**Table 4**
Identity of proteins whose carbonylation or expression changes 2 days after exercise, in comparison with nonexercised, in wild-type or *mdx*.

| | Protein carbonylation after LIT (2 days after the last exercise) | | | | | Protein expression after LIT (2 days after the last exercise) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Spot No. [a] | Accession No. [b] | Protein name | Fold change [c] | Spot No. [d] | Accession No. [b] | Protein name | Fold change [c] |
| Wild type | ↑ | Mitochondria | | | | ↑ Glycolysis | | | |
| | | 38 | Q9D0K2 | SuccinylCoA:3ketoacid coenzyme A transferase 1 | 10 | B8 | P21550 | Beta-enolase | 5.26 |
| | | 26 | Q99KI0 | Aconitate hydratase, mitochondrial | 2.85 | | | | |
| | | Muscle contraction | | | | | | | |
| | | 46 | Q9QZ47 | Troponin T, fast skeletal muscle | 4.16 | | | | |
| | | 18 | Q5XKE0 | Myosin-binding protein C, fast-type | 1.66 | | | | |
| | | Glycogen metabolism | | | | | | | |
| | | 37 | Q91ZJ5 | UTP-glucose-1-phosphate uridylyltransferase | 5 | ↓ | | | |
| | | Others | | | | | | | |
| | | 46 | P07310 | Creatine kinase M-type | 4.16 | | | | |
| | ↓ | Cytoskeleton | | | | | | | |
| | | 5 | P68372 | Tubulin beta-4B chain | -5.93 | | | | |
| | | Spot No. [a] | Accession No. [b] | Protein name | Fold change [c] | Spot No. [d] | Accession No. [b] | Protein name | Fold change [c] |
| *mdx* | ↑ | | | | | ↑ Mitochondria | | | |
| | | | | | | B7 | P56480 | ATP synthase subunit beta, mitochondrial | 3.57 |
| | | | | | | B6 | Q03265 | ATP synthase subunit alpha, mitochondrial | 3.33 |
| | ↓ | Mitochondria | | | | 42 | Q91YT0 | NADH dehydrogenase [ubiquinone] flavoprotein 1 | 2.63 |
| | | 54 | Q60932 | Voltage-dependent anion-selective channel prot 1 | -8.22 | 25 | Q99KI0 | Aconitate hydratase, mitochondrial | 2 |
| | | Muscle contraction | | | | Muscle contraction | | | |
| | | 54 | Q9QZ47 | Troponin T, fast skeletal muscle | -8.22 | 53 | Q9QZ47 | Troponin T, fast skeletal muscle | 3.03 |
| | | 46 | Q9QZ47 | Troponin T, fast skeletal muscle | -3.83 | 52 | Q9QZ47 | Troponin T, fast skeletal muscle | 2.27 |
| | | 18 | Q5XKE0 | Myosin-binding protein C, fast-type | -1.76 | 18 | Q5XKE0 | Myosin-binding protein C, fast-type | 1.96 |
| | | Glycogen metabolism | | | | Glycogen metabolism | | | |
| | | 35 | Q9D0F9 | Phosphoglucomutase-1 | -4.25 | 37 | Q91ZJ5 | UTP-glucose-1-phosphate uridylyltransferase | 1.64 |
| | | 24 | Q9WUB3 | Glycogen phosphorylase, muscle form | -3.03 | Stress response | | | |
| | | Glycolysis | | | | 10 | P21550 | Carbonic anhydrase 3 | 4.16 |
| | | 40 | P52480 | Pyruvate kinase isozymes M1/M2 | -6.27 | ↓ Glycolysis | | | |
| | | Cytoskeleton | | | | 16 | P21550 | Beta-enolase | -1.63 |
| | | 4 | P31001 | Desmin | -2.4 | | | | |
| | | Others | | | | | | | |
| | | 46 | P07310 | Creatine kinase M-type | -3.83 | | | | |

↑Refer to proteins whose carbonylation is higher in *mdx* than in wild-type muscle.
↓Refer to proteins whose carbonylation is lower in *mdx* than in wild-type muscle.
X spots refer to annoted spots in Fig. 3, BX to annoted spots in Fig. 4.

