Is TP53INP2 a critical regulator of muscle mass?

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Purpose of review
The main aim of this review is to summarize current knowledge of tumor protein p53-inducible nuclear protein 2 (TP53INP2) function and its role in skeletal muscle proteostasis.

Recent findings
Autophagy is directly involved in the regulation of skeletal muscle mass. Thus, excessive autophagy is associated with several diseases that cause muscle wasting, and it promotes the loss of muscle protein. Furthermore, compromised autophagy also leads to muscle atrophy. In this regard, TP53INP2 activates autophagy in skeletal muscle, thus causing a reduction in muscle mass. Moreover, TP53INP2 gain of function enhances muscle wasting in a highly catabolic context such as in streptozotocin-induced diabetes. However, TP53INP2 is naturally repressed in human insulin resistance and in murine models of diabetes. These observations suggest that TP53INP2 repression would reduce muscle atrophy under conditions that favor protein loss in skeletal muscle.

Summary
To date, there is no effective treatment for muscle wasting. Thus, the identification of new putative pharmacological targets to effectively treat this devastating condition is crucial. Given current knowledge about the role of TP53INP2 in skeletal muscle, this protein may be an optimal candidate to target for the prevention of muscle wasting.

Keywords
autophagy, muscle atrophy, muscle wasting, skeletal muscle, TP53INP2

INTRODUCTION

Skeletal muscle is the most abundant tissue in humans, accounting for approximately 50% of the total body weight, and is involved in vital functions, such as locomotion and the maintenance of the whole-body metabolic homeostasis. The preservation of skeletal muscle mass is crucial to ensure its correct function, and this is achieved by a fine regulation of the processes involved in protein synthesis and protein degradation inside the myofiber. The proteolytic systems that are quantitatively more relevant in skeletal muscle are the ubiquitin proteasome system (UPS) and macroautophagy (hereafter referred to as autophagy) [1]. Both proteolytic processes are highly activated in several human diseases, such as cancer cachexia [2,3], renal failure [4], and diabetes [5,6▪], causing an accelerated loss of muscle mass. This pathologic muscle wasting has been associated with impaired muscle performance and a reduced quality of life for the patient, together with an increased risk of mortality [7–9]. The most extreme example is cancer cachexia, in which case up to 30% of patients with advanced cancer die from complications (e.g. infections) related to protein malnutrition [9]. However, to date, there is no effective treatment for this condition. It is therefore imperative to identify new regulators of skeletal muscle mass and to improve our understanding of the mechanisms that cause muscle loss. We envisage that such new regulators of skeletal muscle mass will be potential targets of drugs for the treatment of muscle wasting.

In this review, we will focus on the analysis of the current knowledge of tumor protein p53-inducible nuclear protein 2 (TP53INP2, also named DOR) function in skeletal muscle. This protein has been recently reported to regulate muscle mass and to

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KEY POINTS

- TP53INP2 regulates protein metabolism in skeletal muscle by activating basal autophagy.
- TP53INP2 negatively regulates skeletal muscle mass by increasing autophagy-dependent protein degradation.
- TP53INP2 gain of function promotes muscle wasting, but only in conditions in which autophagy contributes to muscle loss.
- Various pathological conditions lead to TP53INP2 repression, and these observations reveal the existence of an adaptative mechanism aimed to preserve skeletal muscle mass.

activate muscle autophagy [6▪], both in basal state and in pathological conditions.

AUTOPHAGY AND SKELETAL MUSCLE

Autophagy is a term that refers to the degradation of cytosolic components (organelles, protein aggregates, glycogen, lipids, etc.) inside lysosomes, independently of the way these substrates have been delivered. In this regard, three types of autophagy have been described in mammals: macroautophagy, microautophagy, and chaperon-mediated autophagy [10]. In this review, we will focus on macroautophagy (hereafter referred to as autophagy).

