae all three fTnThh isoforms are present although the most acidic form, *efTnThh*, is most abundant up until metamorphosis, after which it is downregulated to almost undetectable levels. At metamorphosis and in subsequent stages, *fTnThh-2* is upregulated approximately threefold and becomes the most abundant isoform in halibut muscle. In contrast, *fTnThh-1* expression is constant throughout development. In halibut, a novel teleost-specific *fTnT*-like cDNA (*AfTnT*) expressed exclusively in slow muscle was identified, which had a constant expression throughout ontogeny. The results from this comparative analysis of *fTnTs* in two teleosts suggests that molecular processing is common, but that regulation of isoform expression during muscle ontogeny may be species-specific and adapted to their specific ecologies (Campinho *et al.*, 2007; Silva *et al.*, 2007a).

In the sea bream, two slow skeletal muscle *TnT* genes (*sTnT1sb* and *sTnT2sb*) and a single form, *sTnT2*, were isolated and characterised. A third, intronless, *TnT* gene (*iTnTsb*), which is an apparent orthologue of a previously described zebrafish *TnT*, was also isolated in sea bream. The expression of *sTnT* was restricted to red muscle and *sTnT1sb* was expressed at low abundance and *sTnT2sb* at high abundance. In contrast, *iTnTsb* is predominantly expressed in adult fast muscle. The teleost *sTnT2* and *iTnT* each constitute new, apparently teleost-specific, TnT groups. It remains to be established if the encoded proteins have different structural and mechanistic roles in fish muscle (Campinho *et al.*, 2005a, 2005b and 2007). Treatment of halibut larvae with THs, important post-embryonic morphogens, modified the expression of halibut *fTnT* isoforms, which changed from predominantly basic to acidic isoforms and led to the precocious downregulation of *efTnThh* (Campinho *et al.*, 2007; Silva *et al.*, 2007a). In contrast, the expression of red muscle-specific genes, *AfTnT* and *sTnT2*, in halibut did not change during natural metamorphosis or after T4 treatment (Campinho *et al.*, 2007). Treatment of sea bream larvae with THs revealed that although slow *TnT1* is TH-responsive, *fTnT*, *sTnT2* and *iTnT* expression are unaffected (Campinho *et al.*, 2005a and 2005b).

At the early stages of sea bream development *MLC1* and *MLC2* were expressed exclusively in white muscle and no expression was observed in the superficial red muscle layer. On day 4 the expression of both transcripts was strong throughout the epaxial and hypaxial musculature. From day 10 onwards, two distinct germinal zones appeared in the dorsal and ventral side of the larvae, characterised by small diameter muscle fibres, whereas fibre diameter gradually increased from the lateral germinal zones towards the horizontal myoseptum. Fibre diameter of the deep white muscle layers next to the notochord indicated high hypertrophic activity. At the same time, *MLC*s' expression became restricted to the periphery of the maturing muscle fibres and it was predominant at the germinal zones. This pattern persisted up to day 51, when the germinal zones disappeared and expression of *MLC*s was observed only in cells situated between the mature white fibres, most probably satellite cells (Moutou *et al.*, 2005). In gilthead sea bream, *MLC2* (isoform A) consists of three mRNAs differing in length of the 3′ UTRs. Transcripts of isoform A were detected both in white and red muscle. A 1.56 kb *MLC2* transcript was detectable from the beginning of somitogenesis, whereas a 0.89 kb *MLC2* transcript was present after 27 h post-fertilisation. *MLC2* isoform B differs from the isoform A by 10 amino acids. Isoform B was detected in all tissues examined (red, white, smooth and cardiac muscle, kidney, liver, spleen, brain, gills, epidermis; Sarropoulou *et al.*, 2006).

In the developing Atlantic halibut, first-feeding larvae *MLC1*, *MLC2A* and *MLC3* transcripts were confined to the muscle fibres of the germinal zones located at the dorsal and ventral apices of the myotome and were composed of small-diameter round fibres. In pre-metamorphic larvae, transcripts were highly expressed throughout the epaxial and hypaxial musculature and expression levels reached a maximum in larvae starting metamorphosis coinciding with an increasing concentration of THs. However, at the metamorphic climax, *MLC1*, *MLC2A* and *MLC3* expression was confined to fibres adjacent to the myosepts and to small cells scattered in the musculature, possibly satellite cells. *MLC2A* was also expressed in the red muscle fibres; no transition between larval and adult *MLC* isoforms was detected (Silva *et al.*, 2006). It will be of interest in the future to use the markers developed in sea bream and halibut to establish how changes in larval rearing conditions impact on subsequent muscle growth, fibre number and performance.