[a] Spots refer to annoted spots in Fig. 2.
[d] Spots refer to annoted spots in Fig. 2.

of protein carbonylation were not identified until late. Consistent with our observations (spots 25 and 26 in Fig. 3), a recent study on tibialis anterior muscle of DMD patients [16] showed aconitate hydratase to be overcarbonylated. Also in agreement with our study, mitochondrial proteins appeared to be preferential targets of carbonylation in dystrophic muscle. However, we showed that these proteins were not equally affected by oxidative stress. We found two major groups of proteins: those from the citric acid cycle (Table 1A) and those from the respiratory chain (Tables 2 and 3A). Citric acid cycle proteins were overcarbonylated, consistent with the fact that the function of these proteins was impaired in *mdx* muscle [44]. In contrast, respiratory chain proteins were not overcarbonylated. This suggests that the impact of oxidative stress on mitochondria of *mdx* muscle depends on protein location, since citric acid cycle proteins are mainly located in the matrix, whereas those of the respiratory chain are located in the inner membrane [45].

We also found that other groups of proteins were over carbonylated in *mdx* muscle: those involved in the modulation of contraction, in glycogen metabolism, and in the formation of the cytosketelon. A functional impairment of the proteins of the first group, namely the fast isoforms of troponin T and MyBP-C, has not been reported in DMD. On the other hand and consistent with a recent study, in which a reduced activity of glycogen phosphorylase was observed in *mdx* muscle [46], we found this enzyme to be overcarbonylated. Among proteins involved in formation of the cytoskeleton, we found overcarbonylated levels of actin-associated proteins, such as LIM domain-binding protein 3 and F-actin-capping protein subunit alpha-1. This is consistent with the finding that the actin filament architecture is severely damaged in *mdx* muscle [47]. Taken together our results suggest that protein carbonylation could cause a functional impairment in *mdx* muscle.

*Protein expression in skeletal muscle of nonexercised mdx mice*

Differences in protein expression between wild-type and *mdx* muscles have been widely documented. Our results (Tables 2 and 3A;

