Exploring the potential regulation of DUOX in thyroid hormone-autophagy signaling via IGF-1 in the skeletal muscle (Review)

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Abstract. Dual oxidases (DUOX) are enzymes that have the main function in producing reactive oxygen species (ROS) in various tissues. DUOX also play an important role in the synthesis of H_2O_2, which is essential for the production of thyroid hormone. Thyroid hormones can influence the process of muscle development through direct stimulation of ROS, 5' AMP-activated protein kinase (AMPK) and mTOR and indirect effect autophagy and the insulin-like growth factor 1 (IGF-1) pathway. IGF-1 signaling controls autophagy in two ways: Inhibiting autophagy through activation of the PI3K/AKT/mTOR/MAPK pathway and promoting mitophagy through the nuclear factor erythroid 2-related factor 2-binding receptor Bcl2/adenovirus E1B 19 kDa protein-interacting protein 3. Thyroid hormone deficiency caused by the absence of DUOX should be considered because it might have a significant effect on the growth of skeletal muscle. The effect of DUOX regulation on thyroid hormone autophagy via IGF-1 in skeletal muscle has not been well investigated. The present review discussed the regulatory interactions between DUOX, thyroid hormone, IGF-1 and autophagy, which can influence skeletal muscle development.

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Contents

1. Introduction

Skeletal muscle is an important body tissue with the largest mass in the human body, accounting for ~40% of total body weight and is the main source of protein reserves in the body (1,2). Skeletal muscle is the most flexible and plastic tissue in the human body and is responsible for carrying out its functions in daily physical activities, including movement, gestures and life activities (2,3). Skeletal muscles also serve as the primary tissue involved in energy metabolism, taking in, using and storing substrates, including glucose, lipids, and amino acids (2,3).

In its development into the tissue with the largest mass in the human body, the development of skeletal muscle is influenced by a number of factors, such as nutritional status, physical activity, exercise, injury or disease, autophagy processes and hormones, one of which is thyroid hormone (4,5). Thus, thyroid hormone deficiency has an effect on skeletal muscle and can cause muscle atrophy if it remains at low levels (6,7). The interaction of thyroid hormone with insulin-like growth

factor 1 (IGF-1) and autophagy can also affect muscle development (8-11). One form of thyroid hormone deficiency can be caused by interference with thyroid hormone synthesis, such as a lack of protein enzyme dual oxidases (DUOX) in the formation process (12).

Consequently, DUOX and muscle development are related via autophagy and IGF-1. To the best of the authors' knowledge, no review or study has addressed this mechanism. The regulatory relationships that will subsequently be connected to muscle growth in relation to DUOX, thyroid hormone, IGF-1 and autophagy are covered in the present review.

2. DUOX

Dual oxidase is an enzyme that belongs to the Nox family and performs a role in the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) (13,14). The DUOX enzyme has 2 types, DUOX1 and DUOX2, whose function is mainly to produce reactive oxygen species (ROS) in various tissues such as thyroid, colon, kidney, testis, salivary glands, respiratory and lymphoid (13-15) DUOX has a major contribution in the synthesis of H_2O_2, a substance that has an important role in the host defense system, fertilization, embryogenesis, signal transduction, cell differentiation, cell death programs and hormone synthesis, especially thyroid hormone (16-18). During the maturation phase, additional proteins known as dual oxidase maturation factors (DUOXA1 and DUOXA2) are needed to support the production of H_2O_2 (19,20).

The DUOX and DUOXA genes are located next to each other in an operon-like unit and are paired with each other on the long arm of chromosome 15 (Fig. 1) (21,22). In addition to thyroid cells, the DUOXA1 and DUOXA2 genes are also expressed in human respiratory epithelial cells (DUOXA1) and salivary glands (DUOXA2), although the highest expression occurs in thyroid cells (23,24). Research on mice and zebrafish demonstrates that DUOX expression emerges only when the follicle structure is functioning optimally, specifically at the final stage of cell differentiation during thyroid embryogenesis (25,26).

DUOX then travels toward the apex of the thyroid cell and the N-linked glycosylation process occurs in the Golgi apparatus, where it changes into an active form (27,28). In the absence of DUOXA as a maturation factor for DUOX, the oxidase process is arrested in the endoplasmic reticulum and only a small amount of superoxide is detected (29). The activation of DUOX1 and DUOX2 isoform occurs through Ca^{2+} binding to the EF-hand motif found in the N-terminal cytoplasmic segment (30,31). Based on its sequence homology with NADPH oxidase 2 (NOX2), DUOX should produce only superoxide. However, DUOX1 and DUOX2 co-expressed with DUOXA1 and DUOXA2 produced more H_2O_2 (32). This difference is caused by the presence of the seventh transmembrane domain and the N-terminal peroxidase ectodomain, which showed 40% homology to thyroid peroxidase (TPO), so that the superoxide produced was directly converted into H_2O_2 (33-35).

In the process of forming H_2O_2, DUOX1 requires a second intracellular loop and the COOH terminal tail of DUOXA1, while DUOX2 requires the integrity of the NH2 terminal end of DUOXA2 (36) DUOX2 will produce superoxide if paired with DUOXA1 or DUOXA2, which has changes at the NH2 terminal end (36-38). The expression level of DUOX2 is five-fold higher than that of DUOX1, although both are produced at the same site (34,35,39).

Thyroid stimulating hormone (TSH), via cAMP transmission, significantly regulates DUOX2 mRNA transcription in dog and pig thyrocytes (14,40). A study conducted in mice showed an autoregulatory mechanism by thyroglobulin (Tg) that suppresses DUOX2 and DUOXA2 mRNA to control thyroid hormone synthesis (41). In addition to TSH, increasing intracellular H_2O_2 concentration may affect DUOX function (27,33,42). Excess amounts of iodide (I^-) will inhibit the production of H_2O_2, which causes a decrease in TPO activity and reduced incorporation of I^- into Tg. This effect is called 'Wolf-Chaikof effect' (42-45).

