The Journal of Experimental Biology 214, 1617-1628

doi:10.1242/jeb.038620

REVIEW

Growth and the regulation of myotomal muscle mass in teleost fish

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Accepted 15 December 2010

Summary

Teleost muscle first arises in early embryonic life and its development is driven by molecules present in the egg yolk and modulated by environmental stimuli including temperature and oxygen. Several populations of myogenic precursor cells reside in the embryonic somite and external cell layer and contribute to muscle fibres in embryo, larval, juvenile and adult stages. Many signalling proteins and transcription factors essential for these events are known. In all cases, myogenesis involves myoblast proliferation, migration, fusion and terminal differentiation. Maturation of the embryonic muscle is associated with motor innervation and the development of a scaffold of connective tissue and complex myotomal architecture needed to generate swimming behaviour. Adult muscle is a heterogeneous tissue composed of several cell types that interact to affect growth patterns. The development of capillary and lymphatic circulations and extramuscular organs – notably the gastrointestinal, endocrine, neuroendocrine and immune systems – serves to increase information exchange between tissues and with the external environment, adding to the complexity of growth regulation. Teleosts often exhibit an indeterminate growth pattern, with body size and muscle mass increasing until mortality or senescence occurs. The dramatic increase in myotomal muscle mass between embryo and adult requires the continuous production of muscle fibres until 40–50% of the maximum body length is reached. Sarcomeric proteins can be mobilised as a source of amino acids for energy metabolism by other tissues and for gonad generation, requiring the dynamic regulation of muscle mass throughout the life cycle. The metabolic and contractile phenotypes of muscle fibres also show significant plasticity with respect to environmental conditions, migration and spawning. Many genes regulating muscle growth are found as multiple copies as a result of paralogue retention following whole-genome duplication events in teleost lineages. The extent to which indeterminate growth, ectothermy and paralogue preservation have resulted in modifications of the genetic pathways regulating muscle growth in teleosts compared to mammals largely remains unknown. This review describes the use of compensatory growth models, transgenesis and tissue culture to explore the mechanisms of muscle growth in teleosts and provides some perspectives on future research directions.

Key words: muscle fibre, myogenic precursor cell, myoblast fusion, muscle gene paralogue, muscle protein synthesis, muscle protein breakdown, muscle growth model.

Introduction

The teleosts, or bony fishes, are the most speciose and diverse vertebrate group, exploiting most aquatic habitats from isolated hot springs to the deep ocean. The myotomal architecture and muscle fibre organisation of bony fish is intimately related to the particular requirements to flex the body during swimming and the associated patterns of force generation (Videler, 1993). Over the life cycle there are marked changes in myotomal structure and function associated with a dramatic increase in body mass, in some cases from a few milligrams to several hundred kilograms. Myotomes have a complex architecture and various component parts can be recognised including muscle fibres, myogenic precursor cells (MPCs), nerves, connective tissue, fibroblasts, skeletal osteocytes, adipocytes and capillary endothelial cells. Although the multinucleated muscle fibres are the most abundant component, growth involves interactions between all the cell types and information exchange with other tissues. In larval fish, gas exchange occurs across the skin with the muscle capillaries and associated lymphatic system only developing in juveniles. The complexity of growth regulation is likely to increase during ontogeny with the maturation of other tissues and the elaboration of adult patterns of circulation. In particular, the development of the endocrine, neuroendocrine and immune systems creates additional possibilities for information exchange within the body and between physiological systems and the external environment. Mechanical constraints are also likely to profoundly influence the dynamics of muscle growth and will be dependent on hydrodynamic flow conditions in the habitat.

There are daily rhythms in growth associated with feeding activity, which most often occur during the hours of daylight. Most fish are ectothermic and many species live in highly seasonal environments that impose longer-term rhythms on feeding, metabolic activity and protein balance. Temperature is probably the most important extrinsic factor modulating growth, with major effects on developmental processes at all stages of the life cycle. Day length often serves as a cue for impending changes in temperature and also affects growth, including MPC activity (Johnston et al., 2003a). Thermal imprinting during the early stages of development affects somatic growth trajectory and the number and size distribution of muscle fibres in juvenile and adult fish, although the underlying mechanisms remain unknown (Stickland et al., 1988; Macqueen et al., 2008; Johnston et al., 2009). Other cycles in growth are associated with reproduction in mature individuals. Because the myotomal muscle comprises >60% of

adult body mass in pelagic species, it has an important ancillary metabolic function where sarcomeric proteins constitute a reservoir of amino acids. These are mobilised as an energy source by other tissues and in gonad generation, resulting in seasonal changes in muscle mass and composition.

The increased availability of sequencing resources for teleost species, including several complete or near complete genome sequences, coupled with recent advances in cell biology, has greatly contributed to knowledge about muscle growth mechanisms. The zebrafish (*Danio rerio*) has emerged as a major model of basic biomedical processes and human disease, with several groups focusing on muscle differentiation. Research on fish muscle growth is also important for the rapidly developing global aquaculture industry, particularly with respect to production and quality. This review addresses the processes underlying the dramatic growth of skeletal muscle tissue in teleosts and the diversity of mechanisms arising during evolution and with adaptive variation in different environments.

Myotomal architecture

The trunk of bony fishes is divided into two lateral halves by the median septum, supported by the vertebral column and skeletal processes. Blocks of myotomal muscle delimited by myosepta are arranged on either side of the median septum and, in many species, a collagenous horizontal septum separates the dorsal and ventral compartments. The myoseptum spans a number of vertebrae and its thickness varies along the body and within the myotome, being particularly strong in the region of attachment to the skin (Videler, 1993). The number and shape of the segmentally arranged myotomes show significant variation with ontogenetic stage, position along the trunk, body morphology, phylogeny and style of locomotion. Individual muscle fibres are relatively short, inserting *via* tendons into the myosepta. Patterns of motor innervation vary across the teleosts, with distributed neuromuscular contacts being particularly common. Bundles of fibres are bound together by connective tissue sheets containing proliferative populations of fibroblasts. Adipocytes are present between the fibres, particularly in slow muscle, and are very abundant at the muscle fibre–tendon junction and myoseptal surface in some species. In some fish, the myosepts are strengthened by intramuscular ‘pin’ bones that form intimate contact with muscle fibres. Individual slow fibres are arranged parallel to the longitudinal axis of the fish, forming a relatively thin lateral superficial strip of muscle in all free-swimming stages. Slow fibres contain abundant mitochondria and deliver maximum power at the low tail-beat frequencies associated with sustained swimming behaviour. Internalised bands of slow muscle are also present in the juvenile and adult stages of a variety of species, including Atlantic halibut, tiger pufferfish and tuna. The much more abundant white muscle is composed of larger diameter fast fibres, packed tightly with myofibrils and delivering five to 10 times more power at the higher tail-beat frequencies associated with unsteady swimming behaviours (Altringham and Johnston, 1990). Fast muscle fibres acquire a complex geometry with development, adopting a near helical pattern over several myotomes, resulting in a uniform strain field as the body bends (van Leeuwen et al., 2008). Muscle fibres with intermediate contractile and metabolic phenotypes may arise during the larval or juvenile stages. There is an orderly recruitment of slow, then intermediate and finally fast muscle fibres as swimming speed increases (Johnston et al., 1977). The myotomal muscles show significant plasticity over the life cycle, not least because the contractile and metabolic phenotypes of fibres changes with body size to match the functional demands of swimming.