Autophagy is a conserved process from yeast to mammals and, in fact, studies in yeast set the basis for what is currently known about the molecular regulators of this process. Autophagy involves the formation of double-membrane vesicles called autophagosomes that sequester cytosolic components. Once properly formed, these vesicles fuse with lysosomes and the cargos are enzymatically degraded. The central process of autophagy is autophagosome formation. Briefly, the initiation and nucleation of the autophagosome is regulated mainly by the unc-51 like autophagy activating kinase 1 complex and the phosphatidylinositol-3-kinase class III kinase complex [11–14]. Their action allows the recruitment of the conjugating machinery (Atg12-Atg5/Atg16L complex and Atg7) that will cleave and lipidate LC3, allowing the incorporation of this protein to the phagophore to ensure proper formation of the autophagosome [10,14]. Initially considered a bulk process, it has become clear that basal autophagy is a highly selective process. In fact, several 'autophagy receptors' in charge of targeting the cargos to be degraded have been described. Examples include SQSTM1 protein (p62), neighbor of BRCA1 gene 1 (NBR1) (both proteins target polyubiquitin protein aggregates to degradation) and BCL2/adenovirus E1B 19kDa interacting protein 3 (targeting mitochondria) [15,16].

Specifically in the case of skeletal muscle, a certain level of autophagy is required for the maintenance of muscle mass and function. Autophagy acts as a quality-control mechanism to remove defective or damaged cytosolic components such as proteins and organelles. In this regard, it has been recently reported that blockage of autophagy in skeletal muscle by continuous mammalian target of rapamycin complex 1 (mTORC1) activation causes muscle atrophy as a result of the accumulation of aberrant organelles and protein aggregates, which impair myofiber homeostasis and promote the development of a myopathy [17▪]. In addition, glycogen synthase kinase-3a (GSK-3α) ablation suppressed autophagy and caused sarcopenia in cardiac and skeletal muscle in mice, which was rescued by pharmacological inhibition of mTORC1 [18▪]. In keeping with these data, compromised autophagy and lysosome function are common features of several muscle dystrophies [19].

Furthermore, excessive autophagy has been associated with several diseases or conditions that cause muscle wasting, such as cancer cachexia [2,3], diabetes [5,6▪], and hepatic cirrhosis [20]. Under these conditions, autophagy contributes to muscle loss.

TP53INP2 AS AN ACTIVATOR OF AUTOPHAGY

Tumor protein p53-inducible nuclear protein 2 is a protein of 220 amino acids in human and 221 in rat and mouse that is highly expressed in skeletal muscle and in other tissues with an active metabolism, such as the heart [6▪,21]. Only one homologous protein has been described to date, namely TP53INP1 or stress-induced protein or Tp53inp1, which shares 36% of identity with human TP53INP2 [22]. The genes coding for these two proteins form a small family restricted to metazoan species [22].

Functional characterization of TP53INP2 has revealed that this protein constantly shuttles between the nucleus and the cytoplasm [23], and that it has two distinct functions depending on its localization, serving as a co-activator of various nuclear receptors and as a regulator of autophagy.

Tumor protein p53-inducible nuclear protein 2 was initially described as a protein with nuclear localization under basal conditions [21,24]. More specifically, it localizes in promyelocytic leukemia nuclear bodies [21]. This evidence, together with the observation that TP53INP1 is involved in the regulation of gene expression, suggested that this

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protein plays a similar role. Experiments performed in cultured cells first revealed TP53INP2 as a co-activator of the thyroid hormone receptor α1 (TRα1) [21]. In fact, TP35INP2 enhances the transcriptional activity of several nuclear receptors, such as the mammalian glucocorticoid receptor, vitamin D receptor (VDR), and peroxisome proliferator-activated receptor gamma, in the presence of the respective ligands in gain-of-function studies [22]. In the case of TRα1, TP53INP2 exerts its action as a transcriptional co-activator by physically binding to this nuclear receptor [21]. Moreover, the function of TP53INP2 as a nuclear co-activator is conserved in an in-vivo model such as *Drosophila melanogaster*. Specifically, the TP53INP2 ortholog in *Drosophila* (dDOR) acts as a co-activator of the Ecdisone receptor (EcR) by directly binding to it [25]. In fact, dDOR is required for the maximal transcriptional activity of the EcR [25].

Conditions that activate autophagy, such as pharmacological mTOR inhibition or amino acid starvation, favor the exit of TP53INP2 from the nucleus, after which it is found mainly in autophagosomes [24]. In fact, TP53INP2 promotes autophagosome formation [24]. TP53INP2 presents a typical LC3-interacting region (LIR) motif, through which it interacts directly with LC3 and other Atg8 family members such as GATE16, GABARAP, and GABARAP-L1 [22,24]. It is likely that the binding of TP53INP2 to Atg8 proteins propitiates autophagosome formation and causes enhanced autophagic protein degradation both *in vitro* and *in vivo* [6▪,24] (Fig. 1). However, TP53INP2 is not an essential component of autophagy as its knockdown in cellular models or its genetic ablation *in vivo* reduces autophagy flux without completely blocking this process [6▪,24].

