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Lysosomal dysfunction in muscle with special reference to glycogen storage disease type II

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Abstract

The importance of proper lysosomal activity in cell and tissue homeostasis is underlined by "experiments of nature", i.e. genetic defects in one of the at least 40 lysosomal enzymes/proteins present in the human cell. The complete lack of 1-4 α-glucosidase (glycogen storage disease type II (GSD II) or Pompe disease) is life-threatening. Patients suffering from GSD II commonly die before the age of 2 years because of cardiorespiratory insufficiency. Striated muscle cells appear to be particularly vulnerable in GSD II. The high cytoplasmic glycogen content in muscle cells most likely gives rise to a high rate of glycogen engulfment by the lysosomes. The polysaccharides become subsequently trapped in these organelles when 1-4 α-glucosidase activity is absent. During the course of the disease, muscle wasting occurs. It is hypothesised that the gradual loss of muscle mass is caused by a combination of disuse atrophy and lipofuscine-mediated apoptosis of myocytes. Moreover, we hypothesise that in the remaining skeletal muscle cells, longitudinal transmission of force is hampered by swollen lysosomes, clustering of non-contractile material and focal regions with degraded contractile proteins, which results in muscle weakness.

Keywords: Lysosomal storage; Muscle; Glycogen storage; Lipofuscine; Muscle mechanical performance

1. Introduction

Lysosomal storage diseases are a group of inborn metabolic disorders characterised by accumulation of non-metabolised material inside lysosomes. In the majority of these diseases the pathology is severe, leading to disabilities and often to death. In general, each of the approximately 40 lysosomal enzymes can be affected by a genetic defect [1–3]. Table 1 provides an overview of lysosomal enzymes currently known and of pathological conditions due to impaired synthesis and/or activity.

In one of the most frequently occurring lysosomal storage diseases, i.e. lysosomal glycogen storage disease type II (GSD II), muscle tissue is primarily affected. The hallmarks of this syndrome are skeletal muscle weakness and hypertrophy of the heart as described for the first time in 1932 by the Dutch physician Pompe [4]. In 1963, it was convincingly shown that GSD II is caused by deficiency of the enzyme acid 1-4 α-glucosidase (EC 3.2.1.20) [5]. This defect results in accumulation of glycogen inside the lysosome in a variety of tissues including smooth and striated muscle. As both heart and skeletal muscle are functionally affected, patients eventually suffer from cardiorespiratory failure [6]. The pace of progression of this disease is primarily determined by the residual activity of acid 1-4 α-glucosidase. Patients with a complete lack of enzyme activity die before they are 2 years old [7]. In contrast, patients with more than 25% residual activity hardly show clinical symptoms [8]. The frequency of the various forms of GSD II is estimated to be 1 out of 40,000 births [9].

In this review, attention will be paid to the structure and function of lysosomes in general, to the assembly of lysosomes and the synthesis of lysosomal enzymes, and to the biological activity of lysosomes. Moreover, lysosomal storage disease as a consequence of a genetic defect will be discussed, with special emphasis on GSD II. Finally, a novel hypothesis will be presented explaining

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Table 1
Lysosomal enzymes and related storage diseases