3. Modulation of DUOX protein expression in thyroid hormone formation

The formation of thyroid hormone (Fig. 2) requires I^- as a basic ingredient. I- is taken from the blood vessel circulation by thyrocytes through the Na/I transporter, which is located in the basolateral plasma membrane of the cell (46). This intracellular Na^+ gradient is maintained by Na^+/K^+-ATPase (17) I^- is then transferred into the lumen of the follicle via the chlorine channel CIC5 and pendrin, which are transporters that do not depend on sodium (17). The I^- is then catalyzed by the TPO enzyme using H_2O_2 as an oxidizer produced by the DUOX/DUOXA complex. This process is called 'iodide organification' and is directly sent into the colloid cells (17,47). Studies examining mutations in the DUOX2 gene show a defect in I^- organization in two unrelated families, causing congenital goiter hypothyroidism (48,49). This indicates that the DUOX protein regulates thyroid hormones through its production as an oxidizer during the formation of thyroid hormones.

Tyrosine in Tg produced in follicular cells by the Golgi complex is transported into colloids through the process of exocytosis and binds to the resulting iodotyrosine residue, which ultimately forms iodinated Tg (TgI). TgI then forms a complex with proteolytic cleavage to produce monoiodotyrosine, diiodotyrosine, 3,5,3'-triiodothyronine (T3); and 3,5,3',5'-tetraiodothyronine (T4/thyroxin), all of which will be stored in colloids and released when needed (17,47). When the stimulus to release hormones is received, thyrosite will engulf some of the colloid, form an endocytosis and proteolysis process assisted by lysosomes and then separate Tg from T3 and T4, which will then be transported by monocarboxylate transporters and diffuse into the blood (17,47,50). It has been reported that mice with a double knockout of the DUOXA1/DUOXA2 gene show that the loss of DUOX cells resulted in hypothyroidism and a decrease in H_2O_2 levels due to disruption of T4 production in the thyroid follicles (51,52).

4. Modulation of thyroid hormone levels with IGF-1

Thyroid hormones, particularly T3, have a direct effect on the pituitary gland and regulate the secretion of growth hormone (GH). This direct influence operates through thyroid hormone receptors found in the somatotroph cells of

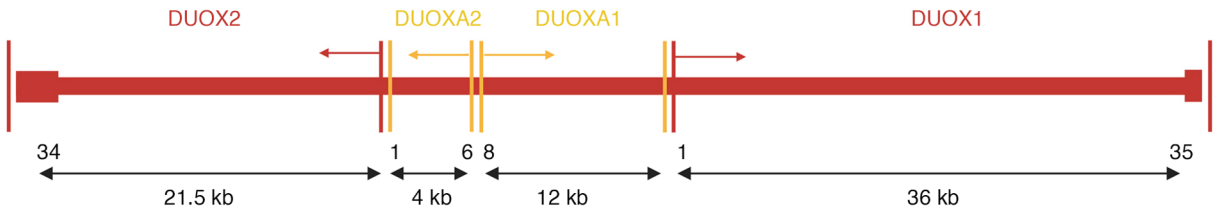

Figure 1. Structure of the DUOX/DUOXA gene. Schematic genomic structure of the DUOX/DUOXA gene locus on chromosome 15. From '*DUOX Defects and Their Roles in Congenital Hypothyroidism*' by X.D. Deken and F. Miot, 2019, Methods in Molecular Biology, Third section, Figure 2, (https://doi.org/10.1007/978-1-4939-9424-3_37) © 2024 Springer Nature (144) DUOX, dual oxidases; DUOXA, dual oxidase maturation factor.