Origin and growth of muscle fibres in teleost embryos

Myogenesis is initiated at an earlier stage of development in fish embryos than in amniotes such as birds and mammals. This probably reflects the requirement to generate swimming propulsion at earlier life stages associated with external fertilisation. Information on the origin of myotomal muscle fibres in teleost embryos has largely come from studies of zebrafish. All embryonic muscle develops in cellular compartments called somites, which are found in pairs along the body axis separated by the notochord and neural tube. Cells of the somite differentiate into a myotome with four main muscle fibre types recognisable in zebrafish embryos: muscle pioneers, slow muscle, fast muscle and medial fast muscle. The specification of cells into each of these lineages depends on members of a family of master-transcription factors for vertebrate myogenesis called myogenic regulatory factors (MRFs) (myoD, myf5, mrf4), which have both specific and redundant functions (Hinits et al., 2009). A fourth MRF called myogenin works in concert with other transcription factors including myoD to induce and maintain differentiation and the initiation of muscle-specific gene expression (Hinits and Hughes, 2007).

MPCs for slow and fast muscle are spatially segregated before the somites form, as early as gastrulation (Hirsinger et al., 2004). A population of mononuclear MPCs called adaxial cells are found next to the notochord and are precursors to both the slow muscle and the muscle pioneer cells, which are located near the horizontal septum (Devoto et al., 1996). Specification of adaxial cells and medial fast fibres requires signaling from a family of proteins called hedgehog (Hh), secreted from the notochord (Wolff et al., 2003; Hirsinger et al., 2004). Committed adaxial cells elongate and then migrate radially away from the notochord to form the slow muscle. This process is critically dependent on a transiently expressed transcription factor called Blimp-1, which is induced by Hh (Baxendale et al., 2004) and functions as a major repressor for fast-fibre-specific gene expression (Liew et al., 2008). Subsequently, embryonic slow fibres form independently of Hh signaling (Barresi et al., 2001) and express a distinct slow myosin heavy chain isoform gene to differentiated adaxial cells (Elworthy et al., 2008). The migration of adaxial cells triggers differentiation and morphogenesis of the main fast muscle cells (Henry and Amacher, 2004), located in the posterior lateral somite. These cells initiate MRF gene expression and differentiate, elongate and fuse to each other to form fibres spanning the length of the myotome (Stellabotte et al., 2007). Several transcription factors have been identified that are required for the expression of fast-muscle-specific genes, including Pbx (Maves et al., 2007) and Six1a (Bessarab et al., 2008).

Myofibrillargenesis

Contractile filaments are packed into ~1 μm myofibrils that run the length of the muscle fibre. The myofibrils contain thousands of serially arranged sarcomeres containing precisely organised arrays of myosin (thick) and actin (thin) filaments and cytoskeletal proteins. Myofibrillargenesis is initiated on actin stress fibres formed on z-bodies (a precursor of the Z-disc) prior to the integration and alignment of the thick filaments and associated proteins in a multi-step process that appears to be conserved within vertebrates (Sanger et al., 2009). In zebrafish, a heat shock protein coding gene (hsp90a) is essential for the late steps of sarcomere assembly (Hawkins et al., 2008; Du et al., 2008). Members of the myocyte enhancer factor 2 gene family of transcription factors (Mef2d and Mef2c) are required redundantly for assembly of zebrafish thick filaments, but not for thin filament gene expression

(actin, tropomyosin and troponin) or earlier steps in differentiation (Hinits and Hughes, 2007).

Origin of MPCs for postembryonic growth

Because muscle is a multinucleate, terminally differentiated tissue, a source of proliferative MPCs is required for postembryonic growth. In zebrafish, a rearrangement of the somite compartment occurs during mid-segmentation that is driven by a secreted cytokine, Sdf1a, and its receptor, Cxcr4a (Hollway et al., 2007). During this process, cells from the anterior region of the somite that express the transcription factors Pax3 and Pax7 become positioned external to the slow muscle in the external cell layer (ECL), which has characteristics of the amniote dermomyotome (Hollway et al., 2007; Stellabotte et al., 2007). The ECL is a source of both primary dermal endothelial cells and proliferative MPCs that migrate through the somite to form a second wave of lateral fast muscle fibres in the late embryo and larval stages (Hollway et al., 2007). The ECL may also provide a population of resident quiescent MPCs equivalent to mammalian satellite cells, which, once activated, provide a source of proliferative cells required for adult muscle growth (Hollway et al., 2007; Stellabotte et al., 2007). In some species the ECL disappears during the early larval stages, by which time a resident population of Pax7-expressing cells is present throughout the myotome (Marschallinger et al., 2009). It has been suggested from a histological study of the pearlfish (*Rutilus meidingeri*) that these cells are derived from the posterior lip of the ECL (Marschallinger et al., 2009).

It is likely that resident MPCs comprise a self-renewing stem cell population and daughter cells committed to terminal differentiation. Theoretically, the balance between signal transduction pathways favouring either proliferation or differentiation could alter the number of MPCs and hence muscle growth potential at each stage of the life cycle and under different environmental situations. Once committed to terminal differentiation, MPCs have one of two fates: they either are absorbed into growing fibres as they expand in length and diameter or contribute to the formation of additional myotubes (Fig. 1).

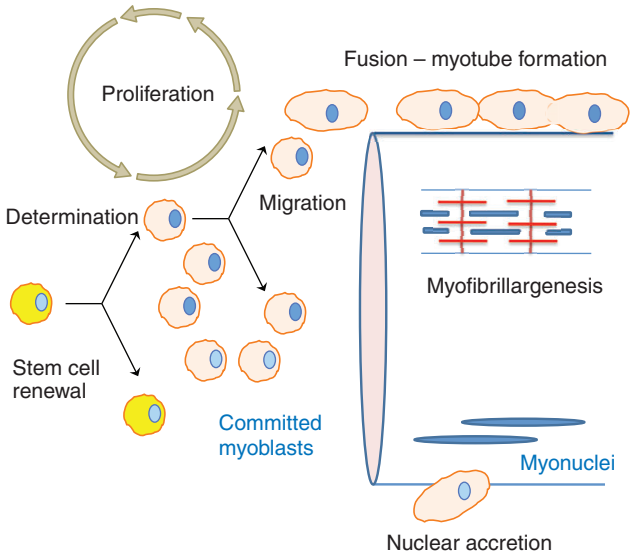

Fig. 1. Postembryonic muscle growth in teleost fish. This model assumes a rare, resident and self-renewing myogenic stem cell population. Daughter myogenic precursor cells (MPCs) are able to proliferate and migrate through the muscle before leaving the cell cycle and entering terminal differentiation. The committed MPCs or myoblasts have one of two fates: they either fuse together to form short myotubes on the surface of muscle fibres (fibre recruitment) or are absorbed into muscle fibres as they expand in length and diameter with growth (nuclear accretion).

Muscle fibre recruitment and hypertrophy

A cross-section through the trunk of adult fish reveals a spectrum of different fibre sizes, reflecting myotube production and subsequent hypertrophy of the resulting fibres. The diameters of individual slow and fast muscle fibres reach a limiting value, set by diffusional constraints, which are largely a function of body mass, temperature and metabolic activity (Johnston et al., 2003a; Johnston et al., 2003b). As fibres expand in diameter and length, they absorb myoblasts in order to maintain the nuclear to cytoplasmic ratio within certain limits (Koumans et al., 1994). Postembryonic muscle growth encompasses the main steps seen during embryonic myogenesis, namely proliferation, fusion and differentiation, encompassing sarcomere assembly and myofibrillogenesis.

