

**Table S1** – Summary and Categorization of publications involving ECC force loss in *mdx* mice

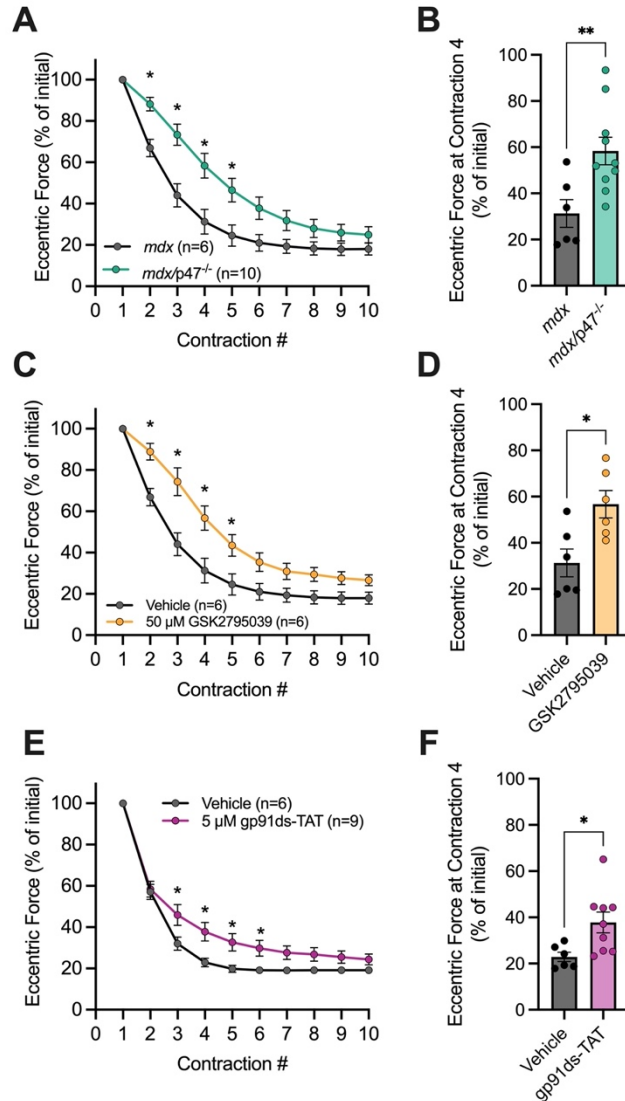
| Author                                | Year | Title                                                                                                                                                             | Implicated Contractile Element        | Muscle   | Method                           |
|---------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|----------|----------------------------------|
| Krag et al. <sup>1</sup>              | 2004 | “Heregulin ameliorates the dystrophic phenotype in mdx mice.”                                                                                                     | Utrophin                              | EDL      | <i>in vitro</i>                  |
| Blaauw et al. <sup>2</sup>            | 2008 | “Akt activation prevents the force drop induced by eccentric contractions in dystrophin-deficient skeletal muscle.”                                               | Utrophin / Redox Homeostasis          | GAS      | <i>in vivo</i> / <i>in vitro</i> |
| Amenta et al. <sup>3</sup>            | 2011 | “Biglycan recruits utrophin to the sarcolemma and counters dystrophic pathology in mdx mice”                                                                      | Utrophin                              | EDL      | <i>in vitro</i>                  |
| Selsby et al. <sup>4</sup>            | 2012 | “Rescue of dystrophic skeletal muscle by PGC-1 $\alpha$ involves a fast to slow fiber type shift in the mdx mouse.”                                               | Utrophin                              | EDL      | <i>in vitro</i>                  |
| Al-Rewashdy et al. <sup>5</sup>       | 2015 | “Utrophin A is essential in mediating the functional adaptations of mdx mouse muscle following chronic AMPK activation.”                                          | Utrophin                              | EDL      | <i>in vitro</i>                  |
| Gibbs et al. <sup>6</sup>             | 2016 | “High levels of sarcospan are well tolerated and act as a sarcolemmal stabilizer to address skeletal muscle and pulmonary dysfunction in DMD.”                    | Utrophin                              | EDL      | <i>in vitro</i>                  |
| Trajanovska et al. <sup>7</sup>       | 2019 | “Muscle specific kinase protects dystrophic mdx mouse muscles from eccentric contraction-induced loss of force-producing capacity.”                               | Utrophin                              | TA       | <i>in situ</i>                   |
| Pratt et al. <sup>8</sup>             | 2013 | “Effects of <i>in vivo</i> injury on the neuromuscular junction in healthy and dystrophic muscles.”                                                               | Excitability                          | Quad     | <i>in vivo</i>                   |
| Call et al. <sup>9</sup>              | 2013 | “Acute failure of action potential conduction in mdx muscle reveals new mechanism of contraction-induced force loss.”                                             | Excitability                          | TA       | <i>in vivo</i>                   |