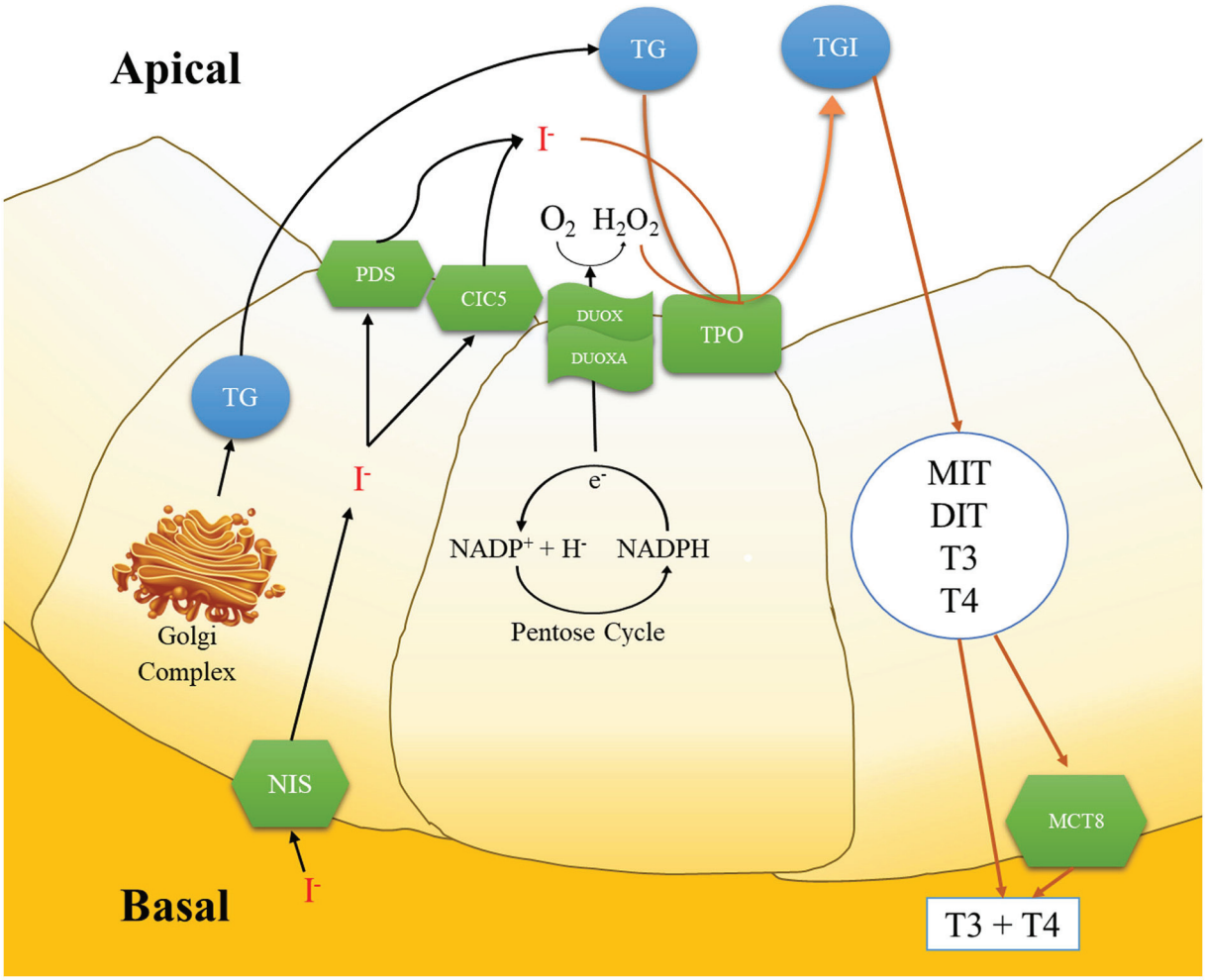

Figure 2. Formation of thyroid hormones requires iodide (I^-) that is taken by thyrocytes through the NIS. I^- is then transferred into the lumen of the follicle via the chlorine channels CIC5 and PDS. The TPO enzyme will catalyze I^- using H_2O_2, which is produced by the DUOX/DUOXA complex. Tg produced in follicular cells by the Golgi complex is transported into colloids and binds to the resulting iodotyrosine residue, which ultimately forms TgI. Then, TgI forms a complex with proteolytic cleavage to produce T3 and T4/thyroxin, which are later stored in colloids and released into the blood via MCT. I^-, iodide NIS, Na/I symporter; CIC5 PDS, pendrin; TPO, thyroid peroxidase; DUOX, dual oxidases; DUOXA, dual oxidase maturation factor; TgI, thyroglobulin; TgI, iodinated Tg; T3, triiodothyronine; T4, thyroxine; MCT, monocarboxylate transporters; MIT, monoiodotyrosine; DIT, diiodotyrosine.

the anterior pituitary gland. Once T3 binds to these receptors, it can adjust the transcription of the GH gene, thereby affecting the synthesis and release of GH. Maintaining appropriate thyroid hormone levels is crucial for normal GH production, as evidenced by decreased GH mRNA levels in the pituitary gland and reduced GH secretion in hypothyroidism cases. Conversely, administering thyroid hormone under hypothyroid conditions can restore GH secretion to normal levels, underscoring the necessity of adequate thyroid hormone levels for regular GH synthesis and release (53,54).

Thyroid hormones also indirectly affect GH secretion by affecting the hypothalamus. The hypothalamus synthesizes two key hormones, growth hormone-releasing hormone (GHRH), which prompts GH secretion and somatostatin, which inhibits GH secretion. Thyroid hormones can regulate the release of hypothalamic hormones, thus indirectly influencing GH secretion. For instance, thyroid hormones

can increase the production of GHRH in the hypothalamus, resulting in increased GH release from the pituitary gland (54,55). The amount of thyroid hormone circulating in the blood is related to an increase in IGF-1, a polypeptide that shares structural similarities with human pro-insulin and is an essential hormone for the growth and development of the body. The primary source of GH production is the liver and is triggered by GH secreted by the anterior pituitary gland (56). The bioavailability and physiological effects of IGF-1 are controlled by a set of proteins called IGF-binding proteins (IGFBP) that are secreted. These proteins have a strong affinity for IGF-1 and serve as transporters of circulating IGF-1 (57).

Thyroid hormone can modulate GH and subsequently affect the production of IGF-1. Some studies have mentioned that hypothyroidism leads to decreased GH levels and consequently lower IGF-1 levels, whereas replacement therapy with thyroid hormone can elevate IGF-1 levels (58,59). Another study found that patients with hyperthyroidism have higher serum IGF-1 levels than those with euthyroidism (60). On the other hand, previous studies have shown that not all effects of thyroid hormones on the IGF-1 pathway are mediated through GH. Thyroid hormones directly affect the transcription of the IGF-1 gene. Specifically, triiodothyronine can attach to thyroid hormone receptors, which function as transcription factors. These thyroid hormone receptors can subsequently bind to thyroid hormone response elements situated in the promoter region of IGF-1, resulting in altered IGF-1 mRNA. This direct regulation of transcription occurs in different tissues, such as the liver and bone, where IGF-1 plays a crucial role in growth and development (60-62).

Thyroid hormones can also adjust intracellular signaling pathways of IGF-1 intracellularly. They can regulate the expression of IGF-1 receptors (IGF-1R) on target cells, thus influencing the sensitivity and responsiveness of these cells to IGF-1. Furthermore, thyroid hormones can affect the production of IGFBP, which controls the availability and function of IGF-1 by binding to it in the bloodstream. Variations in IGFBP levels can change the quantity of unbound or free IGF-1 that can be attached to its receptor to produce its effects (58,60,61). One study showed that T4 replacement therapy increased serum IGFBP1 levels. In hypothyroid animals, serum IGFBP3 and IGFBP4 levels are reduced, and thyroid hormone replacement can correct these changes. Patients who undergo thyroidectomy and have their thyroid hormone replacement discontinued experience a decrease in the levels of circulating IGFBP1. Treatment with thyroxine raises these levels (58). These findings highlight the complex relationship between thyroid hormone levels and the IGF-1 pathway, suggesting that thyroid hormones may influence the activity of IGF-1 and related pathways in multiple ways.