Lysosomal enzyme	Disease
Lipid metabolism	
Cathepsin A	galactosialidosis
β-Galactosidase	GM1-gangliosialidosis (Landing)
Hexosaminidase A and B (β-chain)	GM2-gangliosialidosis (Sandhoff)
Hexosaminidase A and S (α-chain)	GM2-gangliosialidosis (Tay–Sachs)
β-Galactocerebrosidase	galactocerebrosidosis (Krabbe)
Glucocerebrosidase	glucocerebrosidosis (Gaucher)
Sphingomyelinase	sphingomyelin lipidosis (Niemann–Pick A, B)
Acid lipase	cholesteryl ester storage disease (Wolman)
Arylsulfatase A	metachromatic leukodystrophy
α-Galactosidase A	Fabry
Glycoprotein metabolism	
Aspartylglucosaminidase	aspartylglucosaminuria
α-L-Fucosidase	fucosidosis
α-*N*-acetylneuraminidase	sialidosis/mucolipidosis I
α-*N*-acetylgalactosaminidase	Schindler disease
β-Galactosidase	galactosialidosis
α-Neuraminidase	galactosialidosis
α-Mannosidase	α-mannosidosis
β-Mannosidase	β-mannosidosis
Mucopolysaccharide metabolism	
α-L-Iduronidase	MPS I (Hurler/Scheie)
Iduronate-sulfate sulfatase	MPS II (Hunter)
Heparansulfate sulfatase	MPS IIIA (Sanfilippo A)
N-acetyl-α-D-glucosaminidase	MPS IIIB (Sanfilippo B)
Acetyl transferase	MPS IIIC (Sanfilippo C)
α-*N*-acetylglucosamine 6-sulfatase	MPS IIID (Sanfilippo D)
N-acetylgalactosamidase-6-sulfate sulfatase	MPS IV (Morquio A)
β-Galactosidase	MPS IVB (Morquio B)
Arylsulfatase B	MPS VI (Maroteaux–Lamy)
β-Glucuronidase	MPS VII (Sly)
Various lysosomal functions	
Acid 1-4 α-glucosidase	glycogenosis type II (Pompe)
Cathepsin K	pycnodysostosis
Prosaposin (sphingolipid activator)	complex lipidosis
GM2 activator (sap3)	GM2-gangliosialidosis/AMB variant
Palmitoyl-protein thioesterase	infantile neuronal ceroid lipofuscinosis
Pepstatin-insensitive peptidase	juvenile neuronal ceroid lipofuscinosis
(Deficient) cholesterol recycling	cholesterollipidosis (Niemann–Pick C)
Other lysosomal enzymes	
Acid phosphatase (LAP)	no pathology described in humans
Cathepsin B	no pathology described in humans
Cathepsin D	no pathology described in humans
Cathepsin L	no pathology described in humans
Tartrate-resistant acid phosphatase (TRAP)	no pathology described in humans

Based on Gieselmann [1] Bijvoet [71] and Michalski and Klein [79].

the impairment of muscle mechanical function of patients suffering from GSD II.

2. Structure and function of lysosomes

Lysosomes are organelles originating from the endoplasmatic reticulum [10]. Usually, the diameter of a mature lysosome varies from 400 to 500 nm. The lysosomal membrane consists of a phospholipid bilayer that envelops an acidic environment (pH 4–5) in which at least 40 enzymes/proteins are active. To avoid autolysis of the lysosomal membrane, the internal side of the membrane is protected by various forms of lysosome-associated membrane proteins (LAMPs), which contain numerous sialic acid-rich oligosaccharides [11,12]. Vacuolar (H^+)-ATPases maintain the low internal pH of the lysosomes [13].

The main function of the lysosomal system is to engulf and subsequently digest macromolecules. In general, these are either damaged or non-functional compounds from endogenous origin, or exogenous substances and microorganisms that penetrated the cell membrane. Each of the lysosomal enzymes is able to break a specific chemical bond of the engulfed material. Although spatial separation of metabolic activity within the lysosomes is most likely absent, it is believed that the lysosomal enzymes are able to coagulate to form enzyme hypercomplexes that effectively degrade the internalised macromolecules [14]. The degradation products are actively or passively transferred back from the lysosomal interior into the cytoplasm, and can be re-utilised for the synthesis of functional molecules. Recent studies indicate that LAMPs might also be involved in the transport of lysosomal degradation products through the lysosomal membrane [11]. It is tempting to speculate that in the phagocytic process some macromolecules, such as cytoplasmic glycogen, are inadvertently engulfed by the lysosome. To get rid of this 'by catch', the polysaccharides have to be hydrolysed by acid 1-4 α-glucosidase and the glucose molecules produced must be transported back into the cytoplasm, most likely by the facilitating action of LAMP2 [15].

Initially, it was assumed that lysosomes were largely involved in the hydrolysis of tissue proteins [16]. However, in the last decade, several studies have provided evidence that the cytoplasmic ubiquitin proteasome system also substantially contributes to the degradation of contractile and cytoskeletal proteins in muscle tissue [17–23]. There are indications that lysosomes are preferentially involved in the degradation of mitochondrial and sarcolemmal proteins, and in the process of membrane turnover [24,25]. In addition, ligand/receptor uncoupling is accomplished by engulfment of the entire complex and subsequent intra-lysosomal proteolysis [26].