Stratified hyperplasia (SH) involves the production of myotubes in discrete layers, sourced from germinal zones at the lateral edges of the myotome, resulting in a steady increase in fibre diameter moving medially into the myotome. SH generates both fast and slow muscle fibre types. Muscle fibre recruitment in zebrafish is fairly typical of teleosts. In juvenile zebrafish up to 8 mm total length (TL), SH is the only form of fibre recruitment in fast muscle (Johnston et al., 2009). In larger zebrafish, myotubes form on the surface of muscle fibres throughout the myotome [mosaic hyperplasia (MH)], continuing until the fish reach ~50% of the final body length (~28 mm TL) at a rearing temperature of 26°C. MH is responsible for an approximately fivefold increase in fast fibre number in zebrafish (Johnston et al., 2009). Five fast muscle myosin heavy chain genes organised as a tandem repeat on chromosome 5 of zebrafish were downregulated at the mRNA level between ~10 and 1000-fold concomitant with the cessation of MH (Johnston et al., 2009), suggesting they could serve as robust molecular markers for this event. The *in situ* expression of one of these genes, *myhz1*(*2*), was examined and found to be restricted to small-diameter myotubes and muscle fibres (Johnston et al., 2009).

MH has been reported to be absent in some small species, including the live bearing guppy (Veggetti et al., 1993). It was also reported that adult zebrafish do not exhibit MH (Biga and Goetz, 2006). However, results from our and other laboratories (e.g. Patterson et al., 2008) suggest that this conception arises from only sampling small individuals.

Once the maximum fibre number (FN_{max}) is reached, myotube formation is inhibited unless the muscle is injured (Rowlerson et al., 1997). Variation in FN_{max} both between and within species is strongly correlated with body size, although this trend interacts with environmental temperature to modify the relationship. For example, a radiation of Nototheniodeii species into the Antarctic Southern Ocean was associated with a >10-fold reduction in FN_{max} and corresponding increase in the mean and maximum muscle fibre diameter (Johnston et al., 2003c). Low temperature and reduced metabolic power demands resulted in an increase in the maximum permissible fibre diameter because of a relaxation of diffusional constraints. The lower costs of ionic regulation associated with increasing fibre size may have acted as a strong selective pressure for the observed reduction in fibre number in Nototheniodeii species (Johnston et al., 2003c). This appears to have led to the loss of the MH phase of growth in the two most derived families of

Nototheniodeii (Channichthyidae and Harpagiferidae) (Johnston et al., 2003c). The Channichthyidae includes species such as *Chaenocephalus aceratus*, which, at a maximum recorded TL of 84 cm have <15,000 fibres, compared with >160,000 in a closely related percomorph species of the less-derived Eleginopinae family (*Eleginops maclovinus*), which reaches a similar maximum body size but is found outside the polar zone (Johnston et al., 2003c). Selective pressures affecting patterns of MH in relation to body size are also evident within salmonid species, where instances of dwarfism have occurred repeatedly, for example in landlocked populations. Such cases are associated with a reduction in the body length at which myotube formation ceases and a decrease in FN_{max} (Johnston et al., 2004; Johnston et al., 2005).

Control of myoblast fusion

Myoblast fusion is a critical event in myogenesis. Cellular events associated with this process include recognition, adhesion, alignment and breakdown of myoblast membranes and the genes involved appear to be conserved from fruitflies to vertebrates (Richardson et al., 2008). Cytoskeleton remodelling appears to be an important component of many aspects of the fusion process. Initially, *de novo* myoblast–myoblast fusion events result in a syncytial fibre with several nuclei. In a second phase, mononucleate myoblasts fuse with multinucleated myotubes, resulting in myoblast–myotube fusion events. Although there is a growing list of proteins with known involvement in myoblast–myoblast fusion, the details remain rather sketchy (Richardson et al., 2008). In mammals, myoblast–myotube fusion is regulated by a transcription factor called NFATC2 (Horsley et al., 2001). Knockdown of orthologues of several genes required for fusion in *Drosophila* resulted in fusion defects in zebrafish muscle, including Kirrel and Rac1 (Srinivas et al., 2007) as well as Dock1 and Dock5 (Moore et al., 2007). Similarly, nephrin, a myoblast cell surface protein in *Drosophila*, is required for efficient myoblast–myotube fusion in zebrafish and mammalian cell lines (Sohn et al., 2009).

Implications of genome duplication and paralogue retention in teleosts

It is important to realise that many genes involved in muscle growth pathways are found as multiple copies as a result of paralogue retention following a whole-genome duplication (WGD) event at the base of teleost evolution (Jaillon et al., 2004). In salmonids, another WGD event occurred at a later time and many of the resulting paralogues were also retained. For example, two paralogues (*myoD1* and *myoD2*) of *myoD* are conserved in some teleost species from the first WGD event, although *myoD2* was secondarily lost in both the zebrafish and salmonid lineages (Macqueen and Johnston, 2008). The additional lineage-specific WGD event in salmonids and a local duplication event resulted in three *myoD1* genes (*myoD1a*, *1b* and *1c*) (Macqueen and Johnston, 2006). Such paralogue retention has important implications, particularly concerning the design of experiments where gene or protein expression is measured. A relevant example is that in Atlantic salmon, the expression patterns of *myoD1a*, *1b* and *1c* genes during embryonic myogenesis together recapitulate the expression field of the single *myoD1* gene in zebrafish, but individually have distinct patterns (Macqueen and Johnston, 2006). This likely reflects a process called subfunctionalisation, where ancestral gene functions such as expression patterns become shared among paralogues. Paralogues can also gain entirely new functions, or, as mentioned for *myoD2*, become lost differentially among lineages during evolution. The importance of paralogue evolution also pervades studies considering adult tissues. A relevant example is the *akirin* gene family, which regulates gene expression in pathways controlling growth, myogenesis and innate immunity. In salmonids, a family of eight paralogues is present (compared with two in mammals) as a result of the two WGD events (Macqueen et al., 2010a). In both the fast muscle of adult Arctic charr (Macqueen et al., 2010a) and a primary myogenic cell culture derived from adult Atlantic salmon fast muscle (Macqueen et al., 2010b), *akirin* paralogues originating from the salmonid WGD event (the most recent paralogues), were typically less co-regulated than were more distant paralogues (e.g. paralogues separated from WGD events at the base of teleosts or even vertebrates). These results suggest that the regulation of paralogues forming teleost gene families can evolve to be very complex. Accordingly, we suggest that studies where one paralogue in a teleost gene family is considered as representative of a mammalian gene, or worse, uses experimental assays that will not distinguish paralogues, will inherently fail to gain insights into gene function. Researchers should also be aware that antibodies used for western blotting will rarely distinguish teleost paralogues, especially those sharing high sequence identity.

Regulation of growth

Growth is centrally regulated by the hypothalamic–pituitary axis *via* the growth hormone (GH)/prolactin/somatolactin hormone families, which are also involved in the control of feeding behaviour, metabolism, immune function and osmoregulation (Kawauchi and Sower, 2006). Individual growth reflects the opposing processes of catabolism and anabolism and is influenced by numerous physiological processes including food intake, digestion, absorption, assimilation and excretion. These physiological processes are themselves influenced by body size and a range of biotic factors including day length, temperature and oxygen availability. An important feature of individual growth in teleosts is its indeterminate nature, with body length and mass increasing constantly, albeit at a slowing rate until mortality or senescence occurs.