| Roy et al. <sup>10</sup>              | 2016 | “Dystrophin restoration therapy improves both the reduced excitability and the force drop induced by lengthening contractions in dystrophic mdx skeletal muscle.” | Excitability                          | TA / EDL | <i>in situ</i>                   |
| Baumann et al. <sup>11</sup>          | 2020 | “Plasmalemma Function Is Rapidly Restored in <i>Mdx</i> Muscle after Eccentric Contractions.”                                                                     | Excitability                          | TA       | <i>in vivo</i>                   |
| Whitehead et al. <sup>12</sup>        | 2006 | “Streptomycin reduces stretch-induced membrane permeability in muscles from mdx mice.”                                                                            | Calcium Signaling                     | EDL      | <i>in vitro</i>                  |
| Bellinger et al. <sup>13</sup>        | 2009 | “Hypernitrosylated ryanodine receptor calcium release channels are leaky in dystrophic muscle.”                                                                   | Calcium Signaling                     | EDL      | <i>in situ</i>                   |
| Zanou et al. <sup>14</sup>            | 2009 | “Essential role of TRPV2 ion channel in the sensitivity of dystrophic muscle to eccentric contractions.”                                                          | Calcium Signaling                     | EDL      | <i>in vitro</i>                  |
| Morine et al. <sup>15</sup>           | 2010 | “Overexpression of SERCA1a in the mdx diaphragm reduces susceptibility to contraction-induced damage.”                                                            | Calcium Signaling                     | DIA      | <i>in vitro</i>                  |
| Han et al. <sup>16</sup>              | 2011 | “Dystrophin deficiency exacerbates skeletal muscle pathology in dysferlin-null mice.”                                                                             | Calcium Signaling                     | EDL      | <i>in vitro</i>                  |
| Mázala et al. <sup>17</sup>           | 2015 | “SERCA1 overexpression minimizes skeletal muscle damage in dystrophic mouse models.”                                                                              | Calcium Signaling                     | Quad     | <i>in vivo</i>                   |
| Rader et al. <sup>18</sup>            | 2016 | “Role of dystroglycan in limiting contraction-induced injury to the sarcomeric cytoskeleton of mature skeletal muscle.”                                           | Redox Homeostasis / Calcium Signaling | EDL      | <i>in vitro</i>                  |
| Ward et al. <sup>19</sup>             | 2018 | “GsMTx4-D provides protection to the D2.mdx mouse.”                                                                                                               | Calcium Signaling                     | GAS      | <i>in vivo</i>                   |