5. Modulation of IGF-1 expression in autophagy

Research has revealed that IGF-1 signaling controls autophagy in a bidirectional manner (63). Autophagy is a widely occurring recycling process in which cellular material, including organelles, is taken up by membrane-bound vacuoles referred to as autophagosomes and transported to lysosomes and are degraded by the lysosomal compartment's store of proteolytic enzymes. This process is essential for maintaining cell, tissue, and organism homeostasis (64,65).

As an antagonist of autophagy (Fig. 3), IGF-1 binds tightly to the α subunit of IGF-1R, a type 2 tyrosine kinase membrane receptor, thereby exerting cell proliferation, differentiation and survival (66,67). This binding initiates the phosphorylation of tyrosine residues and subsequent activation of intrinsic tyrosine kinase activity of the β subunit. This further causes adaptor proteins, including insulin receptor substrate 1 and 2 (IRS1/2) and Src homology 2 domain containing E (SHE), to become phosphorylated (68). Consequently, they initiate a cascade of reactions involving various intracellular signaling pathways. These reactions ultimately modulate the expression of genes associated with cell proliferation, autophagy, or apoptosis, primarily through the PI3k/AKT/mTOR and Ras-Raf-ERK1/2 (MAPK) pathway (67,69,70). An adaptor protein, Src homology and Collagen (Shc), binds with son-of-sevenless and growth factor receptor-bound protein 2 to activate RAS, whereas IRS1/2 interacts with the p85 regulatory subunit to activate PI3K (66-68).

The PI3K/AKT/mTOR activation pathway involves the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2), a lipid protein, to phosphatidylinositol 3,4,5-trisphosphate (PIP3) by the PI3K kinase subunits p85 and p110. PIP3 signaling proteins, such as phosphoinositide-dependent kinase-1 (PDK1), then activate AKT, which in turn suppresses serine and threonine residues on its targets, including glycogen synthase kinase-3 beta (GSK-3β) and Tuberous sclerosis complex 1/Tuberous sclerosis complex 2 (TSC1/TSC2) (67,71). Inactive GSK-3β and TSC1/TSC2 prevent their inhibition, activating the small G protein Ras homolog enriched in the brain (Rheb) that binds with GTP. GTP-bound Rheb activates mTOR-complex 1 (mTORC1) at the lysosomal surface by binding to specific domains, including N-heat, M-heat, and the focal adhesion targeting domain. This binding allosterically modulates ATP binding at the active site, facilitating subsequent phosphorylation events (67,72).

Through the MAPK pathway, Shc/Ras/Raf/MEK modulates ERK1/2 and phosphorylates and inhibits the TSC complex, thus activating mTORC1. Subsequently, this activation affects downstream effectors such as ribosomal S6 kinase (S6K), Eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) and Unc-51-like kinase (ULK) 1/2, which in turn control processes such as autophagy inhibition, delayed apoptosis, protein synthesis, cell survival and proliferation (73). Several studies have found that changes in IGF-1 levels alter autophagy (74,75) Renna *et al* (76) found that IGF-1R knockdown reduced LC3-II levels in HeLa cells grown in normal media. In addition, IGF-1R knockdown reduced autophagosome formation in mouse embryonic fibroblasts derived from hemizygous IGF-1R mice. In another study, it was found that an increase in IGF-1 was accompanied by an increase in Beclin1, ULK1, and autophagy-related 5 (Atg5), which are markers of autophagy (77).

Conversely, IGF-1 promotes mitophagy (Fig. 4). Following IGF-1 signaling stimulation, there is a notable increase in the expression of peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha. This results in increased levels of cytochrome *c* oxidase subunit 7A1 (COX7A1), transcription factor B1, mitochondrial