Protein synthesis

In vertebrates, GH acts directly through receptors on the muscle sarcolemma and indirectly by initiating the production and release of insulin-like growth factor (IGF) in the liver and peripheral tissues (Wood et al., 2005). The IGF system comprises IGF-I, IGF-II, several receptors and six binding proteins (IGFBPs) and is one of the central pathways regulating protein synthesis in skeletal muscle (Fig. 2). IGFs also have developmental roles in numerous tissues and function in hypoxia responses, osmoregulation and reproduction in adult teleosts (Wood et al., 2005). In zebrafish embryos, two *IGF2* paralogues (*IGF2a* and *b*) regulate midline development and *IGF2b* has a further role in kidney development (White et al., 2009). There are two main families of IGF receptors present in teleosts (IGF-IR and IGF-IIR) with retained paralogues in certain teleost lineages. *IGF-IR* paralogues of zebrafish (*IGF1ra* and *b*) have overlapping essential functions in normal embryonic development, including the regulation of myogenesis, indicating a conserved role compared with mammals (Schlueter et al., 2006). Interestingly, *IGF1rb* has an additional role to *IGF1ra* in controlling patterns of neuron innervation in the developing muscle (Schlueter et al., 2006). In adult salmonids, increased abundance of IGF-IR receptors during periods of food restriction are thought to increase the sensitivity of the muscle to circulating IGF (Chauvigne et al., 2003). The IGF-IIR also functions as a mannose-6-phosphate

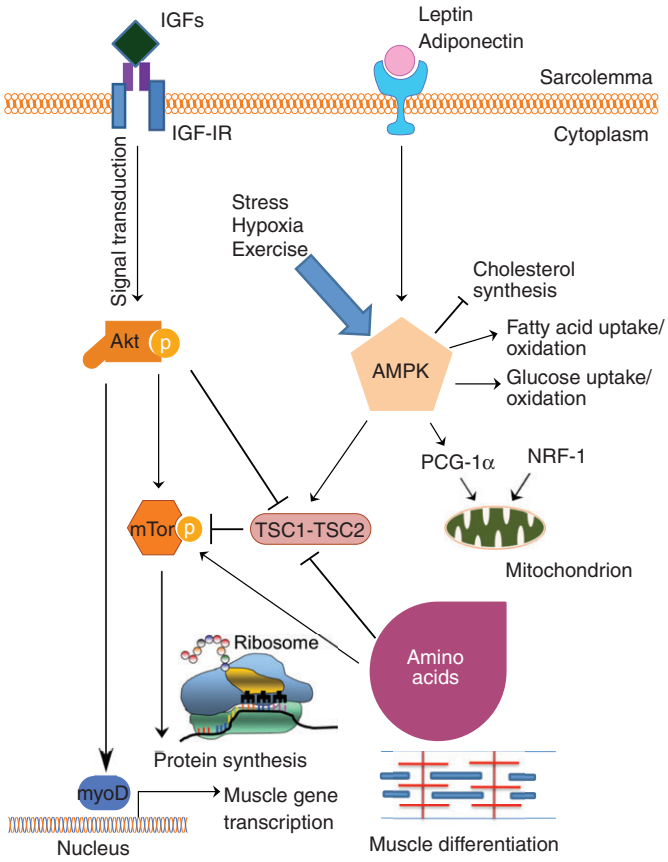

Fig. 2. Signaling pathways controlling protein synthesis and master-gene transcription in skeletal muscle. The diagram is a non-comprehensive introduction based mainly on mammalian literature, with many important intermediate proteins excluded. Thus, the reader is directed to dedicated reviews to learn more about these complex pathways, which have not been studied in detail in teleosts. Briefly, IGF hormones form complexes with IGFBPs, mediating their interaction with the IGF-IR at the cell membrane, an event that serves to initiate a signalling cascade involving activation or inhibition of several proteins *via* phosphorylation/dephosphorylation events. A key protein is Akt, which phosphorylates TOR, culminating in increased levels of protein synthesis by regulating essential proteins controlling mRNA translation. Akt also enhances the transcriptional activities of myoD to increase the transcription of myogenic genes. Other hormones (leptin and adiponectin) and cellular energy stressors (including exercise and hypoxia) stimulate the AMP-activated protein kinase pathway (AMPK). Activation of AMPK promotes catabolic pathways including the uptake and oxidation of glucose and fatty acids to provide ATP. Conversely, AMPK activation inhibits anabolic processes requiring ATP, including cholesterol and protein synthesis. The inhibition of translation by AMPK is mediated by TSC1–TSC2, an inhibitor of TOR.

receptor in mammals. Binding of IGF to the IGF-IR induces its autophosphorylation resulting in the activation of several downstream signal transduction cascades *via* proteins such as insulin receptor substrate 1 (IRS-1) (Duan et al., 2010).

The delivery and effective concentrations of IGFs are regulated through interactions with IGFBPs, each with distinct physiological roles (Wood et al., 2005; Bower et al., 2008; Bower and Johnston, 2010a; Duan et al., 2010). IGFBPs can inhibit and/or potentiate IGF actions depending on the cellular context and environmental conditions (Duan et al., 2010; Ren et al., 2010). The teleost IGFBPs exemplify the inherent increased complexity in understanding how physiological phenotypes are controlled at the molecular level in teleosts compared with mammals. For example, in zebrafish, there are two paralogues of *IGFBP-1*, *IGFBP-2* and *IGFBP-5*, each with established functions. Although their protein products are in all cases able to bind IGFs, each paralogue pair shows differential transcriptional regulation during ontogeny as well as some distinct *in vitro* protein functions, together indicative of functional divergence or subfunctionalisation (Kamei et al., 2008; Zhou et al., 2008; Dai et al., 2010). For example, although mammalian IGFBP5 proteins possess nuclear transactivation activity, in zebrafish this is only conserved in one paralogue because of two N-terminal residue changes in the other (Dai et al., 2010). There is also evidence for lineage-specific changes in *IGFBP* function in teleosts. For example, fasting and refeeding resulted in a marked upregulation of *IGFBP-4* in Atlantic salmon fast muscle whereas transcripts for *IGFBP-1* were below detectable limits (Bower et al., 2008). In contrast, *IGFBP-1a* and *-1b* were the only *IGFBP*s to respond at the level of transcription to a fasting–refeeding challenge in fast muscle of zebrafish (I. G. P. Amaral and I.A.J., unpublished results). Interestingly, *IGFBP-4* is not even represented in the current genome assembly of zebrafish. We therefore advocate the need to rigorously test the function of any teleost gene/protein rather than assume that because a pathway is generally conserved the mechanisms established in mammals can be extrapolated to particular genes in particular lineages.

IGF-I and -II activate the PI3K–Akt–TOR pathway *via* binding to the IGF-IR, leading to a phosphorylation cascade, which results in an increase in translation and protein synthesis (Fig. 2). The pathway also leads to increased transcription of muscle genes in the nucleus, including *IGF-II via* a direct effect on myoD in the nucleus (Wilson and Rotwein, 2006) (Fig. 2). AMP-activated protein kinase (AMPK) is an evolutionary conserved sensor of cellular energy status that integrates nutritional and hormonal signals in the hypothalamus (Kahn et al., 2005) and peripheral tissues such as skeletal muscle (Fig. 2). In mammals, AMP activates AMPK through three mechanisms, namely, allosteric activation, phosphorylation *via* upstream kinases (including LKB1) and inhibition of dephosphorylation (Hardie, 2004). Cellular stresses that deplete ATP and increase AMP levels, such as exercise and hypoxia, activate AMPK and switch on ATP-generating catabolic pathways whilst inhibiting ATP-consuming biosynthetic pathways, including protein synthesis (Fig. 3). The TSC1–TSC2 protein complex negatively regulates translation acting upstream of TOR to cause its inhibition. TSC1–TSC2 is activated by AMPK and inhibited by growth factors such as IGF (Fig. 2). Relatively little is known about the AMPK system in teleosts and key proteins including TSC1–TSC2 remain to be investigated.

