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Thyroid hormones and skeletal muscle — new insights and potential implications

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Abstract

Thyroid hormone signalling regulates crucial biological functions, including energy expenditure, thermogenesis, development and growth. The skeletal muscle is a major target of thyroid hormone signalling. The type two (DIO2) and three (DIO3) iodothyronine deiodinases have been identified in skeletal muscle. DIO2 expression is tightly regulated and catalyzes outer ring monodeiodination of the secreted prohormone tetraiodothyronine (T_4) to generate the active hormone triiodothyronine (T_3). T_3 may remain in the myocyte to signal through nuclear receptors or exit the cell to mix with the extracellular pool. By contrast, DIO3 inactivates T_3 through removal of an inner ring iodine. Regulation of the expression and activity of deiodinases constitutes a cell-autonomous, pre-receptor mechanism for controlling the intracellular concentration of T_3. This local control of T_3 activity is crucial during the various phases of myogenesis. Here, we review the roles of T3 in skeletal muscle development and homeostasis, with a focus on the emerging local deiodinase-mediated control of T3 signalling. Moreover, we discuss these novel findings in the

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context of both muscle homeostasis and pathology, and examine how they can be therapeutically harnessed to improve satellite cell-mediated muscle repair in patients with skeletal muscle disorders, muscle atrophy or injury.

Introduction

Skeletal muscle is a principal target of thyroid hormone signalling, as exemplified by the myopathic symptoms that are observed in many patients with disorders of thyroid function. Whereas the underlying causes of muscle weakness, which is seen in both hypothyroidism and thyrotoxicosis, are diverse and not completely understood, a clearer picture has emerged concerning the effects of thyroid hormones on muscle contractility and metabolism.[1]

Skeletal muscle is characterized by a considerable degree of plasticity, allowing adaptation to changes in use and other external cues.[2] The interplay between the various intrinsic and extrinsic factors that drive muscle gene expression gives rise to four major muscle fibre types: type I, type IIa, type IIx and type IIb, here listed in order of increasing speed of contraction and overall ATP-generating capacity. Type I muscle fibres are characterized by expression of myosin-7 (also known as myosin heavy chain 1), whereas type IIa fibres express myosin-2 (also known as myosin heavy chain 2a), type IIx fibres express myosin-1 (also known as myosin heavy chain 2x) and type IIb fibres express myosin-4 (also known as myosin heavy chain 2b). In addition to these isoforms of myosin heavy chain, a range of fibre type-specific isoforms of other muscle proteins determine the phenotype of each fibre type. Notably, the SERCA2a isoform of the sarcoplasmic-endoplasmic reticulum Ca^{2+}-ATPase is expressed at low levels in type I and type IIa muscle fibres, whereas SERCA1a is highly expressed in type IIx and type IIb muscle fibres.[1, 2] Increased SERCA1a expression in type IIx and type IIb muscle fibres is associated with a more extensive development of the sarcoplasmic reticulum (SR) and a concomitant increase in the mobilizable amount of SR-stored Ca^{2+} that is reversibly bound to calsequestrin 1, a low affinity, high capacity Ca^{2+}-binding protein.[3, 4]

The speed of muscle contraction and muscle relaxation, as well as the energy consumption associated with contractile activity is lowest in type I fibres, intermediate in type IIa and IIx fibers, and highest in type IIb fibres. The higher energy cost associated with the increase in speed is in part related to the above-mentioned fibre type-specific gene expression. In particular, the levels of SERCA isoform expression determine the extent of Ca^{2+} release and ATP-consuming re-uptake by the SR during the contraction–relaxation cycle in every fibre type. Along with the greater reliance on glycolytic ATP production, the higher contraction and relaxation speed in type II muscle fibres is associated with a greater degree of heat dissipation.[1] Mammalian skeletal muscles are composed of varying combinations of slow and fast fibre types, and the graded recruitment of these fibres through their innervating motor neurons enables muscle activities ranging from short bursts of fast contraction to slow sustained contraction.

Thyroid hormone-dependent gene expression is known to involve a wide array of genes in skeletal muscle. The concerted effects of thyroid hormone signalling on both contractile and metabolic properties of muscle initially suggested a uniform mechanism of action in this

tissue. However, studies thus far have indicated that the effects of thyroid hormone signalling in muscle development and function are the result of an exceptionally complex interplay of direct and indirect mechanisms. Adding to this complexity is the discovery of the regulated expression of type 2 iodothyronine deiodinase (DIO2) and type 3 iodothyronine deiodinase (DIO3), which generate and inactivate T_3, respectively, in many tissues, including skeletal muscle.[5-9] Regulation of the expression and activity of DIO2 and DIO3 allows for a tissue-specific mode of modulation of intracellular thyroid hormone activity that is independent of the circulating thyroid hormone levels, thereby increasing the regulatory potential of thyroid hormones in muscle gene expression. Here, we review studies that indicate the relevance of deiodinase-mediated regulation of thyroid hormone action for control of muscle development and regeneration, and further discuss the therapeutic implications of these findings. For a broader perspective on muscle satellite cell function and muscle repair, the reader is referred to more extensive reviews.[10-12]