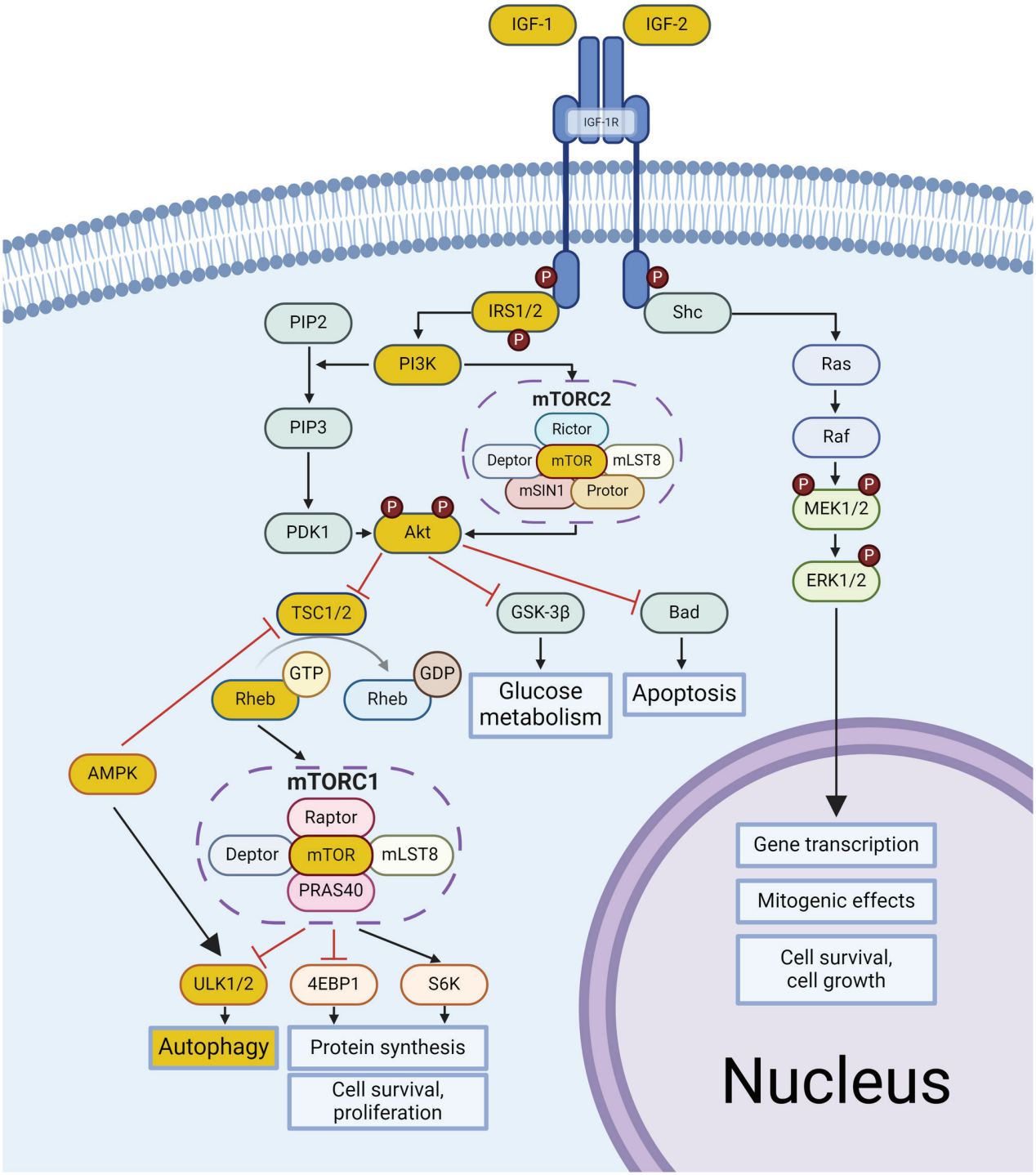

Figure 3. Inhibition of autophagy by the IGF-1 signaling pathway. The interaction of IGF-1 with its receptor IGF-1R initiates a sophisticated signaling cascade. In the initial phase, IRS1/2 phosphorylation occurs, subsequently activating downstream pathways, including PI3K, AKT and S6K. PI3K activates the lipid molecules PIP2 and PIP3, with PIP3 further activating PDK1. Activated PDK1 then phosphorylates and activates AKT. This phosphorylation inhibits TSC1/TSC2 and GSK-3β, preventing their interaction with Rheb, thereby activating mTORC1. Activated mTORC1 stimulates S6K, which reduces the number of autophagolysosome and inhibits 4EBP1, a translational regulator, thereby enhancing protein synthesis. Furthermore, mTORC1-mediated inhibition of ULK1/2 decreased autophagosome synthesis. IGF-1 also activates the MAPK signaling pathway, which includes She, Ras, Raf and ERK1/2. The phosphorylation of ERK1/2 promotes cell survival by activating mTORC1 within the nucleus. IGF-1, insulin-like growth factor 1; IRS1/2, insulin receptor substrate 1 and 2; S6K, ribosomal S6 kinase; PIP, phosphatidylinositol 4,5-bisphosphate; PDK1, 3-phosphoinositide-dependent protein kinase-1; TSC, Tuberous Sclerosis Complex; GSK-3β, glycogen synthase kinase 3 beta; mTORC1, mTOR-complex 1; 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; ULK, Unc-51-like kinase; She, Src homology 2 domain containing E; AMPK, 5' AMP-activated protein kinase.

(TFB1M), and mtDNA, which improve mitochondrial function (78). In addition, IGF-1 also plays a critical role in mitochondrial biogenesis and turnover through the upregulation of factors such as PGC-1β and PGC-1-related coactivator, as well as the expression of the mitophagy receptor Bcl2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) (79,80) BNIP3 contains LC3-interacting regions domains that enable interaction with LC3II in

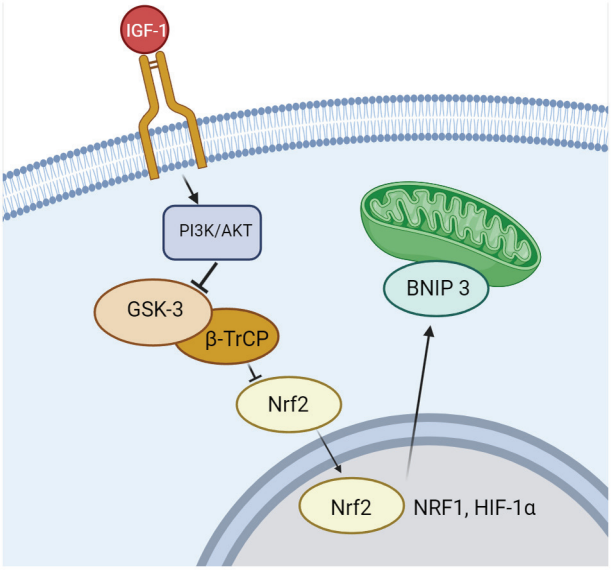

Figure 4. Role of the IGF-1 Signaling Pathway in Mitophagy. IGF-1 upregulates BNIP3 activity through activation of the PI3K/AKT signaling pathway thereby modulating the occurrence of mitophagy. Activated AKT phosphorylates GSK-3β, leading to the subsequent activation of Nrf2. The induction of BNIP3 is driven by either NRF1 or HIF-1α, which are downstream effects of Nrf2 activation. BNIP3 signaling is integral to the enhancement of mitophagy because it sustains mitochondrial dynamics and promotes autophagosome turnover. IGF-1, insulin-like growth factor 1; BNIP3, adenovirus E1B 19 kDa protein-interacting protein 3; GSK-3β, glycogen synthase kinase-3 beta; Nrf2, nuclear factor erythroid 2-related factor 2; HIF, hypoxia Inducible factor.