Environmental impact on skeletal muscle development and consequences for animal growth, carcass and meat quality

Prenatal and early postnatal nutrition
There is evidence for prenatal effects of nutrition on postnatal development of skeletal muscle in a variety of species, but mainly in young offspring of sheep, pigs, cattle and laboratory animals (Greenwood and Cafe, 2007; Brameld and Daniel, 2008; Funston *et al.*, 2010). To investigate the effects of *in utero* nutrition in mammals, two experimental models have been considered in this respect: first, the natural variation in birth weight of litter- or twin-bearing animals, which is most probably a result of different levels of nutrition *in utero,* and second, changes in maternal nutrition at different stages of pregnancy.

Comparison of high- and low-foetal weight or birth weight
Most of the studies concerning these issues have been done in pigs as there is a large natural variation in birth weight. During COST 925 the studies conducted by Bee (2004), Nissen *et al.* (2004), Karunaratne *et al.* (2005), Gondret *et al.* (2006), Lawlor *et al.* (2007), Ruusunen *et al.* (2007a), Bérard *et al.* (2008), Rehfeldt and Kuhn (2006) and Rehfeldt *et al.* (2008b) contributed substantially to our understanding of skeletal muscle development and long-term consequences for growth, body composition and meat quality in pigs. In summary, muscles of pig foetuses small for their gestational age or piglets light at birth (LW) have a lower number of fibres and lower total DNA content than middle (MW) or heavy weight (HW) offspring. During postnatal development, the smallest littermates deposit more fat and collagen at the expense of muscle tissue than the largest littermates. Intrauterine growth retardation (IUGR) together with impaired muscle development has long-term consequences for postnatal growth and later carcass and meat quality. Piglets small at birth grow slower and remain lighter at a certain age of slaughter or they need a longer time to reach a certain market weight compared with their heavier littermates. Importantly, these pigs develop lower carcass quality in terms of higher fat deposition and lower lean accretion compared with piglets of medium or heavy birth weights. This has been found to be more pronounced in female than in male pigs. In addition, lower meat quality in terms of

tenderness scores, pH at 45 min *post mortem*, and water-holding capacity (drip loss) has been observed at slaughter in pigs of low birth weight, with optimum meat quality seen in medium birth weight pigs. As there were only marginal differences in fibre-type frequencies, this seems to be mainly related to the extreme fibre hypertrophy in LW pigs associated with greater MyHC expression, which occurs when the number of fibres is low. Extreme fibre hypertrophy also causes a higher incidence of giant fibres in *post-mortem* muscle, which is a clear sign of poor pork quality (Schubert-Schoppmeyer *et al.*, 2008). However, consistent with the overall higher fatness, the intramuscular fat was higher in LW than in HW pigs, which may even be of advantage in terms of eating quality.

There are only a few studies comparing sheep differing in birth weight by natural variation. Within our COST-related research Ensoy *et al.* (2008) were able to show that lambs of low birth weight (2.6 kg) deposited more fat during postnatal growth than lambs of high birth weight (4.1 kg), which is consistent with results previously obtained by Greenwood *et al.* (1998). Previously, Greenwood *et al.* (1999 and 2000) did not observe differences in myofibre number, but decreased muscle weights, muscular DNA, RNA and protein contents and cell cycle activity at low foetal or birth weight. Similarly McCoard *et al.* (2000) found no differences in myofibre number comparing single and twin lamb foetuses. Moloney and Drennan (2006) studied the effects of birth weight on growth and carcass quality in Charolais cattle and found heavier carcasses that tended to be leaner from high birth weight (54.1 kg) compared with low birth weight (41.4 kg) calves, whereas meat quality characteristics remained unaffected. Papstein *et al.* (1999) have previously shown that the total number of fibres in *M. longissimus* was lower in twin compared with single-born beef cattle that were heavier at birth. Greenwood and Cafe (2007) reported smaller weight and cross-sectional area of *longissimus* muscle in response to retarded intrauterine growth, but apparent fibre number at 30 months of age was not different. Similarly, no differences in beef quality were apparent. Taken together, these sheep and cattle studies suggest that restricted foetal growth resulting in low birth weight has similar consequences for postnatal growth rate and carcass composition as described in the pig and that this is related to myofibre number and/or muscular DNA content, whereas the effects on meat quality seem to be marginal. Species specificities in the nutritional foetal programming have been observed between ovine and bovine, due to differences in the timing of placental and foetal growth (Greenwood and Cafe, 2007)

In conclusion, impaired myogenesis resulting in low skeletal myofibre and myonuclear numbers is considered one of the main reasons for the negative long-term consequences of IUGR on muscle growth.