Moreover, it is also worth mentioning that TP53INP1 activates autophagy in cultured cells [22,26], suggesting that these two proteins from the same family have similar functions.

FUNCTIONAL ROLE OF TP53INP2 IN SKELETAL MUSCLE

TP53INP2 has recently been described as a negative regulator of skeletal muscle mass [6▪]. In this regard, increased TP53INP2 expression in skeletal muscle reduces muscle weight and myofiber size, whereas its ablation causes skeletal muscle hypertrophy by increasing myofiber size [6▪]. TP53INP2 does not function as a co-activator of nuclear receptors in skeletal muscle under basal conditions [6▪]. In fact, the negative effect of TP53INP2 on muscle mass is due to its role as an activator of basal autophagy in skeletal muscle [6▪]. TP53INP2 promotes autophagosome formation and co-localizes with LC3 in skeletal muscle. These observations suggest that the mechanism of action by which TP53INP2 induces autophagosome formation is conserved between

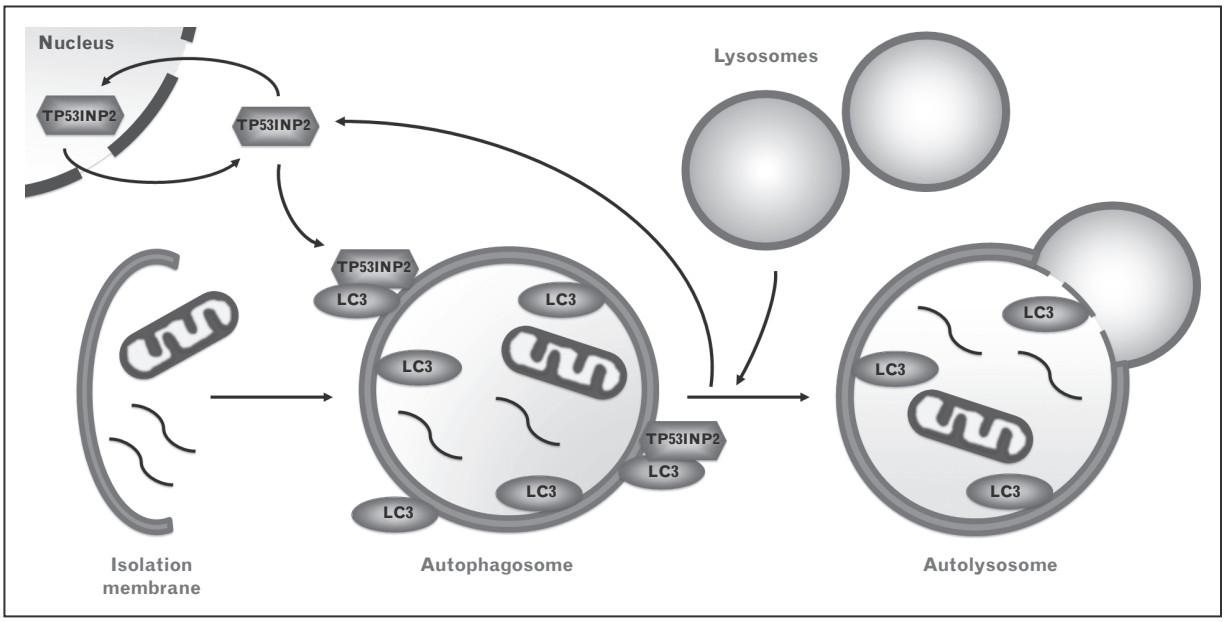

FIGURE 1. Scheme of the involvement of TP53INP2 in autophagy. Gain-of-function and loss-of-function assays in cultured cells showed that TP53INP2 is a highly dynamic protein that constantly shuttles between the nucleus and the cytosol in basal conditions. When localized in the cytosol, TP53INP2 is recruited to the autophagosomes, where it interacts with LC3 and other Atg8 family members and promotes autophagosome formation. However, TP53INP2 leaves the autophagosome before fusion with the lysosomes [22,24]. TP53INP2, tumor protein p53-inducible nuclear protein 2.

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cellular models, *D. melanogaster*, and skeletal muscle [6▪,24]. By increasing the autophagy flux, TP53INP2 increases the rate of protein degradation in skeletal muscle, thus favoring muscle loss. This explains why TP53INP2 gain of function results in a reduced muscle mass, whereas TP53INP2 ablation causes muscle hypertrophy in mouse models [6▪].