autophagosomes. Through AKT-mediated inhibitory phosphorylation of serine 9 of GSK-3β, IGF-1 stimulates the expression of the mitophagy receptor BNIP3, which in turn activates nuclear factor erythroid 2-related factor 2 (Nrf2) and the downstream transcriptional regulators Nrf1 and hypoxia-inducible factor 1-alpha (HIF-1α), implying that BNIP3 is a secondary target gene of Nrf2. Therefore, IGF-1 signaling ensures mitochondrial homeostasis and promotes tumor growth by linking mitochondrial biogenesis to basal levels of mitochondrial turnover through Nrf2 and BNIP3 (67,79).

The bidirectional effects of IGF-1 are context-dependent and are influenced by various factors, including the cellular context and situations. Under normal conditions, where cellular growth and proliferation are prioritized, IGF-1 signaling inhibits autophagy (63,67,69,81). Nonetheless, it stimulates autophagy and mitophagy in pathological situations where cellular recycling processes are required, such as energy deficiencies, starvation, hypoxia and cancer (78-80,82).

6. Modulation of thyroid hormone in autophagy

Muscle development can be directly influenced by thyroid hormones through several pathways and one of them is the autophagy pathway (83) thyroid hormones require autophagy to regulate lipid homeostasis and mitochondrial quality control in the liver (84,85). To date, research data are insufficient to explain the role of thyroid hormones in autophagy.

Lesmana *et al* (86) revealed that thyroid hormone induces autophagy through 5' AMP-activated protein kinase (AMPK) activation by increasing its phosphorylation, inhibiting mTOR signaling as demonstrated by a decrease in mTOR phosphorylation and increasing mRNA and protein expression in LC3, p62 and Ulk1 found in skeletal muscle, which is the key autophagy initiator (86). On the other hand, studies by Kurashige *et al* (87) discovered that T4 suppressed autophagy by decreasing LC3 and increasing p62. Conversely, the authors discovered that TSH increased the process of autophagy through the cAMP-PKA-cAMP response element binding protein/ERK and PKC signaling pathways (87). These disparities in the data suggest that more investigation is required to fully understand the effects of thyroid hormones on autophagy.

7. Modulation of thyroid hormone levels in skeletal muscle growth

Thyroid hormone has a major role in the growth, regeneration and differentiation of skeletal muscle through the induction of autophagy, which involves the stimulation of ROS of AMPK and mTOR-ULK1 signaling (86). Thyroid hormone can also trigger changes in the muscle fiber profile, such as the loss of embryonic and neonatal myosin and increase in fast or slow myosin genes in certain muscles (88). In addition, rats with hypothyroidism exhibit delayed transition to adult myosin in their fast muscles but not in their slow muscles (89-91).

Weight-bearing exercise and electrical stimulation are essential for the postnatal growth of slow fibers, whereas T3 signaling is critical for the development of fast fibers, particularly for the conversion of neonatal fiber to fiber IIb (89,91-93). The typical pattern of fiber dispersion in every muscle is determined in part by the physiological levels of thyroid hormone (92,94). Thyroid hormone, especially T3, induces muscle contractions to become faster in rats by increasing the expression of myosin heavy chain (MYH)2, MYH 1, MYH 4, fibers IIa, IIx, and IIb; and suppressing the expression of MYH7 and myosin from fiber type I. Furthermore, T3 promotes the conversion of muscle fiber types from slow to fast by causing changes from MYH7 to MYH2, MYH2 to MYH1, and MYH1 to MYH4 (95,96). Triiodothyronine induces miR-133a expression in fast-twitch muscles and also induces slow-to-fast muscle fiber transition (97). Furthermore, mice with miR-133a deletion exhibit a fast-to-slow muscle transition (98).

Muscle growth can be directly regulated by T3 hormone, which stimulates signals to myoblast determination protein (MYOD)1, a protein that regulates the transcription process during myogenesis (5). Moreover, MYOD1 stimulates muscle satellite cells to differentiate into myoblasts and myotubes. Furthermore, myogenin in immature myotubes and myosin heavy chain (MYH) in mature myotubes are two additional mechanisms that directly affect muscle development and function caused by T3 (5,99).

8. Modulation of autophagy in skeletal muscle growth

Autophagy provides the fundamental components for metabolism and cellular renewal (11,100,101). Additionally, autophagy controls intracellular quality control, which aids in the breakdown of defective proteins and basal protein turnover (102). Inhibition of autophagy causes the aggregation of ubiquitin

proteins and inclusion bodies in various types of cells, and the abnormalities can also occur in mitochondria, peroxisomes, the endoplasmic reticulum, and Golgi bodies (103-105). Studies using Atg7 knockout mice and focused on muscles that presented abnormal concentric membranous formations, reticulum distension, disordered sarcomere and aberrant mitochondria. The Atg7 knockout mice displayed muscular phenotypes such myopathy's morphological characteristics, muscle atrophy and degeneration under catabolic environments, this showed how autophagy provides benefits for preserving the integrity of myofiber and muscle mass (104,105). Additionally, an Atg16L hypomorph mouse model showed reduced autophagy flux but still present and impaired muscle fiber development and generation (105,106).

Degeneration and atrophy of the muscles are caused by impaired autophagy (105,107). However, excessive autophagy can also cause atrophy, which is associated with mutations in the laminin α2 chain, which cause muscle fibrosis, atrophy and apoptotic phenotypes as well as an increase in the expression of genes related to autophagy (108-110).