Consequences of maternal nutrition

Maternal diet controls growth directly by providing glucose, amino acids and other essential nutrients and metabolites for the conceptus (Robinson *et al.*, 1999). In mammalian species these are transferred by passive and active transport through the placenta, which exhibits a central role for growth. Research during the COST action provided new insights into the effects and mechanisms of maternal nutrition on growth, mainly for pigs and sheep, but also for rodent models such as mice and rats. Both over- and undernutrition of energy and/or specific dietary compounds have been investigated. As recent results for pigs and sheep have been comprehensively reviewed by Brameld and Daniel (2008), only those results obtained during COST 925 will be specifically reviewed here.

High- and low-energy feeding. Researchers have hypothesised previously that an increase in a sow's feed level may increase the growth potential of the pig (Dwyer *et al.*, 1994). On the basis of this hypothesis several experiments have been conducted and analysed during the past few years. Thus, Bee (2004) fed multiparous sows low- (ca. 60%) and high-energy (ca. 140%) diets compared with a standard diet (100%) during the first 50 days of gestation. Progeny of the high-energy sows grew slower and had lower gain-to-feed ratios and higher percentages of adipose tissue (AT) than pigs born to control and/or low-energy sows. Similarly, Nissen *et al.* (2003) found a significant negative effect of *ad libitum* feeding of pregnant sows from days 25 to 50 on the average daily weight gain and muscle deposition rate. The effect on muscle deposition rate was most pronounced in the smaller littermates. Lawlor and co-workers (Lawlor and Lynch, 2005; Lawlor *et al.*, 2007; McNamara *et al.*, 2008) studied the effects of maternal energy intake of multiparous sows feeding at 200% of requirements between days 25 and 50 or days 50 and 80 and 150% from days 80 to 112 of gestation. Growth performance, such as daily weight gain, feed conversion efficiency and pig market weight, was not influenced, but carcass back fat thickness was reduced after feeding with 200% of requirements. Intra-litter variation and the overall sow performance were also unaffected. Increasing energy allowance between days 50 and 80 of gestation even increased the number of stillborn piglets per litter. In addition, Heyer *et al.* (2004) found only marginal effects of increased maternal feed allowance from days 25 to 85 (+35%, +70%, +100%) on the growth, carcass quality and technological meat quality of the offspring. Birth weight and intra-litter variation were not influenced, whereas growth rate was negatively affected in the progeny of second parity sows, but these had higher numbers of weaned piglets. Cerisuelo *et al.* (2006, 2008 and 2009) studied the effects of extra feeding during mid-gestation in the pig. The controls received 3 kg/day (12 MJ ME/kg; 100%) throughout gestation and the experimental group received 150% (primiparous) or 175% (multiparous) from days 45 to 85 of gestation. This additional feed allowance had no beneficial effects on postnatal growth performance of the progeny. Total fibre number and numbers of primary and secondary myofibres were lower in *M. longissimus* after maternal supplementation, which was contrary to the expected higher (Dwyer *et al.*, 1994; Gatford *et al.*, 2003) or unchanged (Nissen *et al.*, 2003) numbers. This was mainly due to lower numbers

of IIB fibres and was associated with improved meat quality in terms of lightness and pH at 24 h *post mortem*, whereas carcass quality in terms of lean meat percentage or back fat thickness remained unchanged.

With regard to the underlying mechanisms, Nissen *et al.* (2005) showed that *ad libitum* compared with restrictive feeding of pregnant sows in early to mid-gestation did increase maternal IGF-I, but not glucose concentration, and did not increase either foetal glucose or IGF-I levels and had no beneficial effects on myogenesis. In agreement, there was no effect of maternal nutrition on the ability of foetal serum to stimulate proliferation and differentiation of primary myoblasts *in vitro*. When pregnant sows were administered GH during early gestation, which stimulated myofibre formation mainly in the small littermates, more glucose became directly available to the foetus (Rehfeldt *et al.*, 2004b). The increase in maternal IGF-I in response to maternal overfeeding is obviously not high enough to increase placental efficiency and thereby to act positively on myogenesis. In summary, additional energy supply to pregnant modern-day sows seems to have no beneficial effects on the growth of the progeny with myogenesis not or only slightly affected.