In mammals, IGF-I stimulates growth *via* effects on myoblast proliferation (Engert et al., 1996) and differentiation involving distinct signalling pathways (Coolican et al., 1997), which are mediated through the IGF-IR (Rosenthal and Cheng, 1995). IGF-I receptor cycling is also essential for normal muscle growth and is mediated by a protein called myoferlin (Demonbreun et al., 2010). Oxygen tension has been shown to influence the cellular responses to the IGF signal (Ren et al., 2010). Under normoxia, IGF induces AKT–TOR and p38 MAPK activity, promoting myogenesis and inhibiting myoblast proliferation (Ren et al., 2010). However, hypoxia suppresses basal and IGF-induced AKT–TOR and p38 MAPK activity but activates the HIF-1 transcriptional program, enhancing IGF-induced Erk1/2 activation, stimulating myoblast proliferation and inhibiting differentiation (Ren et al., 2010). Similar studies on the role of cellular environment on the downstream consequences of IGF-signaling are required in teleosts.

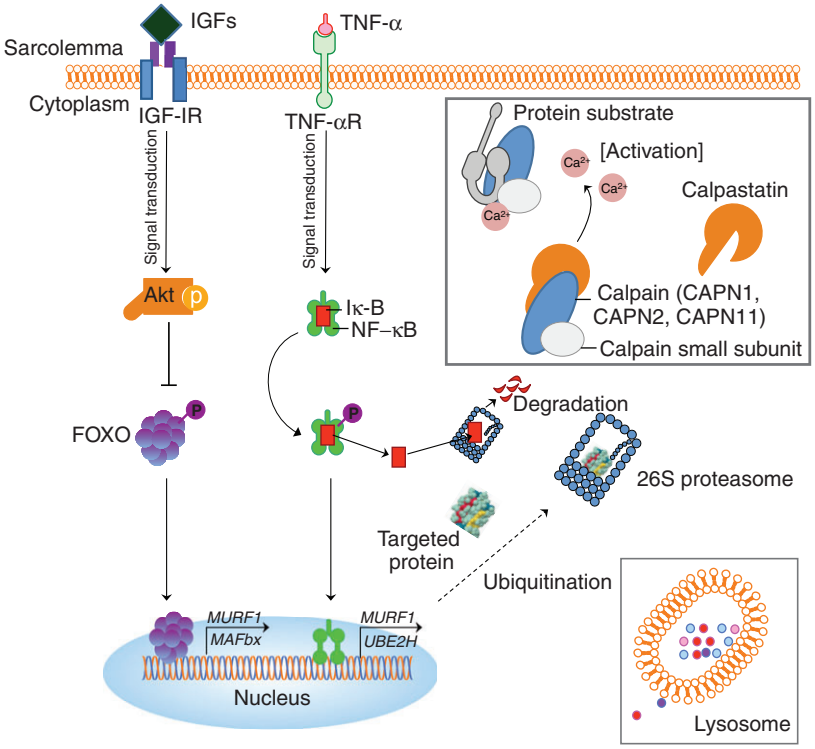

Fig. 3. Some major pathways controlling protein breakdown in skeletal muscle. Ubiquitination encompasses the targeting of structural and regulatory muscle proteins for degradation by proteasomes. This process is inhibited by activation of the IGF–Akt pathway. Specifically, binding of IGF to the IGF-IR at the muscle sarcolemma induces phosphorylation of Akt, leading to the phosphorylation of FOXO transcription factors, causing their nuclear exit and downregulation of *MAFbx* and *MuRF1*, two E3 ubiquitin-ligases necessary for ubiquitination. The NF–κB pathway is an alternative route to transcriptional regulation of *MuRF1*, as well as the E2-conjugating enzyme *UBE2H*. This pathway stimulates muscle atrophy in response to the pro-inflammatory cytokine TNF-α. NF–κB is normally bound to Iκ-B proteins in the cytoplasm. Upon the phosphorylation of this complex *via* a signal transduction cascade induced by TNF-α binding to its receptor, NF–κB and Iκ-B dissociate, allowing NF–κB to enter the nucleus and transcriptionally activate its target genes to induce atrophy. The calpain family constitutes a major cytosolic protein breakdown pathway, and three widely expressed members are expressed in teleost muscle, including CAPN11. These calpains regulate many other physiological processes in muscle, including myoblast fusion. Lysosomes are cellular organelles containing acid hydrolase enzymes.

Protein degradation

The proteins in the body are subject to continuous breakdown and replacement. In many teleosts, skeletal muscle also undergoes an accelerated program of protein breakdown during seasonal periods of fasting and gonad maturation when protein degradation far outweighs protein synthesis, leading to atrophy. Protein degradation is complex and includes the ubiquitin–proteasome system, calpain proteases, the NF–κB pathway and lysosomes (Fig. 3). Damaged proteins and proteins with short half-lives are modified by a process called ubiquitination, leading to their targeting for degradation by a multicatalytic protease complex called the proteasome (Fig. 3). Covalent attachment of ubiquitin to the protein substrate involves a complex group of enzymes including E2-ubiquitin-conjugating enzymes and E3 ubiquitin ligases such as MuRF1 and MAFbx (Fig. 3). In mammals, IGFs induce the phosphorylation of AKT, resulting in the phosphorylation of Forkhead box O (FOXO) transcription factors, causing them to become translocated out of the nucleus, thus inhibiting the expression of their target genes MuRF1 and MAFbx (Witt et al., 2005) (Fig. 3). An alternative route to atrophy by regulation of ubiquitination pathway genes is *via* the NF–κB pathway. NF–κB transcription factor complexes are ubiquitous in animal cells and involved in regulating many response pathways, such as to infection. In mammalian muscle, this pathway is stimulated by the pro-inflammatory cytokine TNF-α and, once activated, is alone sufficient to induce major atrophy *via* upregulation of *MuRF1* (Glass, 2005). The role of the IGF–Akt pathway in inhibiting atrophy appears conserved in teleosts, as IGF-I induced phosphorylation of both Akt and FOXO proteins and concurrent downregulation of *MuRF1* and *MAFbx* was observed in salmonids (Cleveland and Weber, 2010; Seiliez et al., 2010). The NF–κB pathway may also have a role in controlling protein breakdown in salmonids, as there was a large increase in mRNA expression of both *p65* (a subunit of the NF–κB complex) and the NF–κB target genes *MuRF1* and *UBE2H* during fasting (Macqueen et al., 2010a; Bower and Johnston, 2010b). Our understanding of both these pathways in teleosts is in its infancy and both warrant considerable further attention.

Calpains are a large family of Ca^{2+}-dependent proteases that regulate numerous physiological processes by the selective degradation of many substrates (Goll et al., 2003). Two widely expressed calpains have been highly studied in mammals: calpain 1 (CAPN1) and calpain 2 (CAPN2). When bound to a common protein partner called the calpain small subunit, they are functional at micromolar and millimolar Ca^{2+} concentrations, respectively. In teleosts, birds and amphibians, a third widely expressed calpain that binds the small subunit, CAPN11, is also conserved (Macqueen et al., 2010c). The widely expressed calpains cleave hundreds of known protein substrates and are tightly regulated by a specific ubiquitous inhibitor called calpastatin (Fig. 4). CAPN11 is directly ancestral to CAPN1 and CAPN2 and during the course of evolution has evolved a specialist function related to male reproduction in the placental mammals, likely including a change in its affinity to calpastatin (Macqueen et al., 2010c). Once again, this highlights the danger of assuming functional orthology between mammalian and teleost genes or pathways: CAPN11 of teleosts almost certainly regulates the degradation of many substrates that its mammalian orthologues will not even come into contact with and has a different functional relationship with its only known inhibitor (Macqueen et al., 2010c). Additional studies of CAPN11 will be of high value to the teleost research community, as this protease likely has a wide spectrum of essential functions on par with CAPN1 and CAPN2.