Thyroid hormone activation in skeletal muscle

Normal muscle development, homeostasis and regeneration require the binding of T_3 to the thyroid hormone nuclear receptors.[13, 14]. The thyroid hormone transporters MCT8 and MCT10, as well as the thyroid hormone converting enzymes DIO2 and DIO3 are expressed in skeletal muscle of both humans and rodents. [7-9, 15-17] These proteins provide the potential for local control of the uptake of T_4 and T_3, as well as of their activation and inactivation within the skeletal muscle tissue.

As in other DIO2-expressing tissues, DIO2-generated T_3 contributes substantially to the intracellular T_3 pool of the skeletal muscle. This finding is clearly demonstrated by kinetic studies in mice in which the intracellular levels of T_3 that is converted from T_4 by DIO2 were compared with those of T_3 that was obtained from the circulation.[18] The ratio of DIO2-derived to plasma-derived T_3 was found to be twofold to threefold higher in skeletal muscle than in the liver or kidney. This ratio is even higher in hypothyroid mice, in which the expression of DIO2 is elevated in skeletal muscle. By contrast, this ratio was markedly reduced in the muscle of mice lacking Dio2 (*Dio2*$^{-/-}$).[18] During differentiation of primary myoblast cultures from neonatal mice, *Dio2* mRNA levels and DIO2 activity were both found to increase rapidly, leading to an increased ratio of intracellularly converted to extracellularly-derived T_3.[18, 19] This finding indicates an important physiological role for the elevated DIO2 expression in neonatal skeletal muscle development in mice, as also discussed below.[18, 19]

Several studies have clearly demonstrated the conversion of labeled T_4 to T_3 in cultured human skeletal myocytes.[20-22] The enzymatic activity of human DIO2, as measured in mixed fibre-type skeletal muscle homogenates, is comparable with the enzymatic activity of mouse DIO2.[17, 23, 24] Nonetheless, studies on the regulation of DIO2 in human muscle have provided some unexpected results. In contrast to rodents, hypothyroidism does not increase *DIO2* mRNA levels or DIO2 activity in humans.[24] As low T_4 levels promote DIO2 activity through post-translational modifications, the absence of changes in *DIO2* mRNA levels is not surprising.[25] However, the absence of an increase in DIO2 activity is puzzling and could be, perhaps, attributed to technical limitations, given the extremely low DIO2 activity in this

tissue. Indeed, other studies identified a twofold to threefold increase in both *DIO2* mRNA levels and DIO2 activity in skeletal muscle of chronically ill patients that had low T_4 levels in the serum.[23] Moreover, *DIO2* mRNA levels were found to decrease with fasting and increase with insulin infusion, in agreement with rodent studies. [26-28]

In contrast to DIO2, no changes were noted in DIO3 activity in skeletal muscle of patients with any of the above mentioned perturbations, although DIO3 activity and intracellular T_3 concentration have been reported to increase and decrease, respectively, in skeletal muscle of patients during hospitalization in an intensive care unit.[29] Thus, T_3 might decrease in a *DIO3*-dependent manner in skeletal muscle of individuals with severe health problems, but more work is required to determine the cellular compartment in muscle in which T_3 is inactivated by DIO3.

Interestingly, an increase in *MCT8*, but not *MCT10*, mRNA levels occurs in skeletal muscle of chronically severely ill patients dying of complications in a post-surgical intensive care unit.[15] This phenomenon has been hypothesized to be a compensatory change in response to the patients' low T_3 levels. Apart from this observation, little is known about changes in skeletal muscle expression of thyroid hormone transporters.

T_3-dependent muscle gene expression

The principal mode of action of thyroid hormones is through T_3-dependent nuclear receptor-mediated stimulation or inhibition of gene transcription.[14, 30] In muscle, this activity is primarily mediated by the THRA1 isoform of the thyroid-hormone receptor. Thyroid-hormone receptors bind in the unliganded state to thyroid hormone-responsive elements in thyroid hormone-regulated genes, usually forming heterodimers with the ubiquitously expressed retinoid X receptor. The subsequent formation of a protein complex including the co-repressor NCoR2 and histone-modifying enzymes leads to active repression of transcription.[14, 30] When T_3 binds to the thyroid-hormone receptor, repression is relieved and transcription is further stimulated by the recruitment of co-activators to the complex. Among proteins whose expression is transcriptionally regulated by T_3 in muscle are SERCA1a,[31] SERCA2a,[32] uncoupling protein 3 (UCP3),[33] GLUT4,[34] which is the main glucose transporter in muscle, cytosolic malic enzyme (ME1),[35] which catalyzes the NADPH-dependent decarboxylation of lactate, muscle glycerol-3-phosphate dehydrogenase (mGPDH),[36] which is highly expressed in mitochondria of fast muscle fibres, and myosin-7.[37] The latter is the only gene in this list that is transcriptionally repressed by T_3. The regulation of the above-mentioned genes by thyroid hormone signalling is congruent with the thyroid hormone-induced shift to faster contractile function and the concomitant increase in both glycolytic and oxidative capacities.