| García-Castañeda et al. <sup>20</sup> | 2022 | “Postdevelopmental knockout of Orail improves muscle pathology in a mouse model of Duchenne muscular dystrophy.”                                                  | Calcium Signaling                     | EDL      | <i>in vitro</i>                  |
| Lin et al. <sup>21</sup>              | 2022 | “Pharmacological TRPC6 inhibition improves survival and muscle function in mice with Duchenne muscular dystrophy”                                                 | Calcium Signaling                     | GAS      | <i>in vivo</i>                   |
| Whitehead et al. <sup>22</sup>        | 2008 | “N-Acetylcysteine ameliorates skeletal muscle pathophysiology in mdx mice.”                                                                                       | Redox Homeostasis                     | EDL      | <i>in vitro</i>                  |
| Whitehead et al. <sup>23</sup>        | 2010 | “Skeletal muscle NADPH oxidase is increased and triggers stretch-induced damage in the mdx mouse.”                                                                | Redox Homeostasis                     | FDB      | <i>in vitro</i>                  |
| Baltgalvis et al. <sup>24</sup>       | 2011 | “Transgenic overexpression of $\gamma$ -cytoplasmic actin protects against eccentric contraction-induced force loss in mdx mice.”                                 | Redox Homeostasis                     | EDL      | <i>in vitro</i>                  |
| Khairallah et al. <sup>25</sup>       | 2012 | “Microtubules underlie dysfunction in duchenne muscular dystrophy.”                                                                                               | Redox Homeostasis                     | GAS/FDB  | <i>in vivo</i> / <i>in vitro</i> |
| Moorwood et al. <sup>26</sup>         | 2014 | “Caspase-12 ablation preserves muscle function in the mdx mouse.”                                                                                                 | Redox Homeostasis                     | EDL      | <i>in vitro</i>                  |

|                                 |      |                                                                                                                                                                                                 |                                              |          |                                  |
|---------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|----------|----------------------------------|
| Ismail et al. <sup>27</sup>     | 2014 | “Diapocynin, a dimer of the NADPH oxidase inhibitor apocynin, reduces ROS production and prevents force loss in eccentrically contracting dystrophic muscle.”                                   | Redox Homeostasis                            | EDL      | <i>in vitro</i>                  |
| Rebolledo et al. <sup>28</sup>  | 2016 | “Sarcolemmal targeting of nNOS $\mu$ improves contractile function of mdx muscle.”                                                                                                              | Redox Homeostasis                            | TA       | <i>in situ</i>                   |