The results on low-energy feeding of pregnant sows (Bee, 2004) largely confirmed previous studies showing that a mild maternal feed restriction has marginal impact on the growth of the offspring, whereas severe maternal feed restriction is known to impair myogenesis and subsequent postnatal growth (Buitrago *et al.*, 1974).

Comprehensive studies on the influence of maternal nutrition have been conducted by Brameld *et al.* (2003 and 2008) in sheep. The hypothesis being tested was that the critical window for the effects of maternal nutrition on muscle fibre numbers related to the period of proliferation immediately before major fibre formation. The first study (Fahey *et al.*, 2005a), therefore, set out to determine the timing for major fibre formation in foetal sheep in order to identify the periods of proliferation and differentiation prior to major fibre formation. A peak for myogenin and IGF-II mRNA expression was observed on day 85 of gestation, which, together with histochemical analyses, indicated that the differentiation and formation of the majority of muscle fibres in the leg were occurring at this time. The authors then tested their hypothesis by comparing offspring from adequately fed, control ewes with those from ewes that were nutrient restricted (50% of intake of controls) before (days 30 to 70), during (days 55 to 95) or after (days 85 to 115) the peak in fibre formation (Fahey *et al.*, 2005b). In agreement with the hypothesis, maternal undernutrition had no effect during (days 55 to 95) or after (days 85 to 115) major fibre formation in 14-day-old lambs (Fahey *et al.*, 2005b). The critical period was before the peak in fibre formation (days 30 to 70), with maternal undernutrition resulting in reduced secondary-to-primary fibre ratio. Later studies investigated the long-term effects of maternal undernutrition targeted at this critical window. Despite the fact that previous studies targeting the period immediately before major fibre formation had shown effects on muscle fibre development in

neonatal lambs (Fahey *et al.*, 2005b), when sheep were grown to conventional slaughter weights (40 to 45 kg or 17 weeks of age) or beyond (24 weeks; Daniel *et al.*, 2007), those differences were lost and even a slight increase in proportions of fast glycolytic (IIx/b) fibres observed in older animals (24 weeks). However, maternal undernutrition was associated with increased measures of adiposity in older sheep, with no effect on food intake, suggesting a possible small long-term reduction in metabolic rate. In addition to the presented sheep studies, Harrison and co-workers found that severely reduced nutrient availability during late gestation affected growth of the lambs negatively and had prolonged negative effects on lactation performance (Tygesen *et al.*, 2007 and 2008) and changed muscle metabolism in young offspring measured by evoked surface electromyography (SEMG; Tygesen and Harrison, 2005).

In the rat, maternal undernutrition to 50% and 40% of *ad libitum* had opposite impacts on the offspring's postnatal growth rates with the most severe reduction (40%) leading to slower growth and fewer muscle nuclei (Bayol *et al.*, 2004). More recent studies (Bayol *et al.*, 2005 and 2007 and 2008) have used a 'junk food' model in which pregnant rats were given free access to processed human foods rich in fat, sugar and salt. The offspring of these mothers grew heavier, produced more fat and developed a greater appetite and taste for junk food themselves when compared to offspring of control mothers fed a balanced diet. The offspring from junk-food-fed mothers also had atrophied muscles with more intramuscular fat at weaning.

High- and low-protein feeding. Mallinson *et al.* (2007) investigated the effects of feeding a maternal low-protein diet at different stages of pregnancy in the rat on the numbers, proportions and diameters of muscle fibres in the resulting pups at 4 weeks of age. The critical window for rats was mid-to-late pregnancy, when most of the muscle fibres start to form. Thus, maternal low-protein (LP) diet mainly during mid-pregnancy reduced muscle fibre number and density, but there were muscle-specific differences in the fibre types. Metges and co-workers (Metges, 2005; Petzke *et al.*, 2008) have shown in a rat model that both maternal LP and high-protein (HP) intake throughout pregnancy resulted in low birth weight of the pups and increased body fatness in adolescent offspring of HP dams. The results suggested that oxidative losses of amino acids induced by HP feeding may have similar consequences for placental and foetal protein synthesis as the lack of maternal dietary amino acids, both resulted in foetal growth retardation.