In addition, several gene targets are thought to account for the wide range of concerted effects of thyroid hormones in muscle development, homeostasis and regeneration. First, two members of the myogenic regulatory factor (MRF) family, myogenin and myoblast determination protein 1 (MYOD1), are also transcriptionally induced by T_3.[38, 39] Apart from their role in myoblast differentiation, these MRFs can act as down-stream transducers of thyroid hormone signalling in muscle. Thyroid hormone-dependent expression of MYOD1

has indeed been shown to drive part of the fast muscle fibre phenotype, including transcriptional stimulation of the myosin-1, myosin-2 and myosin-4 isoforms.[40-43] Second, T_3 reduces the expression and activity of the signalling protein calcineurin and its downstream transcription factors, which are involved in maintenance of the slow phenotype of muscle fibres.[1] Finally, the overall effect of thyroid hormones on mitochondrial capacity is related to the T_3-mediated transcription of the gene encoding peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), which is an important regulator of mitochondrial biogenesis.[2, 44, 45] This effect is supported by the transcriptional stimulation of mitochondrial-encoded genes through a specific thyroid hormone-receptor isoform (p43) present in mitochondria.[46] Thus, it becomes evident that thyroid hormone signalling regulates the expression of a broad range of genes with central roles in skeletal muscle homeostasis, function and metabolism. The effects of thyroid hormone-dependent transcription in skeletal muscle development, plasticity and repair, as well as in energy expenditure and glucose homeostasis are discussed in detail below.

T_3 and skeletal muscle phenotype

T_3-dependent muscle development

Early embryonic development of skeletal muscles of the trunk and limbs entails the commitment of cells of the dermomyotome to the myogenic lineage. This step is triggered by the transcription factor PAX3 and consolidated by the expression of PAX7. [2] The PAX proteins activate several MRFs, which, in turn, induce muscle-specific gene programs to establish the myoblast lineages. This is a thyroid hormone-stimulated process by virtue of the T_3-responsiveness of several MRFs, as mentioned in the previous section.[47] Fusion of myoblasts results in formation of the primary, multinucleated muscle fibres. Larger numbers of secondary fibres form over the course of fetal development, drawing on the pool of continually proliferating myoblasts.

Postnatal muscle development and growth in rodents entails both *de novo* formation of fibres and muscle hypertrophy, which mainly involves the fusion of additional myoblasts to existing fibres. Hypertrophy is the predominant process of muscle growth in mice and requires accretion of myoblasts during the first three weeks following birth.[48] At this stage the myoblasts are formed from resident satellite cells, which are the myogenic precursors present in skeletal muscles and which are responsible for both fibre growth and muscle regeneration.[12] The role of thyroid hormone signalling in satellite cell function, muscle growth and muscle repair is discussed below.

Postnatal muscle growth coincides with the transition from fetal to various adult fibre phenotypes, and this process depends on both thyroid hormone signalling and maturation of the motor nerve that innervates each individual fibre.[2] The levels of thyroid hormones in plasma increase immediately after birth in rodents, and the capacity of skeletal muscle to increase the intracellular concentrations of T_3 *via* the activity of DIO2 is also high during this period (see also below).[19] The importance of thyroid hormone signalling for the switch in muscle fibre phenotypes in neonates is illustrated by the fact that in the absence of thyroid hormones, the switch from expression of the embryonic and neonatal isoforms of myosin

heavy chain to expression of the adult myosin isoforms is delayed or incomplete,[2] whereas the expression of SERCA1a, which is essential for fast muscle relaxation, fails to increase.[1]

T_3-dependent muscle plasticity

The delayed contraction and relaxation of the deep tendon reflex is a classic observation in hypothyroid individuals, whereas the opposite changes are observed in patients with thyrotoxicosis.[49] These clinical findings illustrate the integrated effect of thyroid hormones on various properties of the skeletal muscle, including the contraction–relaxation cycle. The contribution of thyroid hormones to the plasticity of muscle phenotype is particularly evident in the case of fibres that are innervated by slow motor neurons. Unlike fast fibres**,** development and maintenance of a slow contractility phenotype is dependent on the almost continuous, low frequency stimulation pattern typical of slow motor innervation.[2] The effect of this stimulation is countered by thyroid hormone signalling, which not only drives expression of genes that are involved in fast contractility, as mentioned in the previous section, but also stimulates mitochondrial activity and, particularly, glycolysis.[1] As a result, fibres that are innervated by slow motor neurons can develop a type I, type IIa, type IIx or type IIb phenotype to varying degrees, depending on the relative strength of these opposing forces. The modulation of contractile and metabolic properties of skeletal muscle in response to changes in thyroid hormone availability exemplifies the phenotypic flexibility of skeletal muscle and indicates that thyroid hormones are in a dynamic balance with other external cues to drive muscle gene expression. This balance helps to explain the changes in muscle properties that characterize hypothyroidism and thyrotoxicosis (Table 1).