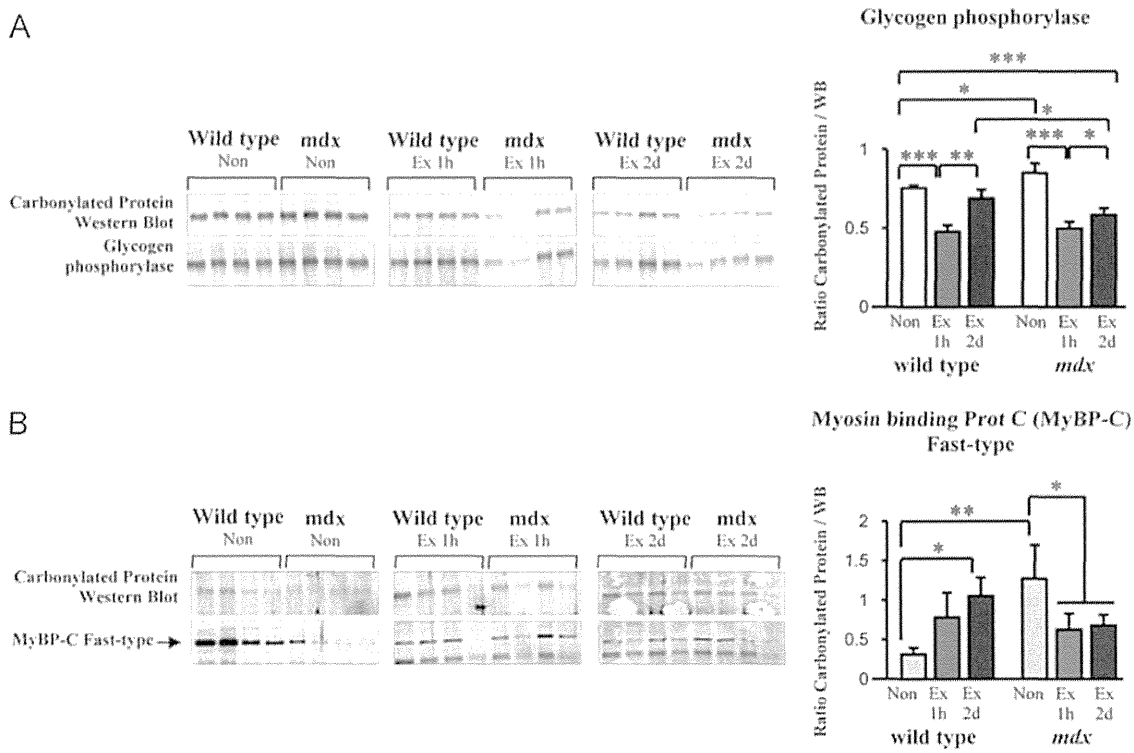


**Fig. 6.** Validation of proteomic results by 1D carbonylated protein Western blot. Carbonylation levels of glycogen phosphorylase (A) or myosin binding protein C (B) were confirmed by coimmunoprecipitation with corresponding antibodies, followed by 1D carbonylated protein Western blot. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ means a significant difference between two groups. $n = 4$–6 per group.

Figs. 4 and 5) are in agreement with previous ones. In particular, we found a downregulation of proteins of the respiratory chain [48] as well as glycogen metabolism [46]. Again consistent with previous reports, vimentin [49], tubulin [50], several enzymes involved in glycolysis [51], and lactate deshydrogenase [52] were overexpressed. Downregulation of fast isoforms of troponin T and MyBP-C have also been reported [53]. As hypothesized, the majority of overcarbonylated proteins were downregulated. However, some proteins of the citric acid cycle, of glycolysis, and of the actin cytoskeleton (27, 28, 29, and 40, 55 in Table 1A and Fig. 3) were overcarbonylated but not downregulated. We suppose the turnover of these proteins to be slower and therefore they might accumulate more oxidative modifications before being degraded.

*Protein–protein interactions in skeletal muscle of nonexercised mdx mice*

Our BN-PAGE analysis showed, for the first time, that ATP synthase subunits α and β were absent in nonexercised *mdx* muscle (Table 3D and Fig. 5). The molecular weights of these complexes correspond to fully assembled monomeres and dimers of ATP synthase, namely 597 and 1194 kDa [54]. This result is consistent with previous findings reporting that the expression of ATP synthase subunit α was not changed in *mdx* muscle, but ATP production was reduced because of a proton leak in the inner mitochondrial membrane [55]. Our study suggests that incomplete formation of the ATP synthase complex in *mdx* muscle could be a cause of this proton leak.

*Effect of low intensity training on skeletal muscle of mdx mice*

The major result of our study is that overcarbonylation, downregulation, and loss of protein–protein interactions in *mdx* muscle are fully corrected by LIT. Swimming is an endurance exercise, and known to affect proteins involved in the respiratory chain, glucose uptake, citric acid cycle, fatty acid metabolism, glycolysis, and oxygen transfer [56]. We found that LIT reduced carbonylation levels and increased the expression of proteins involved in mitochondria function, muscle contraction, glycogen metabolism, and glycolysis (Table 4), but not of proteins involved in glucose uptake, oxygen transfer, or fatty acid metabolism. Previous studies revealed that the destabilization of microtubule networks affects the glucose uptake in *mdx* muscle [57]. LIT was not able to counterbalance this effect, consistent with the fact that cytoskeleton protein remained overexpressed in exercised *mdx* muscle (Table 2).