Compensatory growth models

Fasting–refeeding experiments are commonly used to manipulate growth rate. Following fasting and refeeding, growth is often subsequently faster than in continuously fed controls, a

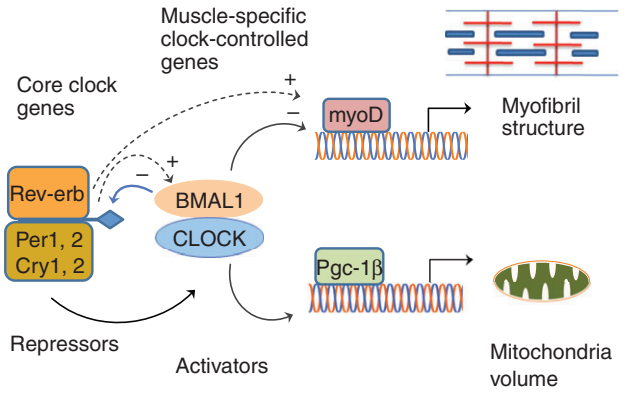

Fig. 4. Proposed model for the circadian regulation of *myoD* and *PCG-1* expression and muscle phenotype by clock genes in mammals [based on Andrews et al. (Andrews et al., 2010)]. The solid arrows indicate known interactions and the dashed arrows indicate potential links that remain to be established. The circadian clock represents a gene regulatory network composed of transcriptional–translational feedback loops. The positive arm of the loop is composed of the transcription factors CLOCK and BMAL1, which heterodimerize and bind to E-box elements on target genes (*Per1*, *Per2*, *Cry1*, *cry2* and *Rev-erb*) to drive the negative part of the feedback loop.

phenomenon known as compensatory growth. Compensatory growth largely reflects increased appetite and feeding intensity following fasting. The results obtained from experiments designed to investigate the molecular mechanisms underlying compensatory growth are highly dependent on the pre-existing metabolic state of the fish, e.g. the extent of fat stores. The outcome of such experiments also varies with the duration of the fast and the nature of the subsequent refeeding regime, particularly on whether the fast is just sufficient to empty the digestive tract or is more prolonged. The time course of the response to feeding is also highly dependent on body size and environmental temperature. In rainbow trout (*Oncorhynchus mykiss*) after a prolonged fast of 30 days, cytoskeleton and myosin mRNA transcripts were elevated after 7 to 36 days refeeding, indicating that a period of recovery or repair from starvation was needed prior to the resumption of growth (Rescan et al., 2007). In slightly smaller rainbow trout, a 60 h fast was just sufficient to empty the gut and produced maximum increases in plasma insulin and amino acid concentration after 30 min and 2.5 h, respectively (Seiliez et al., 2008). Phosphorylation of several kinases indicated significant activation of the TOR signalling pathway 1 to 5 h after feeding (Seiliez et al., 2008). The molecular responses to feeding are surprisingly rapid. For example, zebrafish fasted for 7 d and fed a single satiating meal showed significant increases in phosphorylated AKT after 45 min and induction of mRNA transcripts for IGF-I after only 1 h (I. G. P. Amaral and I.A.J., unpublished results). Many of the published studies on compensatory growth have only sampled fish at relatively long time periods after feeding (several days to weeks) and provide relatively limited information on immediate transcriptional regulation.

Fasting–refeeding experiments have been used to identify novel genes involved in muscle growth regulation using microarrays (Salem et al., 2006; Rescan et al., 2007) or subtracted cDNA libraries (Bower and Johnston, 2010c). With the latter approach, 23 novel nutritionally regulated genes were identified in the fast skeletal muscle of Atlantic salmon. With hierarchical clustering, their expression patterns were compared with 25 genes with established roles in myogenesis and/or growth regulation, providing insights into their function (Bower and Johnston, 2010c). The early stages of the refeeding response were associated with a short-lived increase in expression of genes coding chaperone proteins including DNAJ4, HSPA1B, HSP90A and CHAC1, indicating activation of unfolded protein response pathways (Bower and Johnston, 2010c). A cluster of genes including ASB2, CEBPD, GBP, CTSL1 and HSP30 were highly downregulated upon feeding and their expression was highly correlated with MAFbx and MuRF1 (Bower and Johnston, 2010c). Several of these genes were also downregulated in myogenic cell culture as cells proliferated and differentiated, making them good candidates as negative regulators of growth (Bower and Johnston, 2010c). Myogenesis involves the transition from mutually exclusive proliferative to differentiation states (Fig. 1), involving the coordinated expression and silencing of opposing sets of genes through alterations of chromatin structure. Interestingly, feeding was shown to result in increases in the expression of two poorly characterised genes, SMYD1 and RTN1 (Bower and Johnston, 2010c), each possessing domains associated with histone modification, with putative opposing actions during transcription. It was suggested that these genes, which are transcriptionally regulated by myoD in mammals, may act as epigenetic switches during myogenic differentiation and growth (Bower and Johnston, 2010c). SMYD1 has histone methyltransferase activity and its knockdown in zebrafish disrupts myofibrillar organisation in myotomal muscle and swimming activity (Tan et al., 2006).

Growth models involving genetic manipulation

Transgenesis is a powerful research tool for investigating phenotypes associated with the disruption or overexpression of individual genes. Fish transgenic for GH show body sizes up to 35-fold greater than age-matched controls (Devlin et al., 1994; Nam et al., 2001). In Atlantic salmon transgenic for GH, muscle mRNA levels for IGF-I were elevated whereas IGF-II was reduced and receptors for GH, IGF-I and thyroid hormone were reduced or unaffected (Devlin et al., 2009). Myostatin, a member of the Transforming Growth Factor-B (TGF-B) superfamily, is a potent negative regulator of muscle fibre number and size in mammals (Rodgers and Garikipati, 2008). Natural mutations in the gene are responsible for the ‘double-muscling’ phenotype of Belgian Blue and Piedmontese cattle, Texel sheep and ‘bully’ whippets and the mechanisms of its function have been very well defined (Rodgers and Garikipati, 2008). Thus, research on myostatin in teleosts has been of great commercial interest and the gene has been a target in studies involving genetic manipulation. Injection of antisense morpholinos to myostatin increased the number and size of somites and resulted in the upregulation of myoD and myogenin expression (Amali et al., 2004). Zebrafish transgenic for the prodomain of myostatin (a negative regulator of the biologically active protein in mammals) showed only a small increase in mass relative to controls, a modest ~10% increase in fibre number and no change in mean fibre diameter (Xu et al., 2003). However, a recent study reported a ‘double-muscled’ zebrafish strain with a stable heritable myostatin knockdown genotype, generated by RNAi knockdown (Lee et al., 2009). Transgenic rainbow trout overexpressing follistatin, an inhibitor of myostatin function in mammals, exhibited increased hypaxial and epaxial muscling similar to that observed in double-muscled cattle or myostatin-null mice (Medeiros et al., 2009). However, because follistatin inhibits several other TGF-B family members, it yet to be determined whether such effects are due to myostatin inhibition.