Energy turnover and glucose metabolism

The impact of thyroid hormone availability on the speed of the contraction-relaxation cycle underlies the higher resting energy turnover and lower energetic efficiency of contraction in skeletal muscle in thyrotoxicosis as compared to hypothyroidism.[1] The thyroid-hormone dependent increase in ATP consumption, particularly during activity, is accommodated by quantitative and qualitative changes in the ATP-generating capacity of skeletal muscle. As skeletal muscle comprises 30-40% of body mass in humans, it is this tissue that primarily accounts for the well-known effects of thyroid status on the metabolic rate of the organism, both at rest and during activity. In addition to energy expenditure, thyroid hormone signalling can influence glucose uptake by skeletal muscle and, thereby, glucose homeostasis .[1]

T_3-regulated energy expenditure in muscles

Thyroid hormone signalling can modulate metabolic rate by either decreasing metabolic efficiency, or by uncoupling the ATP synthesis in the mitochondria of skeletal muscle. Activation of the NADH glycerol-3-phosphate shuttle, maintenance of the Na^+-K^+ and Ca^{2+} gradients by the Na^+-K^+-ATPase and by the SERCA Ca^{2+}-ATPases, respectively, or decreasing the efficiency of ATP synthesis via proton leak through mitochondrial UCP3, have all been proposed as mechanisms through which energy is “wasted” and dissipated as heat in the muscles.[50, 51] As mentioned above, it is well established that thyroid hormone signalling promotes a shift from slow type I fibre phenotype to faster type II fibres, with the

associated increase in myosin and SERCA expression leading to greater energy turnover and concomitant generation of heat during activity.[1] Gene expression analyses of T_3-treated and hypothyroid human muscle have identified additional T_3-mediated changes in the expression of multiple other genes related to energy metabolism such as retinol binding protein 1, glycogen synthase 1, muscle pyruvate kinase, and adiponectin receptor 2.[52, 53] The relative contribution of these recently identified thyroid hormone gene targets to changes in muscle energy expenditure are still being defined.

In small mammals and human neonates the UCP3 homologue UCP1 promotes mitochondrial uncoupling in brown adipose tissue (BAT). This is a well-known T_3-dependent mechanism of energy expenditure used to generate heat during the adaptive process of facultative thermogenesis necessary for survival during cold exposure.[51, 52] Individuals that had been treated with the T_3 analogue liothyronine or the T_4 analogue levothyroxine, as well as patients with thyrotoxicosis or with generalized resistance to thyroid hormones that had elevated thyroid hormone serum levels, all exhibit increased mitochondrial uncoupling in muscle, which indicates that mitochondrial uncoupling is an important source of energy expenditure in muscles.[54-56] UCP1 is not found in muscle, but UCP3 is expressed in this tissue in a T_3-dependent manner. [33, 50, 52, 53, 57] Although the precise contribution of UCP3 to energy expenditure has yet to be established, increased UCP3 expression in T_3-treated rats and levothyroxine-treated individuals has been correlated with increased resting metabolic rate and mitochondrial uncoupling in the muscles. [50, 56] Moreover, UCP3 expression has been shown to be increased in the skeletal muscle of a mouse model of alternative facultative thermogenesis owing to BAT dysfunction, which suggests that UCP3 might contribute to muscle energy expenditure under some circumstances.[58] Muscle has been thought to be the major site of facultative thermogenesis in adult humans, nevertheless, recent identification of significant BAT in the neck and clavicle region of adults that can be activated upon cold exposure suggests that this tissue may play a previously unappreciated role in energy expenditure.[59-61] Human BAT appears to have a molecular signature similar to white adipose tissue with increased UCP-1 expression, also termed “beige” adipose tissue.[62] The recent identification of a muscle-derived circulating factor, irisin, that increases UCP-1 levels in white adipose tissue and converts it to beige, suggests that muscle may also have important indirect roles in the regulation of energy expenditure. [63]

T_3-dependent glucose homeostasis

Thyroid status regulates glucose homeostasis, with both thyrotoxicosis and hypothyroidism being associated with insulin resistance.[64] In patients with thyrotoxicosis and experimental animal models of thyrotoxicosis, increased hepatic gluconeogenesis along with a reduced insulin half-life contribute to hypergylcemia, and the increased circulating free fatty acids and enhanced fatty acid uptake in muscle may further add to insulin resistance.[55, 64, 65] Moreover, decreased insulin-mediated glucose uptake in muscle has been observed in animal models of hypothyroidism.[1, 64]