*Low intensity training is more efficient on mdx muscle than on wild type*

Interestingly, the effects of LIT were more pronounced in *mdx* than in wild-type muscle. In the latter, exercise increased protein carbonylation but had little influence on their expression. In contrast, in *mdx* muscle, exercise reduced protein carbonylation and increased their expression. These results highlight differences in sensitivity to training between wild-type and *mdx* muscle.

*Swimming improves expression of slow and fast isoforms of troponin T and MyBP-C*

Pharmacologic agents have been developed during the past years in an attempt to mimic the effects of aerobic exercise on wild-type [58] or *mdx* muscle [59]. Some of these agents improved *mdx* muscle strength and increased the expression of utrophin A and slow myosin heavy chain isoforms through a shift from fast to slow fibers. In our study, we showed that LIT decreased carbonylation and increased the expression level of fast isoforms of troponin T and MyBP-C, and also stimulated the expression of their slow isoforms (Fig. 7). These results encourage investigating the effects of exercise mimicking drugs on a larger scale of muscle proteins, especially regarding their isoforms in fast muscle.

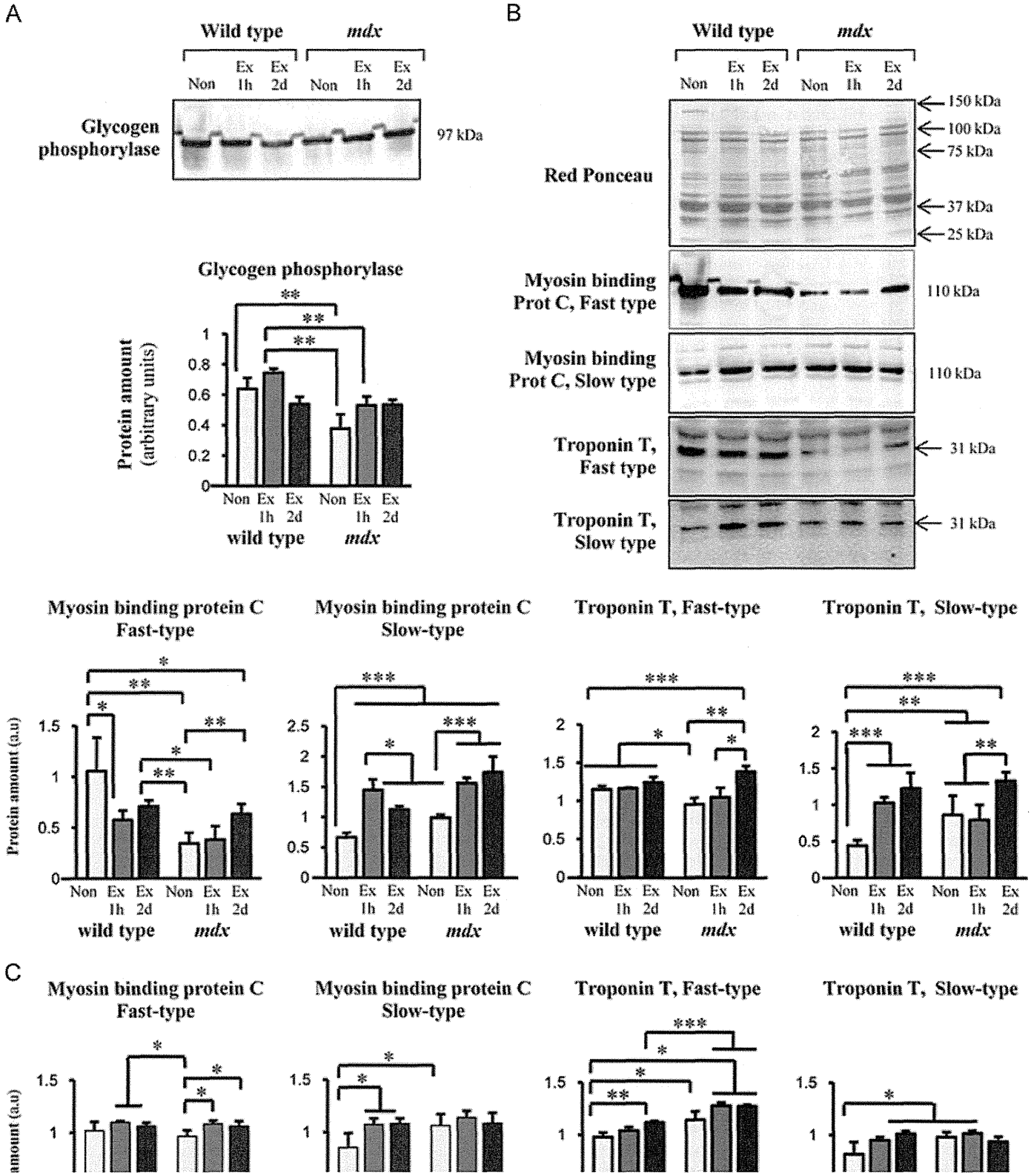


**Fig. 7.** Expression of slow and fast troponin T and myosin binding protein C isoforms. Protein expression level of glycogen phosphorylase (A), then troponin T and myosin binding protein C slow and fast isoforms (B), was assessed by Western blot using corresponding antibodies. Ponceau red staining is shown as loading control. mRNA level was assessed by PCR analysis (C). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ means a significant difference between two groups. $n = 4$ per group.

*Multiple proteins identified in a single spot*

High sensitivity MALDI TOF/TOF analysis [60] revealed that 22% of spots from 2D electrophoresis gels and 33% of spots from BN-PAGE gels contained multiple proteins (Supplementary Fig. 1). Because it was difficult to determine which proteins underwent changes, we limited our analysis to observations made in previous publications or consistent with other results. Using this approach, we detected, for example, an increased expression of vimentin and tubulin alpha1B chain in nonexercised mdx muscle (spot 3 in