3. Lysosome assembly

Like any cellular structure, the assembly of lysosomes starts with the transcription of genes encoding their specific proteins. Transcription of genes and translation of mRNA encoding for the different lysosomal enzymes is inherently complex [27–29]. Most of the lysosomal genes described so far lack the specific TATA and CAAT motifs adjacent to the transcription start site. The absence of these motives in the promoter region is characteristic for mammalian ''housekeeping'' genes [30]. The expression of the individual lysosomal enzymes is not mutually linked, and the lysosomal content of distinct enzymes may differ between tissues and metabolic situations [31]. Information on the regulatory mechanisms underlying lysosomal protein expression is still very fragmented, but points towards a multitude of factors that are able to influence gene transcription and mRNA translation of the distinct lysosomal enzymes [28,32–35]. These include, among others, hormones (e.g. growth hormone and insulin) and metabolically challenging situations such as starvation [36].

Though the precise regulation of gene expression of lysosomal proteins is still incompletely understood, detailed information on post-translational handling of lysosomal enzymes is available [37–39]. Precursors of lysosomal enzymes are synthesised in the cytoplasm at the endoplasmatic reticulum. Substantial post-translational modification occurs in subsequent steps required for the transport of (pro)enzymes to the lysosomes. Maturation of the precursors of lysosomal enzymes involves processes in the endoplasmatic reticulum and the Golgi complex, where protein folding and chemical modification through the addition of carbohydrate chains (i.e. attachment of mannose 6-phosphate (M6P) groups) take place. These M6P groups are in the trans-Golgi network recognized by M6P receptors and subsequently bound. These receptor/ligand complexes are packaged into clathrin-coated vesicles that fuse with endosomes, where the ligand is released. The M6P receptor returns to either the trans-Golgi network or the cell surface. To avoid autolysis, lysosomal pro-enzymes usually contain a pro-peptide region, i.e. a polypeptide chain that blocks their active site as long as the enzyme is not transferred into the lysosome. In general, the abovementioned polypeptide chain is removed by proteolytic processing by cathepsins. This step subsequently results in the activation of the lysosomal enzyme.

4. Biological activity of lysosomes

Lysosomes are present in all eukaryotic cells. Their specific activity appears to differ between tissues and species, and is age-dependent [40]. In spleen and liver, lysosomal activity is reported to be high, in differentiated muscle tissue it is low [12]. During cellular differentiation, lysosomes appear to be of importance, as the activity of at least a number of lysosomal enzymes is increased in differentiating tissue [41]. Moreover, the activity of lysosomal enzymes, particularly the cathepsins, is high during development of muscle tissue [42], while during ageing the activity diminishes [40].

Whereas the activity of the lysosomal system differs between tissues, it also depends on the metabolic status of the organ or organism. Several stimuli have been identified that regulate lysosomal activity, none of which however is exclusively targeting the lysosome. In starvation and other catabolic situations, the activity of lysosomal enzymes in the muscle, especially cathepsin-L, is increased [43,44]. This resulted in enhanced proteolysis, most likely due to an increased lysosomal contribution to protein degradation [43,44]. In inflammation, cancer cachexia, hyperthyroidism and various neuromuscular disorders the activity of a selected number of lysosomal enzymes was found to be increased as well [16,45–49]. A variety of hormonal stimuli (e.g. insulin, growth hormone, catecholamines, and clenbuterol) are exerting a negative effect on lysosomal activity [48,50]. Experimental studies have revealed that pharmacological agents are able to decrease the activity of the lysosomal system in vitro [51–54].

Due to the complexity of the system, it is comprehensible that the majority of factors capable of influencing lysosomal activity have not yet been fully identified. In the cases mentioned above, little information is available on the cellular signalling pathway through which lysosomal activity is modulated. Moreover, it is not clear whether the observed changes in activity could be ascribed to an altered number of lysosomes in the cells or to a specific change in the activity of the lysosomal enzymes under investigation.

5. Common features in lysosomal storage diseases

Lysosomal storage diseases comprise a group of over 30 different syndromes. Commonly a division in lipidoses, mucopolysaccharidoses and disorders of glycoprotein degradation is made (Table 1). The common denominator of these syndromes is a deficiency of one lysosomal enzyme/protein, usually the result of a genetic disorder. If either an enzyme or a transport protein is affected, progressive accumulation of the corresponding, non-metabolized substrate within the lysosome occurs. The lack of activity is usually generalised, and accumulation of material is observed in lysosomes of all tissues.