Muscle is one of the major tissues involved in glucose uptake, and, as mentioned above, the expression of GLUT4 is T_3-dependent. So, decreased GLUT4 expression has been

hypothesized to contribute to lower glucose uptake in patients with hypothyroidism.[34] In addition, GLUT4 translocation to the surface of the cell is an insulin dependent event, and further studies have indicated that normal muscle responsiveness to insulin requires local DIO2-mediated conversion of T_4 to T_3.[22, 66] Primary DIO2-deficient myotube cultures have a blunted increase in the downstream target of insulin, phosphorylated AKT, while DIO2 activity is upregulated by the insulin sensitizer pioglitazone in myotubes suggesting that other insulin-dependent events, such as GLUT4 translocation, may also be compromised. [22] Studies showing that mice with a targeted deletion of the *DIO2* gene (*Dio2*$^{-/-}$ mice) are insulin resistant further confirm an important role for DIO2 in insulin action. [67]

In humans, as mentioned previously, skeletal muscle is a site of major insulin-induced glucose uptake. A common polymorphism in the human *DIO2* gene results in a Thr92Ala substitution in the DIO2 enzyme.[68] About 19% of the population is homozygous for this allele.[69] This amino acid change does not affect a crucial catalytic region of the DIO2 protein, nor is the threonine residue conserved among species. However, homozygosity for this allele has been associated with a lower glucose disposal rate in a group of 972 obese women, as well as with an increased homeostatic model assessment (HOMA) index in patients with type 2 diabetes mellitus.[68, 69] Interestingly, DIO2 activity was found to be significantly reduced in specimens of *rectus abdominis* muscle, sternocleidomastoid muscle and thyroid tissue from individuals that are homozygous for the DIO2 Thr92Ala polymorphism, as compared with heterozygous individuals or with individuals lacking this polymorphism, although no differences were observed at the *DIO2* mRNA level.[69] Comparisons between the wild-type threonine-containing DIO2 and the alanine-containing DIO2 mutant showed no kinetic differences after transient expression *in vitro*.[69] To explain these results, the researchers proposed that the DIO2 Thr92Ala polymorphic allele is in linkage disequilibrium with another nearby gene that affects DIO2 function, or that this polymorphism might reduce DIO2 protein stability or mRNA translation. Strikingly, this polymorphism has also been associated with a reduced bone density and osteoarthritis. [70] However, it did not correlate with the efficiency of levothyroxine to suppress TSH in patients with hypothyroidism.[71] More studies are required to identify the mechanism for these intriguing congruent associations of the DIO2 Thr92Ala polymorphism with abnormal glucose homeostasis and skeletal disorders. However, these patient data, taken in context with the findings that insulin action is impaired in a DIO2-deficient myoblast cell culture model and that *Dio2*$^{-/-}$ mice are insulin resistant, strongly suggest that the local T_3 generated from T_4 by DIO2 in muscle plays a significant role in insulin action and glucose homeostasis. [22,67]

T_3-dependent skeletal muscle repair

Skeletal muscle is a stable tissue with terminally postmitotic myonuclei that normally do not divide. Nonetheless, mammalian muscles exhibit the capacity for extensive regeneration in response to injury.[72] Muscle repair is a function of satellite cells, which, when activated, can proliferate and supply new myofibres, as well as reconstitute the satellite cell pool for later rounds of regeneration.[73, 74] Regeneration is a highly orchestrated sequence of events that involves four sequential phases: first, a degenerative phase characterized by an inflammatory response; second, the activation and proliferation of satellite cells; third, the

differentiation and fusion of myoblasts; and, finally, the growth and maturation of newly formed myofibres (Figure 1).[72] These events require a strictly regulated cross-talk between myofibres and paracrine and autocrine regulatory factors. Defects in these processes are the leading cause of muscle loss in patients with various muscular dystrophies. By contrast, a reduction in the expression of growth factors that are powerful inhibitors of muscle differentiation leads to premature differentiation of myoblasts and early fusion of myocyte precursor cells to form multinucleated myotubes.[75] Differentiation is intimately coupled to the cell cycle, and transcription of MRFs starts only when myoblasts are arrested in the G1-G0 phase.