| Marrocco et al. <sup>29</sup>   | 2017 | “Pharmacological Inhibition of PKC $\theta$ Counteracts Muscle Disease in a Mouse Model of Duchenne Muscular Dystrophy.”                                                                        | Redox Homeostasis                            | EDL      | <i>in vitro</i>                  |
| Lindsay et al. <sup>30</sup>    | 2018 | “Xanthine oxidase is hyper-active in Duchenne muscular dystrophy.”                                                                                                                              | Redox Homeostasis                            | EDL      | <i>in vitro</i>                  |
| Vitiello et al. <sup>31</sup>   | 2018 | “Drug Repurposing for Duchenne Muscular Dystrophy: The Monoamine Oxidase B Inhibitor Safinamide Ameliorates the Pathological Phenotype in mdx Mice and in Myogenic Cultures From DMD Patients.” | Redox Homeostasis                            | GAS      | <i>in vivo</i>                   |
| Olthoff et al. <sup>32</sup>    | 2018 | “Loss of peroxiredoxin-2 exacerbates eccentric contraction-induced force loss in dystrophin-deficient muscle.”                                                                                  | Redox Homeostasis                            | EDL      | <i>in vitro</i>                  |
| Demonbreun et al. <sup>33</sup> | 2021 | “Anti-latent TGF $\beta$ binding protein 4 antibody improves muscle function and reduces muscle fibrosis in muscular dystrophy.”                                                                | Redox Homeostasis                            | TA       | <i>in situ</i>                   |
| Bonato et al. <sup>34</sup>     | 2023 | “Cyclin D3 deficiency promotes a slower, more oxidative skeletal muscle phenotype and ameliorates pathophysiology in the mdx mouse model of Duchenne muscular dystrophy.”                       | Redox Homeostasis                            | EDL      | <i>in situ</i>                   |
| Blaauw et al. <sup>35</sup>     | 2010 | “Eccentric contractions lead to myofibrillar dysfunction in muscular dystrophy.”                                                                                                                | Myofibrillar dysfunction                     | GAS      | <i>in vivo</i> / <i>in vitro</i> |
| Baumann et al. <sup>36</sup>    | 2022 | “Mechanisms of weakness in <i>mdx</i> muscle following <i>in vivo</i> eccentric contractions.”                                                                                                  | Calcium Signaling / Myofibrillar dysfunction | TA / EDL | <i>in vivo</i> / <i>in vitro</i> |
| Russell et al. <sup>37</sup>    | 2023 | “Modulating fast skeletal muscle contraction protects skeletal muscle in animal model of Duchenne muscular dystrophy.”                                                                          | Myofibrillar dysfunction                     | EDL      | <i>in vitro</i>                  |

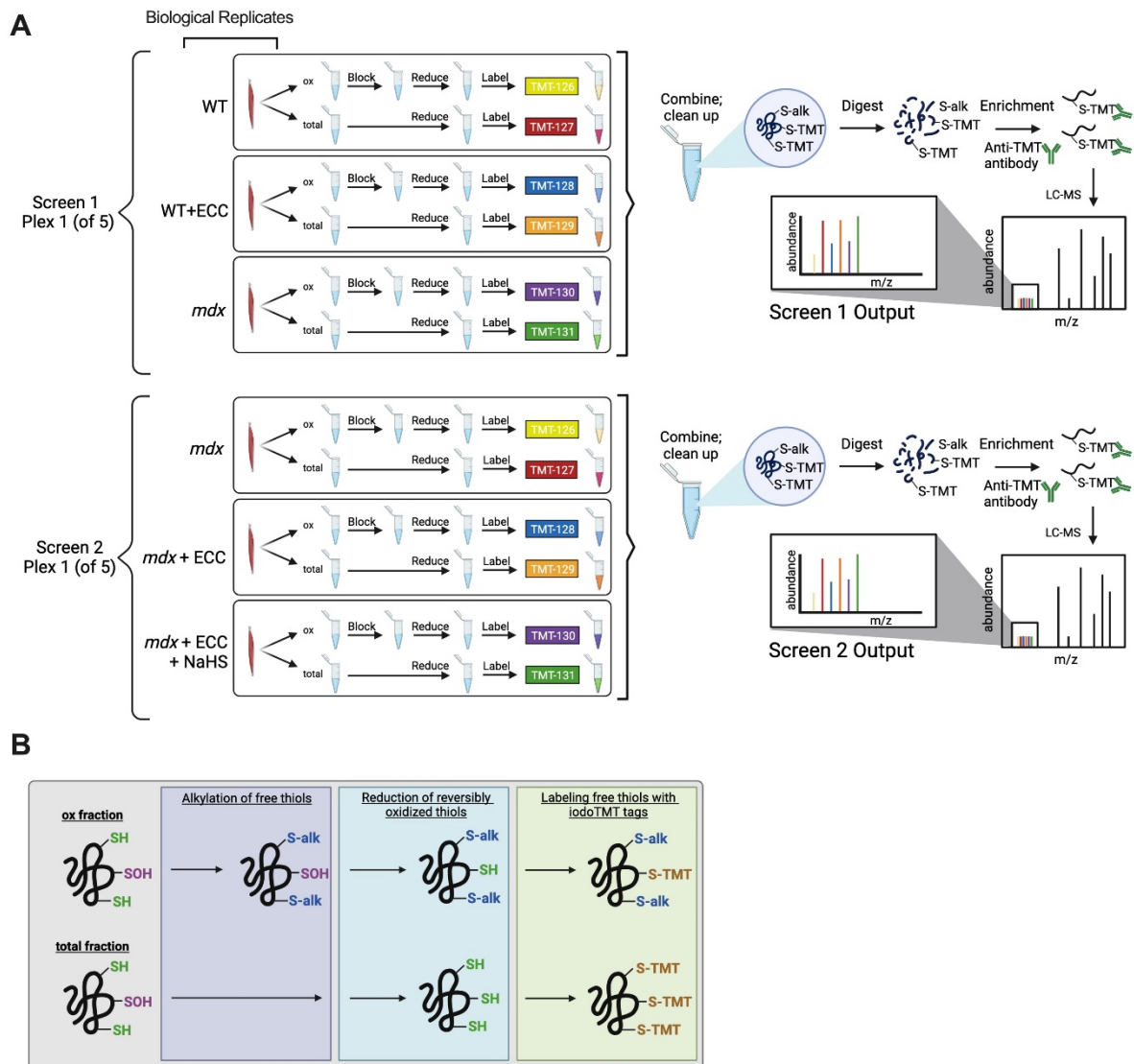
Abbreviations: EDL: extensor digitorum longus, SOL: soleus, GAS: gastrocnemius, FDB: flexor digitorum longus, TA: tibialis anterior, Quad: quadriceps.