In a mouse model, females of three different strains (selected for long distance running (LDR), for high body weight (HBW) or unselected controls (CON)) were exposed to three prenatal–postnatal dietary combinations: HP-C (high-protein control diet), C-HP and C-C (Langhammer *et al.*, 2006; Kucia *et al.*, 2007; Metges *et al.*, 2008). Birth weight was reduced in response to HP diet throughout pregnancy in the CON and LDR lines, but not in the HBW line. Effects on muscle cellularity are currently being investigated. The offspring of all lines grew

slower in response to the HP lactation diet. Overall, the results showed that programming response due to maternal HP diet in mice is genotype-dependent.

While detrimental effects of postnatal LP diets on growth and carcass quality in pigs are well known and have been confirmed recently (Ruusunen *et al.*, 2007b), little is known about the effects of different protein levels in the maternal sow diet. Preliminary results on maternal HP (250% above) and LP (50% below) feeding throughout gestation to sows also reveal that birth weight was reduced in response to both diets and is thus detrimental to foetal growth, and were associated with changes in metabolism, body composition and muscular gene expression (Metges and Rehfeldt, 2006; Gondret *et al.*, 2008; Rehfeldt *et al.*, 2008a).

Specific nutrients. Due to the effects of maternal undernutrition on muscle cell proliferation/differentiation observed in the various *in vivo* studies, Brameld and co-workers have also investigated direct effects of nutrients on muscle differentiation *in vitro* (Hurley *et al.*, 2006). They found that a number of unsaturated fatty acids (both poly- and mono-unsaturated) altered differentiation of L6 muscle cells, with no effect of palmitic acid, the only saturated fatty acid studied. This may be a mechanism for the effects of maternal diet on muscle development.

Soya-based formulas are used as regular food supplements in livestock production and are consumed by growing numbers of infants. The effects of constituent isoflavones such as daidzein and/or genistein have been examined when supplemented to sows during gestation as well as in a porcine muscle satellite cell culture model. Supplemental daidzein (leading to ca. 1 μmol/l in serum, similar to a typical diet containing soyabean meal) in the maternal diet during late gestation (from day 85 to term) marginally affected carcass quality, meat quality and skeletal muscle cellularity of the progeny (Rehfeldt *et al.*, 2007). The *in vitro* studies on the direct effects of isoflavones on muscle cells may be a model for the effects of maternal diet on muscle development. Results revealed that genistein and daidzein act as inhibitors of porcine myoblast proliferation at concentrations of >1 and >10 μM, respectively (Mau *et al.*, 2008a), and that they interact with growth factor (IGF-I; EGF)-stimulated porcine muscle cell proliferation (Mau *et al.*, 2008b; Kalbe *et al.*, 2008). Reduced proliferation, in part, resulted from the inhibition of the expression of these growth factors and their receptors. Both genistein and daidzein also affected protein metabolism of porcine myotube cultures in a dose-dependent manner (Rehfeldt *et al.*, 2009), reducing protein synthesis at high concentrations (100 μmol/l), but decreasing protein degradation rates at low concentrations, thereby potentially acting as stimulators of protein accretion.

Cross-talk between muscle and adipose cells

As described in previous sections, maternal undernutrition in mammals may reduce muscle hypertrophy and predispose offspring to lipid accumulation, which suggests either a prioritisation or competition in the nutrient partitioning. These adaptations could have postnatal consequences on the lean-to-fat ratio as the interplay between muscle and adipose growth constitutes an important factor in the regulation of muscle development well documented in Bonnet *et al.* (2010).