MYOD1 is the master transcriptional regulator of myogenesis, and its expression is sufficient for the transdifferentiation of mesenchymal-like cells to muscle cells. As mentioned above, MYOD1 transcription is directly controlled by T_3.[38] Thus, thyroid hormone signalling can control multiple events within the myogenic process through the direct and indirect regulation of the expression of an array of muscle-specific genes (Figure 1). DIO2 expression is elevated not only in neonatal mouse muscle, but also during myoblast or myocyte precursor cell (MPC) differentiation. Loss of DIO2, either through proteasomal degradation or through genetic deletion, impairs MPC differentiation, as it prevents up-regulation of MYOD1 and the downstream myogenic factors.[19] The differentiation defects of DIO2-deficient MPCs are coupled with an increase in their proliferative potential. Indeed, DIO2-null muscles contain an increased number of satellite cells, which suggests that a reduction in the levels of intracellularly-activated T_3 enhances the proliferative capacity of the MPCs *in vivo*.[19] Strikingly, a similar phenotype has been described in satellite cells from *Myod1*$^{-/-}$mice.[76]

DIO2 has been demonstrated to be a direct target of FOXO3, a forkhead transcription factor that is a downstream target of the PI3K-AKT signalling pathway.[19, 77] In skeletal muscle, FOXO proteins contribute to several cellular processes, such as myocyte fusion and regulation of myocyte metabolism,[78, 79] and are key players in both atrophy and autophagy.[80, 81] Furthermore, FOXO3 has been shown to cooperate with PAX3 and PAX7 in driving MYOD1 expression,[82] and *Foxo3*$^{-/-}$ mice have defects in muscle regeneration as a result of reduced MYOD1 expression.[82] These studies provide compelling evidence for a functional link between DIO2 induction *via* FOXO3 and myogenic differentiation.

In addition, our preliminary data indicate that the expression of DIO3 is specifically induced in proliferating MPCs and suppressed in differentiated MPCs.[83] Sequential expression of DIO3 followed by DIO2 in activated satellite cells could balance the different thyroid hormone requirements during the cell lineage progression with DIO3-mediated low intracellular T3 allowing for the expansion of the satellite cell pool, whereas increases in DIO2 facilitate MPC differentiation (Figure 2). These recent findings provide novel insights into the role of deiodinases in the linear progression of the myogenic program. In addition, they open new hope for the use of hormonal regulation as a tool to manipulate the physiology of muscle stem cells, modulating their expansion and differentiation.

Thyroid hormones in muscle pathology

The term muscular dystrophy collectively describes a group of genetic diseases characterized by progressive muscle weakness owing to defective muscle function. Defective muscle function leads to premature exhaustion of the skeletal muscle stem cell pool. Duchenne Muscular Dystrophy (DMD) is a progressive disorder caused by deficiency of dystrophin, which is a crucial component of the cytoskeleton.[84, 85] Various animal models have been developed for studying muscle dystrophy, including a DMD mouse model. *Dmd*^{mdx} mice lack dystrophin, and this defect triggers repeated cycles of muscle degeneration and regeneration, causing a progressive reduction in the satellite cell population.[86] It has been reported that alterations in thyroid hormone signalling can exacerbate the dystrophic phenotype of *Dmd*^{mdx} mice by affecting cell cycle control and proliferation-differentiation balance in satellite cells.[87, 88] In particular, hypothyroidism exacerbated the phenotype of *Dmd*^{mdx} mice by prolonging the replication phase of satellite cells and delaying the fusion of MPCs precursors into myotubes.[88] By contrast, thyrotoxicosis promoted the transition from proliferation toward fusion in regenerating muscles in both *Dmd*^{mdx} and control mice, thus demonstrating that excess T3 negatively affects the regeneration process by reducing MPC proliferation and inducing premature MPC fusion into myotubes. [89] As a result, both excesses and reductions in thyroid hormone signalling are detrimental for the correct progression of muscle regeneration and therefore amplify manifestations of the dystrophic phenotype.

These early observations have been confirmed by recent studies on the role of iodothyronine deiodinase-mediated control of thyroid hormone signalling in satellite cell function. The regeneration of cardiotoxin-injured skeletal muscles of *Dio2*$^{-/-}$ mice was markedly delayed compared with injured muscles of wild-type mice, and this delay was accompanied by a failure to up-regulate the major markers of terminal muscle differentiation. Moreover, *Dio2*$^{-/-}$ muscles developed a distinct phenotype following injury that was characterized by the presence of small, centrally-nucleated myofibres within the damaged area.[19] The failure of satellite cells to differentiate into myotubes in the *Dio2*$^{-/-}$ skeletal muscle has been associated with an increase in their proliferative capacity as a result of the attenuation of thyroid hormone signalling. These alterations lead to the observed delay in muscle regeneration after injury in *Dio2*$^{-/-}$ mice. Consistently, a comparable delay has been observed in the regeneration of injured muscles from mice lacking FOXO3, which lies upstream of DIO2 induction. [19, 82] Importantly, these data indicate that normal levels of T_3 in the plasma of *Dio2*$^{-/-}$ mice are not sufficient for proper MPC differentiation during the late phases of regeneration. Consistent with its expression in proliferating MPCs and with its observed role in other models of injury repair (i.e. nerve repair or liver regeneration), DIO3 is highly expressed in the early phases of muscle regeneration, [83] thus suggesting a common requirement for low T_3 activity in the initial waves of the regeneration process. Taken together, these results illustrate the importance of cell-autonomous mechanisms for the temporal and muscle-specific control of intracellular T_3 levels. As modulation of the local T_3 levels can profoundly affect MPC proliferation, thyroxine deiodinases could potentially be used to manipulate intracellular thyroid hormone signalling and improve the proliferative

or differentiative capacity of transplanted satellite cells for the treatment of muscular dystrophy.