The consequences of the lack of activity of one specific lysosomal enzyme on the overall lysosomal function is only partially understood. Commonly, the dimensions of the lysosomes appreciably increase in lysosomal storage syndromes [55]. While the volume increases, the intra-lysosomal pH must be kept low to ensure proper function of the lysosomal enzymes. However, it is unlikely that the proton pumps in the lysosomal membrane are able to entirely cope with a substantial increase in lysosomal volume [56]. This

may imply that in lysosomal storage diseases, lysosomal pH gradually rises and that the actual activity of originally unaffected lysosomal enzymes declines with the progression of the disease.

As indicated in more detail above, the formation of lysosomes is a complex process which involves a number of steps (transcription, translation, trafficking of primary proteins, post-translational modification). Therefore, the molecular origin of the lysosomal dysfunction can differ even within a particular storage syndrome. In GSD II, for instance, over 40 polymorphisms are described [57]. In the majority of lysosomal storage disorders the relationship between genotype and phenotype is poorly understood. Almost all lysosomal storage diseases show an appreciable variability in clinical progression, and the onset and progression of symptoms vary with the residual activity of the affected enzyme. In many lysosomal storage diseases, a distinction in a severe infantile, an intermediate juvenile and a mild adult form is made. This classification is somewhat arbitrary as it represents a continuum of clinical severity, and it is safe to assume that the accumulation of undigested material already starts during the fetal stage in all patients.

A common feature observed in lysosomal storage disorders is the formation of lamellar, roundly shaped electron dense structures within cells. These structures are indicated by a variety of names such as ceroid, myelin figures, electron dense bodies or lipofuscin. Since lipofuscin accumulation is typical in lysosomal storage disorders, the mechanism underlying and the functional consequences of lipofuscin formation are discussed in more detail below.

6. Mechanisms underlying lipofuscin formation

Lipofuscin is formed in the lysosomes, most likely after peroxidation of autophagocytized material [58]. The chances that this material becomes peroxidized in the free radical-rich environment of the lysosome rise when the amount of undigested material and/or its dwelling time inside the lysosome increase. In lysosomal storage diseases, the size of the lysosomes can increase several fold as a result of accumulation of undigested material. In addition, osmotic swelling might occur. In case of lysosomal glycogen storage, the hygroscopic properties of glycogen will also promote lysosomal swelling. As indicated above, swelling of lysosomes most likely increase the intra-lysosomal pH when the proton pumps in the lysosomal membrane fail to maintain the H^+ gradient over the membrane [59]. Since lysosomal enzymes are less active at elevated pH, passage time of the engulfed material will increase. This in turn most likely leads to increased formation and deposition of lipofuscin. In tissue with a high cell turnover, enhanced deposition of lipofuscin may not harm the cell, as the cells are most likely removed before lipofuscin accumulation becomes detrimental. In tissues with a relatively stable cell population such as liver, muscle and nerve tissue, lysosomal lipofuscin formation might exert large effects. As the regenerative capacity of these tissues is relatively limited, damaged cells are not, or not in sufficient numbers, replaced in time. This consideration may explain why, despite the fact that the lysosomal dysfunction is usually generalised, the pathological features are most prominent in tissues with relatively stable cell populations.

Experiments exploring the effect of a decline in lysosomal activity have been performed in a variety of cultured cell types [52,54,60,61]. In all experiments where lysosomal activity was diminished, cells rapidly develop an abnormal appearance. In general, lipofuscin accumulation is a common and prominent feature. It is of interest to note that in senescent cells, where lysosomal activity also declines, lipofuscin accumulation becomes apparent as a typical feature of physiological ageing [62,63].

7. Putative functional consequences of lipofuscin accumulation

Though the pathological significance of accumulation of lipofuscin in the cells is not fully understood, several studies strongly suggest that cellular accumulation of this material is a trigger for cell death [64–66]. Nakae et al. [67] found a significant correlation between lipofuscin accumulation and apoptosis in the diaphragm muscle of mdx mice, a well-established model for Duchenne muscle dystrophy. They hypothesised that lipofuscin accumulation was caused by elevated oxidative stress. Since satellite cells in the diaphragm of mdx mice also showed lipofuscin granules as well as apoptosis, it was concluded that the regenerative capacity of the diaphragm muscle was severely depressed. As a consequence, overall diaphragm function is impaired, which might eventually cause respiratory insufficiency.

As tissue degeneration readily occurs in lysosomal storage diseases, the question remains whether the cells become jeopardised due to improper functioning of the lysosomal system in general, or due to cellular accumulation of lipofuscin in particular. Since exposure to mild oxidative stress triggers lipofuscin formation, this experimental condition can be used to discriminate between these two options. The mortality rate both of cells with blocked lysosomal function and of cells exposed to mild oxidative stress was found to be high. This finding might suggest that accumulation of lipofuscin rather than improper functioning of the lysosomes per se causes cell death.