Autophagy plays an important role in skeletal muscle regeneration due to its ability to regenerate muscle stem cells/satellite cells by maintaining a state of quiescence and preventing aging (111,112). In senescent muscle stem cells, the phosphorylation of AMPK and its downstream target P27Kip1 is reduced and the accompanying stress of inhibited autophagy renders muscle stem cells more susceptible to apoptosis (113). Autophagy helps prevent aging by clearing the autophagosome and providing an energy source for activation (111,112). Failure of autophagy in satellite cells will cause aging, oxidative stress and mitochondrial dysfunction, as well as accumulation of organelles and proteins, but satellite cells are not the cause of muscle fiber hypertrophy because satellite cells are only needed for the *de novo* formation of new fibers (114-118). These results show that the decrease in the number of satellite cells may not be due to atrophy.

Previous studies have reported that the autophagy process occurs throughout the entire myoblast differentiation cycle, so it can be concluded that there is a two-way process between autophagy and muscle cell differentiation (112,119-121). There is a relationship with thyroid hormone, where T3 is needed for the process of differentiation and fusion of myoblasts, which will later trigger upregulation of autophagy (122). Disruption of the autophagy process, such as knockdown of Atg5 and Atg7, affects myogenesis, which is followed by mitochondrial dysfunction (121).

The differentiation of primitive myoblasts into mature myotubes necessitates a metabolic change to meet the increasing energy demand, which involves mitochondrial renewal, which has been proven to be an essential step (123,124). In this situation, autophagy plays an important role, as evidenced by an increase in mitophagy prior to a rise in the amount of mitochondrial proteins at the beginning of the mitochondrial renewal process during myogenic differentiation (124).

Autophagy is required in the myoblast differentiation process due to its relationship with signaling preventing the apoptosis process (125,126). Inhibition of Atg7 enhanced transient caspase 3 activation, DNA fragmentation and the proportion of apoptotic nuclei (125). In addition, mitophagy also has the function of removing damaged mitochondria prior to apoptotic signaling, reducing cell stress and death (126). Notably, the increased ROS levels induced by cellular stress are also required for skeletal muscle development and inhibition of mitochondrial ROS production leads to the failure of myoblast differentiation (127,128). Furthermore, DUOX, which is a member of the NADPH family, may produce ROS, leading to the hypothesis that there is a link between DUOX gene and skeletal muscle growth.

9. Modulation of DUOX, thyroid hormone, IGF-1, and autophagy in skeletal muscle growth

From the various interactions, Fig. 5 summarizes of the relationships among DUOX, thyroid hormone, IGF-1 and autophagy in skeletal muscle. The DUOX gene generates H_2O_2, which is an oxidant that aids in the production of thyroid hormone (17,18). Thyroid hormones can promote autophagy by inhibiting mTOR and increasing the production of AMPK (86). Nevertheless, another study claims that thyroid hormones, particularly T4, have an effect and that they directly inhibit the autophagy process (87). In turn, autophagy recycles damaged organelles and macromolecules and the byproducts of this degradation are used by muscle cells for their development, differentiation and regeneration (105,107,121,125,129). Moreover, thyroid hormone also affects autophagy and the development of muscle cells in another pathway by increasing GH and IGFBP through IGF-1 (58-60). Furthermore, IGF-1 raises At, which then cascades down into two pathways: Upregulating mTOR, which inhibits autophagy and downregulating GSK-3β, which increases autophagy, especially mitophagy (67,73). Despite the opposing effects on autophagy, both of these processes directly enhance muscle development. Thyroid hormone, particularly T3, can directly affect muscle growth and differentiation by raising MYOD1, myogenin, and MYH (5,99). Although several pathways still require further research, such as the relationship between DUOX, autophagy and muscle growth, it si hypothesized that there is a relationship between these components that can be explained through available research.

To the best of the authors' knowledge, DUOX research on autophagy and cell or tissue growth is currently limited to smooth muscle organs such as the respiratory system. A study using mice with inflammation in their lungs showed that autophagy regulates the increase in superoxide levels by directing DUOX1 to the apical surface of the airway epithelium (130). Another similar study in *Drosophila* showed the activation of the DUOX gene downstream of autophagy by activating the ATG1-dependent lipophagy pathway, which is required for tumor necrosis factor receptor-associated factor 3 (TRAF3)-AMPK/Warts gene (WTS)-pathway-induced DUOX activation (131,132). Additionally, NOX, which is in the same family as DUOX, produces ROS, which affects autophagy. The exact methods by which ROS trigger autophagy remain unclear. For example, by directly oxidizing parts of the autophagic machinery, this activation serves as a compensatory and survival mechanism to reduce cellular death caused by excess ROS (133,134). Another study reported that ROS produced from NOX activates autophagy by stimulating the protein kinase RNA-like endoplasmic reticulum kinase signaling pathway, which in turn enhances