In addition, recent evidence suggests that TP53INP2 promotes not only autophagosome formation but also the degradation of polyubiquitinated proteins in skeletal muscle [6▪]. As previously commented, selectivity in basal autophagy is a crucial feature to ensure a proper quality control mechanism inside the cell. In this regard, TP53INP2 promotes the degradation of polyubiquitinated proteins in skeletal muscle, co-localizes with ubiquitinated protein aggregates in myotubes, and interacts with ubiquitin preferentially when conjugated on a substrate as monoubiquitination or as K63-linked polyubiquitin chains [6▪]. These data suggest that TP53INP2 may be a novel autophagy receptor involved in selective autophagy by interacting with both ubiquitin and LC3, and promoting the degradation of protein aggregates in a similar way as to that described for p62, NBR1, and Alfy [16].

TP53INP2 AND MUSCLE WASTING

Muscle wasting has traditionally been associated with an increase in the activity of the UPS, which promotes the degradation of muscle proteins [1,2,4,27]. However, accumulating evidence supports the notion that autophagy is also highly activated in several conditions that promote muscle wasting, such as starvation, cancer cachexia, hepatic cirrhosis, and diabetes [1,3,4,6▪,20], and contributes to the loss of muscle mass. In keeping with this view, as an autophagy activator, TP53INP2 favors muscle atrophy in mice under a highly catabolic stimulus such as streptozotocin-induced diabetes [6▪]. More specifically, TP53INP2 gain of function increases muscle loss upon diabetes induction, whereas TP53INP2 ablation partially preserves muscle mass [6▪]. However, TP53INP2 enhancement of muscle wasting is blunted by pharmacological inhibition of autophagy or when using muscle atrophy models in which autophagy is shut off, and this process does not participate in muscle loss (such as denervation) [6▪,28].

Another interesting observation is that TP53INP2 is repressed in skeletal muscle in various murine models of muscle atrophy, including db/db mice and streptozotocin-induced diabetes [6▪]. The observation that a protein that promotes muscle wasting is naturally repressed under highly catabolic conditions suggests that this repression is an adaptation of the skeletal muscle to prevent and/or ameliorate muscle loss. In fact, TP53INP2 repression takes place before muscle loss is observed. An example of this occurs in type 2 diabetic patients, in which muscle mass is even higher than in healthy individuals (with the exception of elderly type 2 diabetic individuals) [29]. However, diabetes is not a prerequisite for TP53INP2 repression. Even overweight individuals who start to develop insulin resistance and do not present muscle atrophy display reduced TP53INP2 expression [6▪]. Deficient insulin action is a condition directly linked to an increased catabolism in various tissues, including skeletal muscle. In this regard, the early repression of TP53INP2 is coherent with a mechanism in skeletal muscle destined to maintain muscle mass.

Furthermore, TP53INP2 expression is intimately associated with insulin sensitivity in nondiabetic healthy individuals. More specifically, there is a positive correlation between TP53INP2 mRNA levels and the M index (used to measure insulin sensitivity in humans) in these individuals [6▪].

Considering all these lines of evidence, we propose that TP53INP2 is an allostatic factor that belongs to an adaptative mechanism aimed to maintain skeletal muscle proteostasis (Fig. 2). Allostasis is defined as the maintenance of stability in changing situations and implies that some factors have to change in order to maintain other basic parameters constant in order to allow adaptation to the new conditions [30]. One example of a changing situation may be the development of insulin resistance. Thus, impaired insulin action may lead to an imbalance in protein metabolism in skeletal muscle, thus favoring protein catabolism and enhancing the risk of muscle loss. Thus, TP53INP2 repression under these conditions may reduce the risk of muscle loss by decreasing basal autophagy. In fact, autophagy is reduced in skeletal muscle in mice fed a high-fat diet [31]. In contrast, physiological conditions with high insulin action may cause an excessive inhibition of protein catabolism in skeletal muscle that may be compensated by an increase in TP53INP2 expression and the corresponding increase in basal autophagy (Fig. 2). Thus, the regulation of TP53INP2 may be a mechanism by which to maintain protein homeostasis or the balance between protein synthesis and degradation in skeletal muscle (Fig. 2).