It has been shown that accumulation of lipofuscin is reversible, when the extent of accumulation is relatively small, and lysosomal function is restored in due time [68]. Since the mortality rates of the rescued cells returned to normal, these findings may have important clinical implications. It can be inferred that therapies aiming to restore proper lysosomal function, such as enzyme replacement therapy, should be started before a critical amount of lipofuscin has been accumulated in the affected cell.

8. Muscular dysfunction in GSD II

GSD II is the result of a genetic defect in the acid 1-4 α-glucosidase gene resulting in an insufficient degradation of glycogen inside the lysosomes. From an energetic point of view, the amount of glycogen accumulating within the lysosomes is inconsequential. It is unlikely that it creates a shortage of glucose required for glycolytic and oxidative energy conversion. This notion is supported by the observation that the muscle content of high-energy phosphates in an experimental knockout mouse model for GSD II was equal to that in non-affected controls [69].

As the genetic defect is generalised, the question remains why particular muscular tissues are severely affected in GSD II. A major cause is most likely the high concentration of glycogen in the cytoplasm of cardiac and skeletal muscle cells. As pointed out above, cytoplasmic glycogen is most likely inadvertently engulfed by the lysosome and, hence, lysosomal sequestration of this carbohydrate is most pronounced in muscle cells when 1-4 α-glucosidase activity is impaired. Since hepatocytes also contain relatively high levels of cytoplasmic glycogen it is of interest to note that despite the fact that glycogen accumulates in hepatic lysosomes to the same extent as in myocytes [6], patients suffer from muscular insufficiency rather than from liver malfunction in GSD II.

Both clinical studies in GSD II patients [70] and experimental investigations in 1-4 α-glucosidase null mice ($AGLU^{-/-}$) [71] show that impaired muscle function is a prominent feature of this disease. Developed force by hind limb muscles of $AGLU^{-/-}$ mice fell by approximately 50% when the animals reached the age of 18 months [69]. This decline in mechanical function could be partially explained by loss of muscular mass. Compared to age-matched controls, the wet weight of the hind limb muscle was on the order of 25% less in $AGLU^{-/-}$ mice. The precise cause of muscle wasting in GSD II is unknown, but one may speculate that lipofuscin-mediated apoptosis contributes to this process. Recent findings in $AGLU^{-/-}$ mice are in support of this notion. In regions of the affected muscle cell with marked lipofuscin deposits, nuclei with typical apoptotic features were readily observed (Hesselink, unpublished findings). Under normal conditions, these regions could regenerate by the action of satellite cells [72,73], but in GSD II, satellite cells may be affected as well. In this respect, it is worth to mention that in the diaphragm of mdx mice, the presence of lipofuscin precipitates was associated with satellite cell apoptosis and, hence, a substantial decline in regenerative capacity [74]. If a similar process occurs in satellite cells in GSD II patients and $AGLU^{-/-}$ mice, muscle wasting is inevitable.

Since the loss of skeletal muscle mass cannot fully account for the decline in muscular developed force [69], additional factors exerting a negative effect on mechanical performance should be considered. Recently, we hypothesised that direct mechanical effects of the non-contractile inclusions impair muscle strength [69]. Even in the early stages of GSD II, lysosomal volume is substantially increased. These swollen lysosomes (Fig. 1) disturb the highly organized architecture of the contractile machinery by interruption of myofibrils. Lysosomes do not contribute to the generation of force and are unlikely to be attached to