**Table S2 - Cysteine residues of interest from proteins related to muscle contraction or redox homeostasis**

| Master Protein Name                                         | Master Protein Accession | Gene ID       | Peptide Sequence<br>[Position in Master]          | Cysteine Position |
|-------------------------------------------------------------|--------------------------|---------------|---------------------------------------------------|-------------------|
| Sodium/potassium-transporting ATPase subunit alpha          | D3YYN7                   | <i>Atp1a2</i> | NI <u>C</u> FFSTN <u>C</u> VEGTAR [239-253]       | 241; 247          |
| Sarcoplasmic/endoplasmic reticulum calcium ATPase 1 (SERCA) | Q8R429                   | <i>Atp2a1</i> | ANAC <u>N</u> SVIR [468-476]                      | 471               |
|                                                             | Q8R429                   | <i>Atp2a1</i> | EVTGSIQL <u>C</u> R [606-615]                     | 614               |
|                                                             | Q8R429                   | <i>Atp2a1</i> | SMSVY <u>C</u> SPAK [493-502]                     | 498               |
|                                                             | Q8R429                   | <i>Atp2a1</i> | VDGDV <u>C</u> SLNEFSITGSTYAPEGEVLK [372-397]     | 377               |
| Catalase                                                    | P24270                   | <i>Cat</i>    | LGPNYLQIPVNC <u>P</u> YR [366-380]                | 377               |
| Aspartate aminotransferase, cytoplasmic                     | P05201                   | <i>Got1</i>   | DIRPY <u>C</u> YWDAEK [155-166]                   | 160               |
| Myosin-binding protein C, slow-type                         | A0A571BEN1               | <i>Mybpc1</i> | AVNDLGTVEIE <u>C</u> K [1090-1102]                | 1101              |
|                                                             | A0A571BEN1               | <i>Mybpc1</i> | VFAENM <u>C</u> GLSEDATMTK [974-990]              | 980               |
| Myosin-binding protein C, fast-type                         | Q5XKE0                   | <i>Mybpc2</i> | DVCDSC <u>S</u> FNVDVEAPR [138-153]               | 140               |
|                                                             | Q5XKE0                   | <i>Mybpc2</i> | <u>C</u> FTELFVK [330-337]                        | 330               |
|                                                             | Q5XKE0                   | <i>Mybpc2</i> | <u>C</u> TLADDAAYEVAVQDEK [313-329]               | 313               |
|                                                             | Q5XKE0                   | <i>Mybpc2</i> | RPSPFDAGTYS <u>C</u> R [1104-1116]                | 1115              |
| Myosin-4                                                    | Q5SX39                   | <i>Myh4</i>   | SNAAC <u>A</u> ALDK [1439-1448]                   | 1443              |