Figs. 3 and 4), as reported previously [50]. This result is consistent with the increased expression of desmin and tubulin beta 4B chain (spot 4 and 5 in Figs. 3 and 4). Along similar lines, glycogen phosphorylase and SERCA1 were identified in the same spot (B13 in Fig. 5). Downregulation of glycogen phosphorylase has been previously reported [46] and is noted under Results. However, downregulation of SERCA1 has not been documented and is not noted.

*Influence of infiltrated immune cells on proteomic analysis of exercised mdx mice*

In dystrophic muscle, infiltration of immune cells occurs during early stages of the disease and plays a role in progression of DMD pathology [61]. In *mdx* mice, this infiltration reaches a peak between 4 and 8 weeks of age, which corresponds to the period of LIT. We need to evaluate the extent of infiltrated cells, since they may influence results of our proteomic analysis on nonexercised and exercised wild-type and *mdx* samples.

According to Evans et al., at 8 weeks of age, macrophages are the principal immune cells that infiltrate *mdx* muscles [61]. For this reason, we immunostained macrophages in sections of gastrocnemius muscles and determined the stained area using ImageJ software. Results showed that the area of infiltrated immune cells was less than 1% of the total muscle area, even in exercised *mdx* muscle (J. Hyzewicz et al., personal communication). As a consequence, the influence of the infiltrated immune cells on the proteomic study is negligible.

## Conclusion

In our study, we have used an extensive proteomic method to assess the effects of 4 weeks of LIT on carbonylation, expression, and protein–protein interactions of proteins in gastrocnemius muscle of 8-week-old *mdx* mice. We found that proteins of mitochondria, muscle contraction, and glycogenolysis were overcarbonylated and downregulated in nonexercised *mdx* muscle. Furthermore, we demonstrated that LIT corrected these impairments by decreasing carbonylation and increasing expression levels of fast isoforms of troponin T and myosin binding protein C, as well as increasing the expression of slow type isoforms. In addition, the results point to different sensitivities of wild-type and *mdx* muscle in response to LIT.

The present research confirms the beneficial effects of LIT at the protein level and provides pertinent information which could help to design exercise mimicking drugs for DMD therapy.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.freeradbiomed.2015.01.023.

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