The lean-to-fat ratio is the result of a dynamic balance between the number and size of muscle and adipose cells. There is striking evidence for developmental and functional links between muscle and AT – in bovine foetuses the successive waves of growth of muscle and AT suggest a priority for muscle growth. In double-muscled Belgian blue cattle, increased muscular development is concomitant with a decrease in the carcass and muscular AT. Thus, adipose and muscle cells seem to be linked by competition or prioritisation in their commitment, differentiation and/or uptake and metabolism of nutrients, all of which determine their number and size (Bonnet *et al.*, 2010). In addition to the metabolic and endocrine regulations specific for each tissue, a cross-talk between adipose and muscle cells that leads to the reciprocal regulation of their differentiation has been deciphered by *in vitro* studies. In the COST action, models of primary co-culture and of conditioned medium have been used to study the direct interactions that occur during myogenesis and adipogenesis in bovine foetuses. One study revealed that myogenesis was impaired by proliferative preadipocyte-conditioned media as shown by a low fusion index, an indicator of myoblast fusion (Cassar-Malek *et al.*, 2006). Conversely, myogenesis was enhanced by adipocyte-conditioned medium through an increase in the myotube area. These cross-talks could be mediated at least, in part, by adipokines such as leptin (Bonnet *et al.*, 2010). Furthermore, the differentiation of foetal brown preadipocytes was enhanced by co-culture with primary bovine myoblasts. This may result both from a regulation by paracrine signals and from physical cellular interactions as already described for white adipocytes and endothelial cells. Among the paracrine signals that have been identified myostatin has been shown to impair the differentiation of bovine white preadipocytes by inhibiting the expression of PPARγ and C/EBPα. These data highlight the complexity of the cross-talk between muscle and adipose cells, as they involve both secreted factors and cell–cell interactions, and concern different cell types depending on the chronology of the growth of muscles and ATs.

Nutritional influences on muscle development in fish and poultry

The environment determines the rate of myogenesis, the composition of sub-cellular organelles, patterns of gene expression (Fernandes *et al.*, 2006) and the number and size distribution of muscle fibres in fish (reviewed by Johnston, 2006). Knowledge about the influence of nutrition on muscle development and growth is still rudimentary in fish, but was explored during the COST action by Silva *et al.* (2009b) who analysed muscle cellularity in blackspot sea bream (*Pagellus bogaraveo,* Brunnich) juveniles fed on diets with different protein contents (20% to 60%). Fish fed HP diets (>40%) had higher final BWs and total muscle weights due to increased fibre area and fibre number, independent of muscle

type and localisation. In Atlantic salmon, muscle cellularity and flesh quality were relatively insensitive to the dietary protein-to-energy ratio (Johnston *et al.*, 2002; Björnsson *et al.*, 2007).

Several *in vivo* and *in vitro* studies have explored the impact of feeding regime on muscle growth. In rainbow trout fed different ration levels, Kiessling *et al.* (1991) reported an increased importance of hypertrophy during periods of rapid growth. Starvation and re-feeding of brown trout (*Salmo trutta*) induced changes in muscle composition and muscle structure (smaller mean muscle fibre diameter in starved fish) that contributed to an increase in flesh firmness (Bugeon *et al.*, 2004). Recovery growth in muscle in response to fasting and re-feeding was studied in trout using a cDNA microarray and revealed a complex response. The principal groups of upregulated transcripts were involved in protein catabolism, myofibre and muscle remodelling and regulation of transcription (Rescan *et al.*, 2007). Other studies of re-feeding in fish have shown enhanced muscle expression of kinases involved in the mTOR signalling pathway known to promote protein accretion in mammalian muscle (Seiliez *et al.*, 2008).

The mechanism by which nutrition and feeding regime affect muscle growth in fish remains to be established but almost certainly involves modification of endocrine factors such as GH and IGF, which have a recognised role in regulating muscle mass, fibre size and nutrient partitioning (Reinecke *et al.*, 2005; Codina *et al.*, 2006). For example, in both rainbow trout and gilthead sea bream, fasting increased plasma GH levels and decreased tissue expression and plasma levels of IGFs and upregulated IGF-I binding (Gabillard *et al.*, 2006a; Montserrat *et al.*, 2007a and 2007b). In trout, fasting followed by re-feeding causes a switch to fast growth and involves the local upregulation of several components of the IGF system (Gabillard *et al.*, 2006a). Moreover, IGF-I stimulates cell proliferation in both rainbow trout (Castillo *et al.*, 2004 and 2006) and gilthead sea bream (Montserrat *et al.*, 2007c) muscle cells *in vitro* and IGF-II has both mitogenic and metabolic effects in trout muscle cell cultures (Codina *et al.*, 2008).