Conclusions

Thyroid hormone is a key endocrine regulator that primarily functions through binding to nuclear thyroid hormone receptors and imposing a signature of gene expression. Whereas the important role of thyroid hormone signalling in muscle physiology has been recognized for many years, the contribution of local modulation of thyroid metabolism by the iodothyronine deiodinases to muscle physiology is a novel area in this field. Iodothyronine deiodinase function influences not only the mature properties of different muscles, but, importantly, also the properties of the stem cell-like satellite cells. Early results suggest that there is a temporally restricted expression of DIO2, and probably DIO3, in satellite cells during muscle cell differentiation and repair. The impact of this regulation is mostly unknown, but a requirement for DIO2-mediated local conversion of T_4 to T_3 in the target tissues is clearly emerging from the above mentioned studies. Future *in vivo* studies are required to clarify the kinetics and coordination of DIO2 with DIO3 activity in developing and regenerating muscles, as well as to define the role of other important components that regulate thyroid hormone supply, such as the thyroid hormone transporters. On a more speculative note, given the major role of skeletal muscle tissue in determining basal metabolic rate, manipulation of iodothyronine deiodinase activity in skeletal muscle could be a potential avenue to enhance energy expenditure as a weight management strategy in obese individuals, as this could bypass the adverse systemic effects of an increase in circulating thyroid hormones.

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Review Criteria

Pubmed searches were performed in English from 1980 to 2013 with an emphasis on the last 5 years. The following topics were searched: thyroid hormone, deiodinase, energy expenditure, glucose, insulin, diabetes, skeletal muscle, muscle, gene expression, development, UCP3, satellite cells, muscular dystrophy, and calsequestrin. Full text papers were used, and the reference list of some articles was used to further identify relevant articles.

Key points

- Thyroid hormone signaling is required for skeletal muscle development, contractile function and muscle regeneration.
- As skeletal muscle comprises 30–40% of body mass, the altered basal metabolic rate in patients with thyroid hormone excess or deficiency is largely due to changes in skeletal muscle energy turnover.
- Functional studies indicate that the active thyroid hormone isoform T_3 signals predominantly through the thyroid-hormone receptor α1 (THRA1) isoform in skeletal muscle.
- Expression of the Type 2 iodothyronine deiodinase (DIO2), which converts the prohormone T_4 to the active thyroid hormone isoform T_3, is increased in developing or injured muscles.
- In the absence of DIO2, the muscle-specific thyroid hormone-dependent gene expression programme fails to be induced in the stem cell-like satellite cells of skeletal muscle, resulting in impaired muscle regeneration.
- Current studies suggest that the dynamic control of thyroid hormone activity through the regulation of deiodinase expression can be harnessed to optimize myogenesis in patients with muscle diseases or injury.

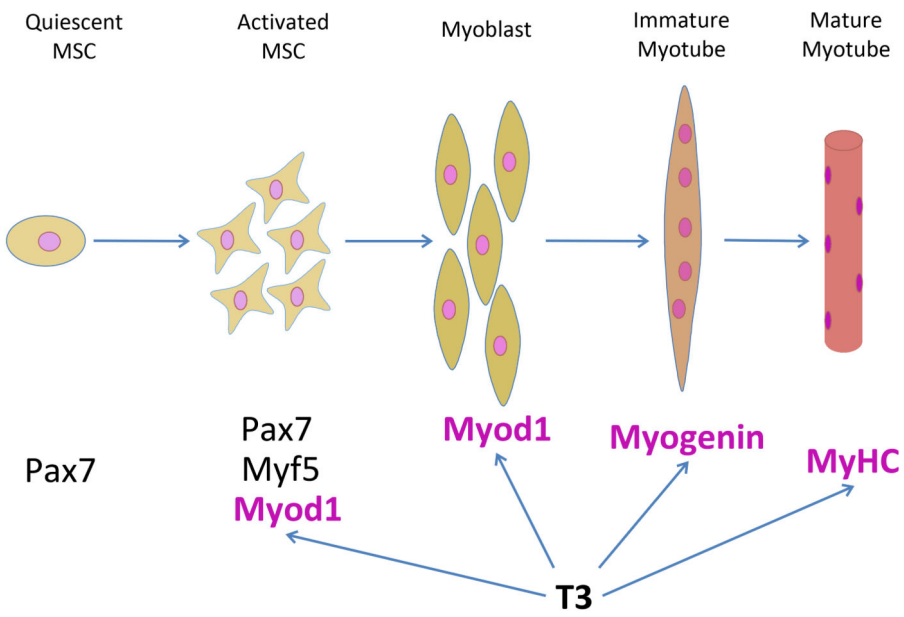

Figure 1.