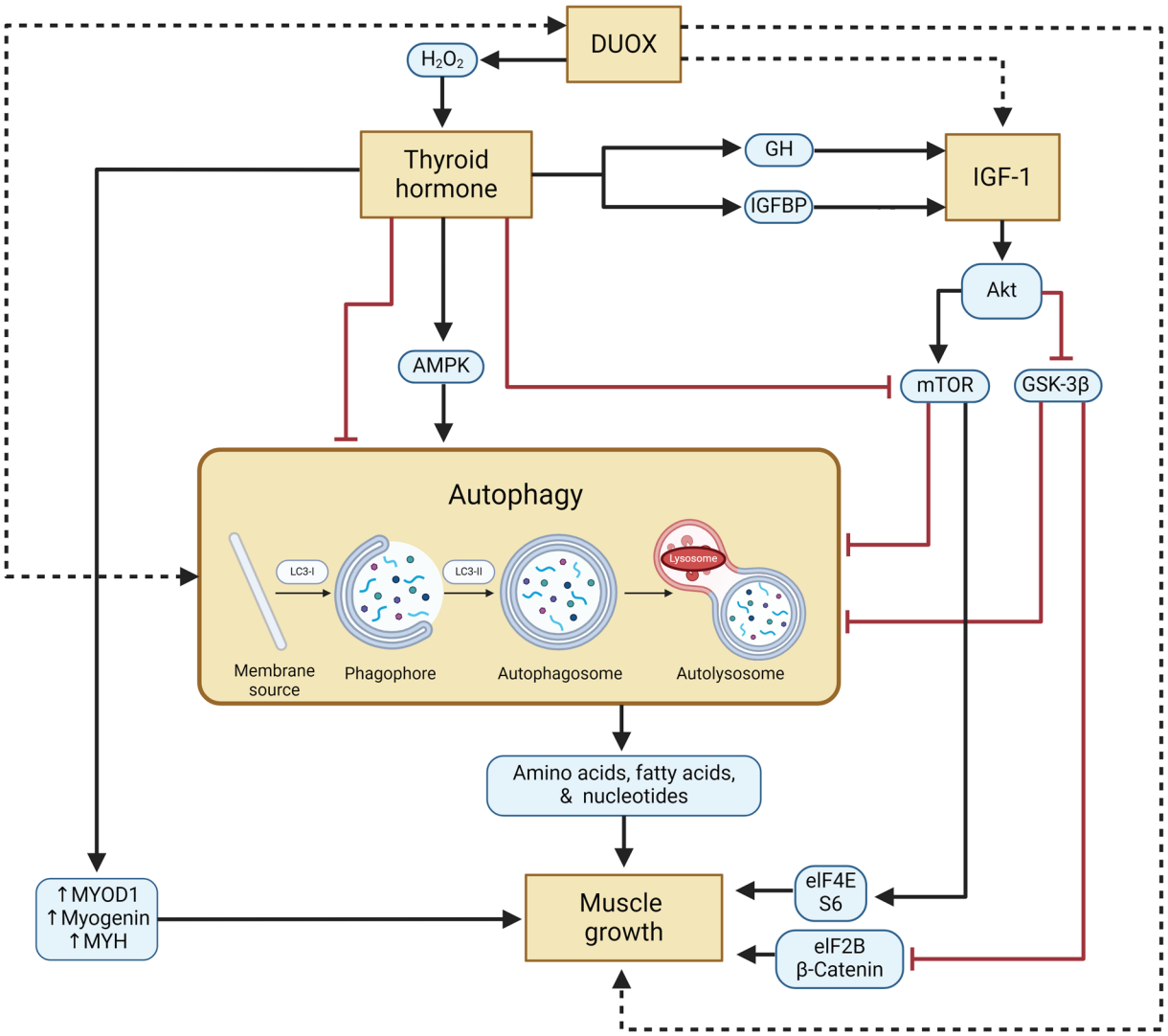

Figure 5. Modulation of DUOX gene expression, thyroid hormone, IGF-1 and autophagy in skeletal muscle. The DUOX gene produces H_2O_2, which is required for thyroid hormone formation. Thyroid hormones, particularly T4, have an effect that directly suppresses autophagy, although they can also enhance AMPK production and inhibit mTOR, which are beneficial for boosting autophagy. Thyroid hormone can also increase IGF-1 levels by stimulating GH and IGFBP. Furthermore, IGF-1 upregulated At, which enhances mTOR and inhibits GSK-3β. Thus, these two mechanisms have opposite effects on autophagy but have the same effect in enhancing muscle growth. Muscle growth can be directly affected by autophagy through its degradation products, whereas thyroid hormone can directly affect muscle growth by increasing the levels of MYOD1, myogenin and MYH. DUOX, dual oxidases; IGF-1, insulin-like growth factor 1; AMPK, 5' AMP-activated protein kinase; GH, growth hormone; IGFBP, IGF-binding protein; GSK-3β, glycogen synthase kinase-3 beta; MYOD, myoblast determination protein; MYH, myosin heavy chain.

the activation of autophagy and survival in cardiomyocytes in response to food restriction and ischaemia (135).

Hypothetically, ROS produced by the DUOX gene has a similar effect to NOX in directly regulating autophagy, where autophagy is triggered when the cell is under stress (136-142) or, in the other words, DUOX and autophagy have a reciprocal relationship (143). Furthermore, ROS has an effect on muscle tissue development and it is hypothesized that DUOX has a direct effect on muscle development via ROS production. Skeletal muscle formation depends on elevated ROS levels brought on by cellular stress, and inhibition of mitochondrial ROS synthesis impairs myoblast differentiation (127,128). It is also hypothesized that IGF-1 promotes muscle growth by upregulating DUOX. However, no studies have specifically investigated this relationship, and the direct interactions are largely unknown.

10. Conclusion

In conclusion, the DUOX gene has several benefits in various life processes, including muscular development. By understanding the function of DUOX, clinicians will be able to diagnose and administer appropriate treatment if a disorder occurs in this gene. DUOX is an enzyme that can produce H_2O_2, which is needed for thyroid hormone production. In addition, thyroid hormone can trigger muscle growth directly and indirectly through the IGF-1 signaling pathway. IGF-1 will later have a bidirectional effect on the autophagy process. Autophagy itself is a process necessary for muscle development. In this pathway, the effect of DUOX on skeletal muscle growth is unclear. It was hypothesized that there is a direct relationship between DUOX and IGF-1, autophagy and muscle development. Therefore,

further studies are required to provide new insights into the influence of DUOX on skeletal muscle growth through IGF-1 signaling.

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Availability of data and materials

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Authors' contributions

AAT completed the first draft of the manuscript. HG and RL proposed ideas. HG, RL and AC reviewed and edited the manuscript. NS and JWG analyzed the data and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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