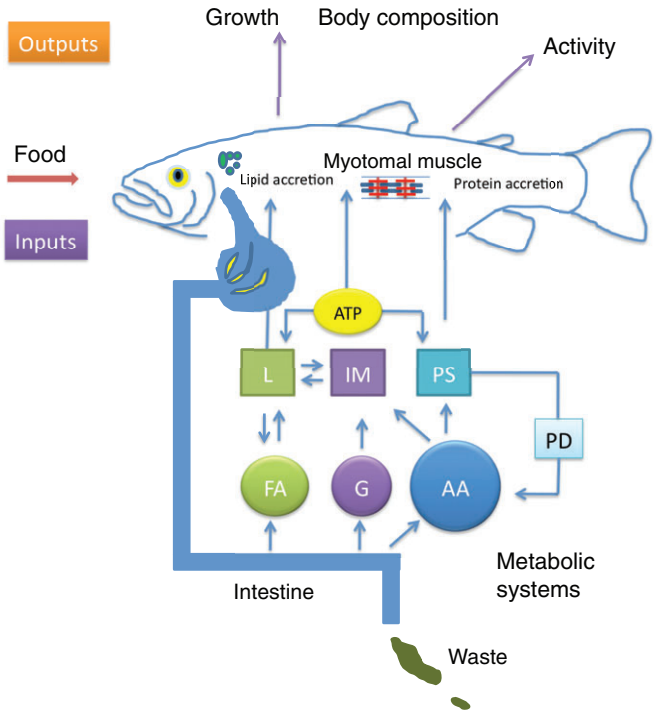

Fig. 5. A proposed systems model of nutrient pathways, growth and body composition in fish. AA, amino acid pool; ATP, adenosine triphosphate; FA, fatty acid pool; G, glucose pool; IM, intermediary metabolism; L, lipid metabolism; PD, protein degradation; PS, protein synthesis. See Bar et al. (Bar et al., 2007) and Bar and Radde (Bar and Radde, 2009) for further details.

In vitro models of muscle growth

In vitro models such as C2C12 cell lines have been extremely useful for expanding knowledge about the molecular mechanisms of muscle growth and differentiation in mammals. Such studies are in their infancy in teleosts, partly because equivalent immortal muscle cell lines are currently unavailable. However, primary cell cultures derived from MPCs harvested from the fast muscle of juvenile fish readily proliferate and fuse to form confluent multinucleated myotubes in cell culture (Montseratt et al., 2007; Diaz et al., 2009; Bower and Johnston, 2010a; Bower and Johnston, 2010b). Such teleost models contribute to an understanding of growth by allowing specific hypotheses about mechanisms to be tested using manipulative and pharmacological experiments. Furthermore, classical gain or loss of function assays can readily be performed, providing valuable information about the function of individual genes and their associated phenotypes. Other tools have been developed to monitor myogenic differentiation *in vitro*. For example, Gabillard et al. (Gabillard et al., 2010) produced transgenic rainbow trout expressing green fluorescent protein under the control of a fast myosin light chain promoter. Cell cultures derived from these fish expressed the fluorescent protein once myoblasts started to fuse and differentiate to form myotubes.

Primary cell cultures have already been used to examine various pathways in teleosts including insulin and IGF regulation of glucose transporters (Diaz et al., 2009) and TOR signaling (Seiliez et al., 2008; Cleveland and Weber, 2010). Myogenic cells isolated from Atlantic salmon withdrew from the cell cycle and entered a quiescent state following starvation induced by the withdrawal of amino acids and serum. Addition of combinations of IGF-I, amino acids and insulin to starved cells resulted in synergistic effects on IGF-I, IGFBP-4 and IGFBP 5.2 expression, indicating the existence of positive feedback and multiple routes of IGF production, including paracrine pathways stimulated directly by amino acids (Bower and Johnston, 2010a) (Fig. 2). In mammals, branch chain amino acids such as leucine can stimulate the PI3K–Akt–TOR pathway (Nicklin et al., 2009) and this phenomena may be conserved in fish, as insulin and amino acids regulate TOR signaling (Seiliez et al., 2008) and leucine has been shown to decrease both protein degradation rates and levels of *MAFbx* mRNA (Cleveland and Weber, 2010).

Plasticity of the myogenic phenotype

The metabolic and contractile phenotype of myotomal muscle can be modified throughout the life cycle in response to environmental conditions, migration and spawning. For example, in temperate species, several weeks of cold-acclimation results in a shift to a more aerobic phenotype in all fibre types and is associated with an increase in the density of mitochondria and muscle capillary supply (Johnston, 1982; Egginton and Sidell, 1989). The pathways controlling muscle mitochondrial biogenesis in fish appear to differ from those described in mammals (Fig. 2), which are coordinated by the peroxisome proliferator-activated receptor-g co-activator-1 (PGC-1) family of transcriptional coactivators. Several studies have failed to detect increases in expression of PGC-1α and PCG-1β in aerobic muscle in response to cold acclimation, e.g. in goldfish (*Carassius auratus*) (LeMoine et al., 2008) and threespine stickleback (Orczewska et al., 2010). The roles of other signaling molecules initiating mitochondrial biogenesis in mammals, including TOR, Ca^{2+}, reactive oxygen species and nitric oxide, remain to be investigated in fish. In several species, fast-start performance and maximum sustained swimming speed at low and high temperatures are increased in response to cold and warm acclimation, respectively (reviewed in Johnston and Temple, 2002). The mechanisms are complex, but can include a significant remodelling of the sarcoplasmic reticulum and marked changes in the expression of contractile protein isoforms including the myosin II gene family (Watabe et al., 1992; Johnston and Temple, 2002). Fast myotomal muscle in medaka (*Oryzias latipes*) differentially expresses eight active myosin heavy chain genes at particular acclimation temperatures, a process potentially controlled by MEF2 family members (Liang et al., 2008).

Perspectives for future research

Fish exhibit daily rhythms of locomotory and feeding behaviour driven by oscillators in the brain that are synchronised by environmental cycles and coordinated with peripheral clocks that regulate physiological systems, including protein synthesis. The regulation of food intake is particularly complex, involving the central nervous system, the gastrointestinal system, adipocytes and interactions with the environment (reviewed in Kulczykowska and Sánchez-Vázquez, 2010). In aquaculture, feeding cycles entrain biological rhythms and behaviour such that fish anticipate meal times and prepare physiological systems for an intake of nutrients (e.g. Sánchez et al., 2009). Studies in mammals provide clues about how daily rhythms of feeding and muscle growth might be regulated in fish. Microarray studies in the mouse identified 267 rhythmically expressed genes in skeletal muscle, including clock genes and myogenic genes, e.g. myoD and IGF-I (Miller et al., 2007). AMPK signalling cascades, which regulate cellular energy status (Fig. 2), may also control the transcription of clock-related genes (Vieira et al., 2008). For example, a rhythmic and inverse correlation between AMPK activity and the nuclear localisation of the clock component CRY1 has been demonstrated (Lamia et al., 2009). The pharmacological activation of AMPK reduced myotube

formation and myosin accumulation in C2C12 cells (Williamson et al., 2009) and increased the expression of MuRF1 and MAFbx (Tong et al., 2009). Recently, myoD was shown to be a direct target of the circadian transcriptional regulators Clock and Bmal1, which bind in a rhythmic manner to the core enhancers of the myoD promoter (Andrews et al., 2010). Clock and Bmal1 knockout mice showed defects in myofibril structure and force generation as well as a 40% reduction in mitochondrial volume and altered PCG-1α and PCG-1β expression (Andrews et al., 2010). Mammalian clock genes are broadly conserved in teleost fish and are regulated by seasonal cues (Davie et al., 2009). The role of clock mechanisms and the AMPK pathway in regulating muscle mass and metabolic phenotype in teleosts is a promising area of future research. A recent model proposed for the regulation of muscle phenotype by Clock/Bmal1 in mammals (Fig. 4) provides an excellent starting point for exploring hypotheses about circadian and seasonal rhythms of muscle growth in fish.