The role of thyroid hormone signalling in skeletal myogenesis. During muscle fibre development and in muscle regeneration, quiescent muscle satellite cells (MSC) that are characterized by the expression of the transcription factor PAX 7 require the induction of MYOD1 and MYF5 for their activation and entry into the cell cycle. T_3 promotes MSC differentiation by inducing MYOD1 expression. In addition, T_3 signalling is involved in the upregulation of the myogenic regulatory factor (MRF) family member Myogenin in immature myotubes and some isoforms of the myosin heavy chain (MyHC) in mature myotubes, thereby impacting muscle function.

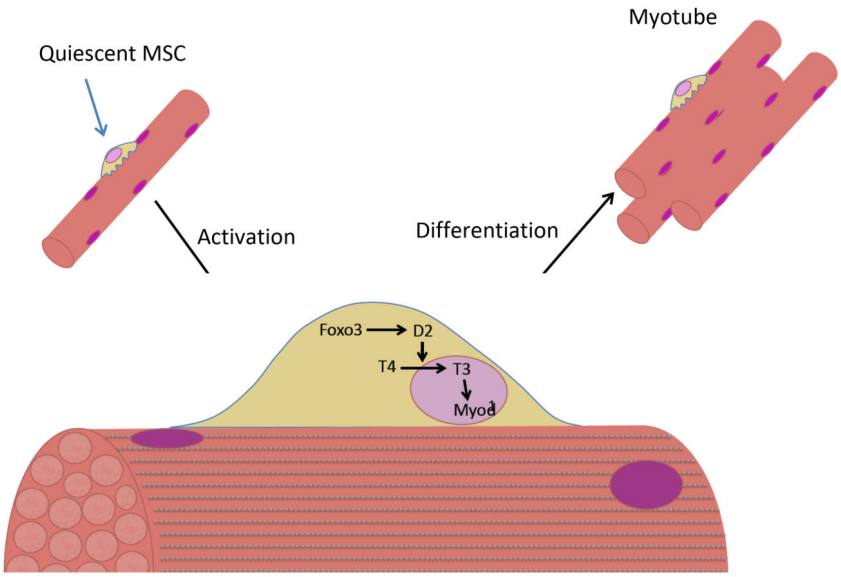

Figure 2.

The thyroid hormone signalling cascade in myotube differentiation. Thyroid hormone signalling is involved in the differentiation of quiescent muscle satellite cells (MSCs) into myotubes. Differentiating MSCs express the transcription factor FOXO3, which, in turn, induces expression of type 2 iodothyronine deiodinase (DIO2). DIO2 catalyzes the monodeiodination of the prohormone T_4 to produce the active hormone isoform T_3. T_3 then enters the nucleus, binds to the nuclear thyroid-hormone receptors, and activates transcription of MYOD1 and other downstream myogenic regulatory factors (MRFs) that lead to myotube differentiation.

Table 1

Effects of thyroid hormone signalling on skeletal muscle properties

Properties	Key thyroid hormone-regulated proteins	Associated effect
Skeletal muscle contractility	myosin-7 ↓, myosin-2 ↑ myosin-1 ↑, myosin-4 ↑	Increased rate of contraction
	SERCA1a ↑, SERCA2a ↑	Increased rate of relaxation
Skeletal muscle metabolism	Na^+/K^+ ATPase ↑, SERCA1a ↑, SERCA2a ↑	Decreased energetic efficiency of contraction due to higher ATP consumption associated with fluxes of Na^+/K^+ and Ca^{2+} at rest and during activity.
	GLUT4 ↑, ME1 ↑	Increased glycolytic capacity leading to increased ATP generation
	PGC1α↑	Increased mitochondrial density leading to increased ATP generation
	UCP3 ↑, mGPDH ↑	Decreased mitochondrial efficiency

In addition to direct transcriptional regulation of a number of genes, thyroid hormone signalling has secondary effects, among them the action of muscle regulatory factors, such as MYOD1 and myogenin, as well as adaptive effects related to changes in energy metabolism and to modulation of Ca^{2+}-dependent signalling by the changes in intracellular Ca^{2+} handling during contractile activity. Because thyroid hormone signalling promotes expression of genes related with faster muscle fibre phenotypes, its effects are more pronounced in muscles with a higher content of slow fibres. Abbreviations: GLUT4, glucose transporter 4; mGPDH, muscle glycerol-3-phosphate dehydrogenase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; SERCA, sarcoplasmic-endoplasmic reticulum Ca^{2+} ATPase; UCP3, uncoupling protein 3, ME1, cytosolic malic enzyme.