In chicks, 2 days delayed feeding after hatching decreased satellite cell proliferation in *Pectoralis major* muscle and lowered the expression of neonatal isoform relative to embryonic isoform of MyHC (Berri *et al.*, 2006). The deprivation of nutrients during this period also prevented the postnatal increase in the expression of IGF-I and of myostatin in skeletal muscle (Guernec *et al.*, 2004). Furthermore, it was shown that the effect of insulin (and probably IGF-I as well) on protein metabolism was exerted through stimulation of S6K1 activity. Tissue-specific regulation of the *S6K1* gene has been shown (Duchene *et al.*, 2008a). In chicken muscle, the AKT and the ERK1/2 MAPK pathways appear instrumental in this regulation, despite the fact that IRS-1 and PI3K did not respond to insulin stimulation in the muscle tissue (Duchene *et al.*, 2008b).

Influence of physical factors
During the COST action some research teams investigated the influence of selected physical factors, including temperature, neuromuscular stimulation, and oxygen levels on muscle development in fish and/or poultry.

In fish, water temperature has a significant effect on the growth process of axial white muscle (hyperplasia/hypertrophy) during early stages that can affect the subsequent white muscle growth process of juveniles. Nonetheless, not all processes associated with myogenesis increase to the same extent as temperature rises, resulting in differences in muscle cellularity (reviewed by Stickland *et al.*, 1988; Johnston, 2006). As mosaic hyperplasia is the main contributor to overall muscle growth, the developmental stages at which this process is activated may be critical for subsequent muscle growth. If the proliferative capacity of myogenic cells is affected at such stages, this could affect the growth potential of larvae, since both the ultimate size and growth rate are related to the number of muscle fibres in young fish (Weatherley, 1990). Atlantic salmon embryos grown at 5°C and 10°C until first feeding and at 5°C thereafter exhibited significant differences in muscle cellularity and by 21 weeks larvae maintained at 5°C were longer and heavier (Albokhadaim *et al.*, 2007). The authors suggested that the differences might be explained by the influence of temperature on appetite and activity. In rainbow trout juveniles, the temperature-induced increase in growth rates was associated with high plasma GH and IGF-1 levels (Gabillard *et al.*, 2005). Moreover, the temperature-induced increase in muscle growth was associated with an increase in expression of GH receptor 1 (Gabillard *et al.*, 2006b) suggesting that this receptor has a key role in the response to temperature. In European sea bass, early thermal environments influenced white and red muscle hyperplasia in later stages suggesting the existence of early programming of axial white muscle hyperplasia (Alami-Durante *et al.*, 2006a, 2006b and 2007). For example, white muscle hypertrophy was stimulated at 20°C and hyperplasia at lower temperatures in embryos, whereas both hypertrophy and hyperplasia were stimulated at 20°C in free-swimming larval sea bass (Alami-Durante *et al.*, 2006a). In contrast, in blackspot sea bream *P. bogaraveo* (Brunnich) high temperatures (18°C *v.* 14°C) accelerated both embryonic (hatching) and pre-larval (mouth opening) development (Silva *et al.*, 2007b) but failed to modify cross-sectional fibre area or total number of white fibres at hatching. The non-uniform behaviour of different species of fish highlights the need for more studies to characterise this numerous but divergent class of vertebrates.

In rainbow trout, low oxygen saturation levels affect carcass quality with an increase in the proportion of red muscle in the muscle mass, although there is a minimal effect on flesh quality even at low oxygen levels (76% saturation). Stress before slaughter decreased the mean diameter of red muscle fibres, flesh colour, mechanical resistance and pH, but no major interaction between rearing oxygen level and slaughter stress was formally demonstrated in rainbow trout (Lefevre *et al.*, 2008).

In turkeys, it was demonstrated that small differences in incubation temperature for a few days early in development significantly influenced post-hatch muscle growth. A regime of 38.5°C caused an increased myonuclear and fibre number in ST, along with a delay in differentiation (Maltby *et al.*, 2004). In chickens, Hammond *et al.* (2007) have shown that

these small temperature manipulations alter muscle cellularity, possibly through an effect on *in ovo* movement activities (higher temperatures produced sustained increases in movement). Werner and Wicke (2008) reported that increased temperature (38.5°C) between embryonic days 7 and 10 of incubation positively influenced the post-hatch muscle development in cocks, but not in hens. Heat conditioning during embryonic development in chickens has also been considered as a possible tool to favour the adaptation of birds to subsequent heat stress. Collin *et al.* (2007) and Tona *et al.* (2008) showed that such treatment has no detrimental effects on muscle growth and meat quality. In summary, environmental temperature is a critical factor for growth and development of skeletal muscle in both fish and poultry. The mechanisms by which temperature exerts these effects remain to be identified.

Acknowledgements

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