Much remains to be discovered about transcriptional regulation in teleost genomes. Non-coding RNAs represent a significant fraction of the transcriptional output. In zebrafish, 245 target mRNAs were identified that were post-transcriptionally regulated by muscle micro RNAs (miRNAs) (Mishima et al., 2009). miRNAs modify gene expression by inhibiting translation and through the deadenylation or degradation of target mRNAs (Bushati and Cohen, 2007). miR-1, miR-133 and miR-206 play a major role in embryonic myogenesis (Mishima et al., 2009). The cessation of muscle fibre recruitment in adult zebrafish was shown to be associated with reciprocal changes in miRNAs and their computationally identified target mRNAs (Johnston et al., 2009). The role of miRNAs and other non-coding RNAs in regulating muscle growth and adaptation to environmental change is another promising area of research. The widespread methylation of cytosines in animal genomes serves to regulate gene expression, cell differentiation and silencing of transposons (Bird, 2002). The role of DNA methylation and other such epigenetic phenomena as mechanisms for establishing persistent effects of embryonic environmental conditions on patterns of adult growth and muscle phenotypes also requires investigation.

Another area that has been little studied in teleosts, likely because of its complexity, is the role of interactions between muscle fibres and other cell types in the regulation of growth. In mammals, the hormone leptin, which is strongly expressed in adipocytes, acts as a satiety factor and regulates glucose and lipid metabolism (Fig. 2), immunity, reproduction and blood pressure homeostasis (Margetic et al., 2002). Absence of leptin was also associated with reduced skeletal muscle mass and fibre diameter (Sáinz et al., 2009). Leptin treatment may also increase the proliferation of MPCs, as it activates regulators of cell cycle progression (Sáinz et al., 2009). The multifunctional cytokine IL-6 is produced by mammalian muscle in response to inflammation and exercise and the IL-6 receptor (IL-6Rα) is present on the sarcolemma (Pedersen and Febbraio, 2008). IL-6 has been shown to have a role in myogenic precursor cell-mediated fibre hypertrophy acting *via* the Janus kinase–signal transducers and activators of transcription (JAK–STAT3) signaling pathway (Serrano et al., 2008).

Muscle growth is best considered in the context of the whole organism and its feeding behaviour, suggesting that both systems and reductionist approaches are required. For example, somatic growth is dependent on food intake and composition as well as the efficiency of digestion and the assimilation of nutrients. A major challenge is to integrate the explosion of information on cellular and molecular interactions during growth with traditional physiological and whole-animal studies. One approach is to develop structured mathematical models of growth. A few non-linear systems biology models have already begun to appear in the literature, which take into account extrinsic factors such as temperature, the flow of nutrients and metabolites, rates of metabolic processes and energy budgets as a function of time (Bar et al., 2007; Bar and Radde, 2009). Input variables to these models included food ingredients and amount, system variables included amino acids, proteins and tricarboxylic acid cycle intermediates, and outputs included growth and body composition (Fig. 5). Structured mathematical models of this type, when combined with empirical data, not only enable growth under different conditions to be predicted, but also allow hypotheses about mechanisms to be tested, thereby increasing understanding of the underlying processes.

Glossary

Adaxial cells
The first specified myogenic precursor cells, found in the somite and destined to form the embryonic slow muscle.

Dermomyotome
A tissue layer in the amniote somite that gives rise to muscle and skin cells. Often used interchangeably with external cell layer in teleosts.

External cell layer
A superficial layer of the teleost embryonic myotome that provides a source of myogenic and skin cell precursors.

Mosaic hyperplasia
The formation of nascent myotubes on the surface of existing muscle fibres. Occurs during juvenile and adult stages of the life cycle.

Myofibril
Muscle organelle containing filaments of contractile protein.

Myogenesis
The formation of muscle fibres involving the differentiation, fusion and absorption of myogenic precursor cells to form syncytial fibres, followed by the onset of myofibrillargenesis.

Myogenic precursor cells
Cells destined to participate in myogenesis.

Myogenic regulatory factors
A family of four basic-helix–loop–helix proteins that control the expression of hundreds of muscle-specific genes, acting as master regulators of myogenesis.

Myosepta
Collagenous sheets delimiting the myotome.

Myotome
Tissues within the embryonic somites that form the trunk muscles.

Paralogue
One of a pair of genes that arose from a common ancestral gene *via* an inherited mutation involving duplication of a region in the genome.

Sarcomere
Repeated functional unit of a myofibril containing the protein complexes that form the contractile filaments and delimited by two Z-discs.

Somites
Transient segmented embryonic structures formed of mesoderm and distributed in pairs along the trunk. Give rise to the first muscle, skin and skeletal tissues.

Stratified hyperplasia
The formation of nascent myotubes at discrete germinal zones in embryonic, larval and early juvenile phases of the life cycle.

Syncytial fibre
Multinucleated tissue structure formed from myogenic precursor cells.

Whole-genome duplication
An inheritable mutation involving a doubling of all sets of chromosomes and usually followed by massive loss of gene duplicates through evolutionary time. Occurred twice in a common ancestor to vertebrates, again in a common teleost ancestor and again in several other lineages; many paralogues generated from these events are still retained.

List of gene and protein names

ABS2	novel protein similar to vertebrate ankyrin repeat and SOCS box-containing
Akt	v-akt murine thyoma viral oncogene homolog
Blimp-1	PR domain zinc finger protein 1
BMAL1	Aryl hydrocarbon receptor nuclear translocator-like 1
CEBPD	CCAAT/enhancer binding protein delta
CHAC1	cation transport regulator-like protein 1
Cry1,2	cryptochrome 1,2
CTSL1	cathepsin L1
Cxcr4a	chemokine (C-X-C motif) receptor 4a
DNAJ4	DNaJ-like subfamily A member 4
Dock1, Dock5	dedicator of cytokinesis 1, dedicator of cytokinesis 5
Erk1/2	extracellular signal-regulated kinases 1 and 2
FOXO	sub-class of forkhead box protein transcription factor
GBP	GSK-3 binding protein
HIF1	hypoxia inducible factor 1
HSP30	heat shock protein 30
HSP90A	cytosolic heat shock protein 90 alpha
HSPA1B	heat shock 70 kDa protein
IGF	insulin-like growth factor
IGF-IR	insulin-like growth factor-I receptor
Iκ-B	Inhibitor of κB
Kirrel	kin of IRRE like (*Drosophila*)
MAFbx	Atrogin-1
MEF2C, D	Myocyte-specific enhancer factor 2C, D
MURF1	muscle ring finger 1
Myhz1(2)	myosin heavy polypeptide 1.2
MyoD	myoblast determination factor
NFATC2	nuclear factor of activated T-cells cytoplasmic 2
NF–κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NRF1	nuclear respiratory factor 1
P38 MAPK	p38 mitogen-activated kinase
Pax3, Pax7	Paired box protein 3, Paired box protein 7
Pbx	pre B-cell leukemia transcription factor
PCG-1α	peroxisome proliferator-activated receptor gamma-1 α, coactivator 1
PCG-1β	peroxisome proliferator-activated receptor gamma-1 β
Per1, 2	period circadian protein homolog1, 2
PI3K	phosphoinositide 3-kinase
Rac1	ras-related C3 botulinum toxin substrate 1
Rev-erb	retinoic acid-related orphan nuclear receptor
RTN1	reticulon-1-A
Sdf1a	stromal cell-derived factor 1
Six1a	Six homeobox 1a
SYMD1	SET and MYND domain containing 1
TGFB	transforming growth factor B
TNF-αR	tumour necrosis factor-α receptor
TOR	mechanistic target of rapamycin
TSC	tuberous sclerosis protein
UBE2H	ubiquitin-conjugating enzyme E2H

Acknowledgements

The authors' work was supported by grants from the Natural Environment Research Council (NE/E015212/1), the LIFECYCLE program funded by the European Commission (contract 506359) and the Scottish Funding Council through the Marine Alliance for Science & Technology, Scotland (MASTS).

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