All these properties make TP53INP2 a highly attractive candidate as a putative target to ameliorate muscle wasting. First, TP53INP2 is a positive regulator of autophagy and this process is activated in skeletal muscle during several diseases that cause muscle wasting (i.e. cancer cachexia, hepatic cirrhosis, diabetes, etc.) [1,3,4,6▪,20]. Although evidence

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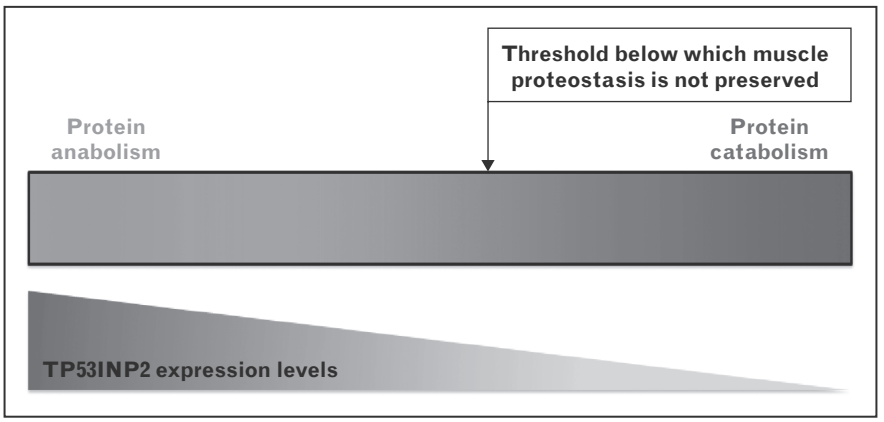

FIGURE 2. TP53INP2 as an allostatic factor in skeletal muscle. TP53INP2 expression in skeletal muscle is intimately related to the state of protein metabolism in this tissue. More specifically, TP53INP2 is repressed in conditions in which protein catabolism is predominant, whereas conditions characterized by increased protein anabolism enhance TP53INP2 expression. These changes in TP53INP2 expression may contribute to the maintenance of skeletal muscle proteostasis and mass that is acceptable for normal tissue function. Under extreme catabolic conditions, these changes in TP53INP2 expression may not be sufficient to maintain skeletal muscle proteostasis within the acceptable range [6▪]. TP53INP2, tumor protein p53-inducible nuclear protein 2.

to date only shows that TP53INP2 expression is regulated in human type 2 diabetes and in several murine models of diabetes [6▪], TP53INP2 may be naturally repressed in other diseases that lead to a highly catabolic state. Hence, further TP53INP2 repression may contribute to reducing the excessive autophagy found in skeletal muscle under other pathological conditions.

Second, TP53INP2 is a regulator of autophagy, but it is not an essential component of the process in skeletal muscle. Thus, the repression of TP53INP2 may be valuable for the treatment of muscle wasting without completely compromising autophagy and thus allowing the maintenance of a certain level of autophagy that is crucial to preserve this quality control mechanism inside the cell.

Finally, given that TP53INP2 repression may be a natural adaptative response, this protein may become an interesting target for the prevention of muscle loss in patients with a high risk of developing this condition, such as patients with advanced cancer. Thus, the pharmacological repression of TP53INP2 in patients before they present muscle loss may provide a strategy to prevent this process, and to enhance not only patients' quality of life but also their resistance to aggressive treatments such as chemotherapy.

CONCLUSION

Further studies are required to fully understand the relevance of TP53INP2 in regulating skeletal muscle mass and how this regulation is associated with protein metabolism in this tissue. First, the specific mechanisms through which TP53INP2 exerts its function are still not completely understood. What is known so far is that TP53INP2 binds LC3 family members and ubiquitin [6▪,22]. However, how TP53INP2 interacts with the other machinery required to generate autophagosomes is still unknown. Second, it is imperative to determine the impact of TP53INP2 on skeletal muscle mass in pathological conditions (such as cancer cachexia and chronic kidney disease) other than human insulin resistance and murine diabetes, and to define how TP53INP2 expression is regulated in these contexts. More specifically, the identification of the signaling pathways and transcription factors involved in the regulation of TP53INP2 expression will be highly valuable to define and characterize an adaptative mechanism aimed to preserve skeletal muscle proteostasis and in which we postulate that TP53INP2 is involved. In fact, on the basis of the data obtained to date, one of the putative factors may be insulin *per se* [6▪,21]. However, given that TP53INP2 expression probably depends on the metabolic state of the muscle, other regulators of skeletal muscle metabolism may also be involved.

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Conflicts of interest

There are no conflicts of interest.

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