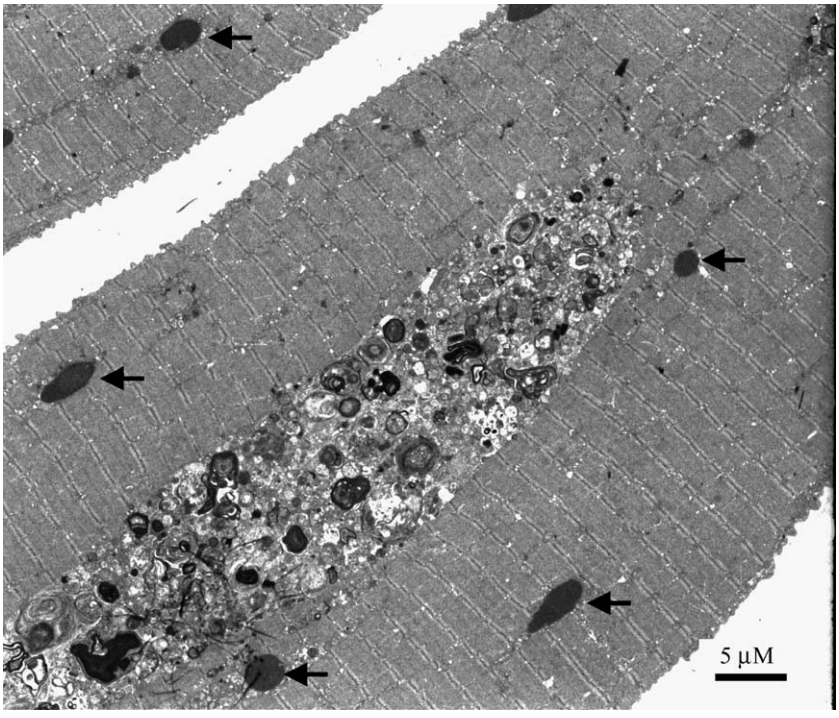

Fig. 1. Muscle fiber of an $AGLU^{-/-}$ mouse in an advanced stage of GSD II. Arrows indicate swollen lysosomes.

the contractile machinery. Therefore, shortening of sarcomeres of the interrupted myofibrils near the site of interruption is likely to occur. As force can be transmitted from interrupted to non-interrupted myofibrils by shearing, elongation of sarcomeres of the non-interrupted myofibrils adjacent to the lysosome will occur at the same time. This will decrease the total force of a bundle of myofibrils centred around an inclusion because inhomogeneities in sarcomere length develop during contraction. These inhomogeneities diminish the force generating capacity of the entire bundle.

By means of a recently developed numerical model of contracting muscle which makes use of the Finite Element Method [75], the loss of mechanical performance was calculated as a function of the volume density of glycogen-filled lysosomes. At a density of 15%, reflecting the situation in muscles of 12-month-old AGLU$^{-/-}$ mice, the loss in mechanical performance was calculated to be about 25% (Drost, unpublished results). This implies that about half of the observed loss in muscle function may be caused by hampering of mechanical activity by the swollen lysosomes.

When GSD II progresses, deposits of extra-lysosomal material also become apparent in the affected muscle cells (Fig. 1) [76,77]. Electron microscopical analysis revealed that at the borders of the large inclusions, degradation of myofibrillar material occurred and that degraded myofibrils were often present inside these inclusions. This focal myofibrillar degradation will directly affect mechanical performance.

In more progressed stages of GSD II, short cell segments show degeneration over their entire cross-section. Apoptotic nuclei are present in these regions and the contractile material is in complete disarray while the basal membrane remains intact. In this situation, force is most likely transmitted to adjacent cells. Though cell to cell transmission of forces has been shown to be very effective in healthy muscles [78] it remains to be seen whether this is also the case in muscles of which most fibres are structurally in disarray.

Although all striated muscles are affected, the decline in mechanical function in cardiac and respiratory muscle is most life threatening. In the clinical situation, patients suffering from a complete lack of 1-4 α-glucosidase activity commonly die before the age of 2 years, because of cardiorespiratory insufficiency. In the past, all therapeutic measures to relieve the severity of the disease failed. Very recently, a breakthrough was reached by treatment of a limited number of very young patients with recombinant human 1-4 α-glucosidase [70]. In the two youngest of the four children included in the study at an early stage of their disease, clinical signs of GSD II remained absent and patients showed a normal development after treatment with recombinant human 1-4 α-glucosidase [70].

In summary, a brief overview has been provided on the structure, assembly and biological function of lysosomes. Special attention was paid to one particular kind of lysosomal dysfunction due to a genetic defect, i.e. 1-4 α-glucosidase deficiency. Lack of this enzyme particularly affects the cardiorespiratory system since mechanical performance of striated muscle is severely depressed. Skeletal muscle wasting, either a result of apoptosis or disuse atrophy, substantially contributes to the loss of force generation. Furthermore, it has been hypothesised that longitudinal force transmission inside the remaining myocytes is hampered by increased lysosomal dimensions, cytoplasmic deposition of non-contractile material and focal regions of contractile protein degradation.

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