| Myosin light chain kinase 2                                 | Q8VCR8                   | <i>Mylk2</i>  | VEVGQAL <u>C</u> LTAR [255-266]                   | 262               |
| Myomesin-3                                                  | A2ABU4                   | <i>Myom3</i>  | ELIEL <u>C</u> SGR [144-152]                      | 149               |
| Myotilin                                                    | Q9JIF9                   | <i>Myot</i>   | HFIQPQN <u>P</u> CGSR [9-20]                      | 17                |
| Parkinson disease protein 7                                 | Q99LX0                   | <i>Park7</i>  | VTVAGLAGKDPVQ <u>C</u> SR [33-48]                 | 46                |
| Peroxisredoxin-1                                            | P35700                   | <i>Prdx1</i>  | HGEV <u>C</u> PAGWKPGSDTIKPDVVK [169-190]         | 173               |
| Ryanodine receptor 1                                        | E9PZQ0                   | <i>Ryr1</i>   | <u>C</u> SN <u>C</u> YMVWGGDFVSPGQQGR [1490-1509] | 1490; 1493        |
|                                                             | E9PZQ0                   | <i>Ryr1</i>   | GYPDIGWNP <u>C</u> GGER [2318-2331]               | 2327              |
|                                                             | E9PZQ0                   | <i>Ryr1</i>   | MYLS <u>C</u> LTTSR [117-126]                     | 121               |
| Troponin I, fast skeletal muscle                            | P13412                   | <i>Tnni2</i>  | HKV <u>C</u> MDLR [131-138]                       | 134               |
| Thioredoxin                                                 | P10639                   | <i>Txn</i>    | <u>C</u> MPTFQFYK [73-81]                         | 73                |

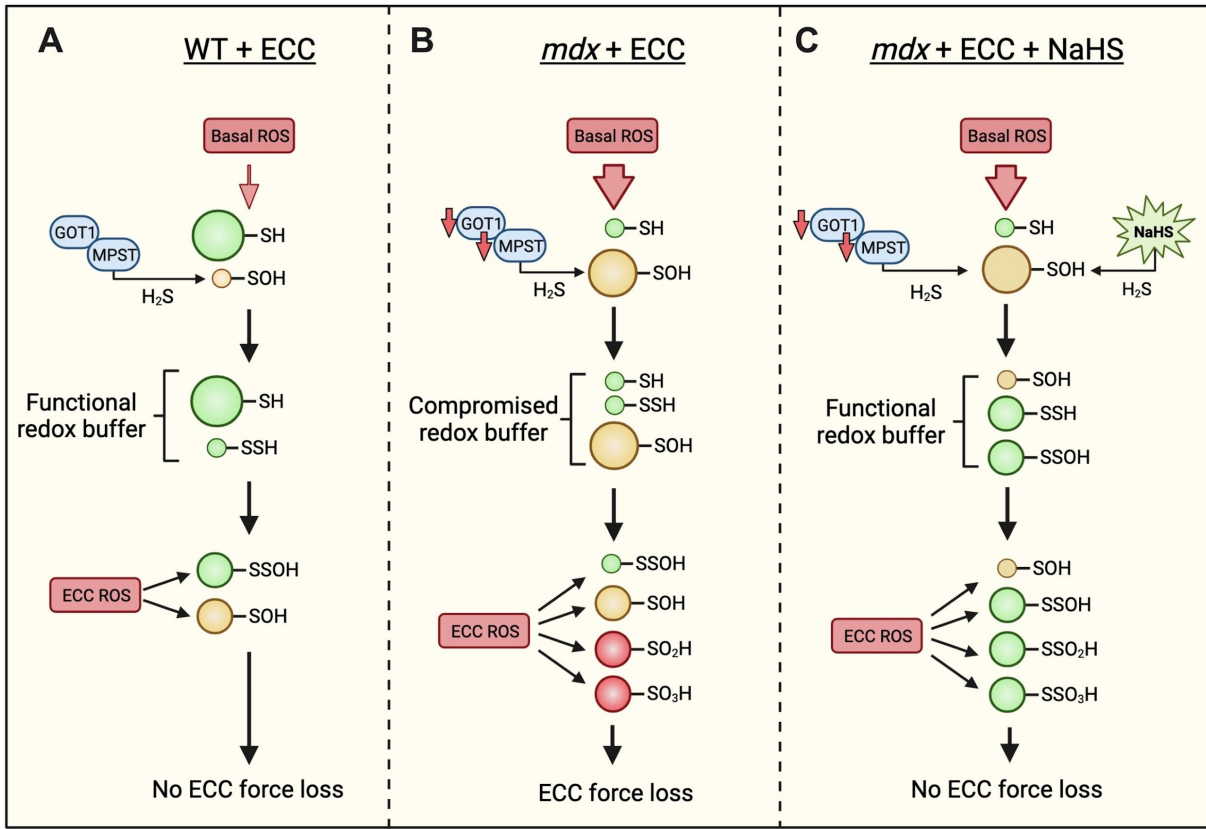


**Fig. S1. Genetic ablation or pharmacologic inhibition of Nox2 partially protects *mdx* muscle from ECC force loss.** (A and B): (A) Change in eccentric force during 10 ECCs in EDL muscles isolated from *mdx/p47<sup>-/-</sup>* and littermate control mice. (B) Eccentric force produced at ECC #4 in panel (A) showing individual data distribution for each genotype. (C and E): (C) Change in eccentric force during 10 ECCs in *mdx* EDL and incubated with vehicle or the NOX2 inhibitors (C) 50 $\mu$ M GSK2795039 or (E) 5 $\mu$ M gp91ds-TAT. (D), (F) Eccentric force produced at ECC #4 from panels (C) and (E), respectively, showing individual data distribution for each treatment condition. All ECC force data in (A-C) are expressed as a percentage of the force generated during the first contraction. Results are presented as mean  $\pm$  SEM. \* $p$ <0.05, \*\* $p$ <0.01 by Student's t-test in (B), (D), and (F), \* $p$ <0.05, \*\*\* $p$ <0.001, or \* $p$ <0.05 by two-way repeated measures ANOVA in (A), (C), and (E).



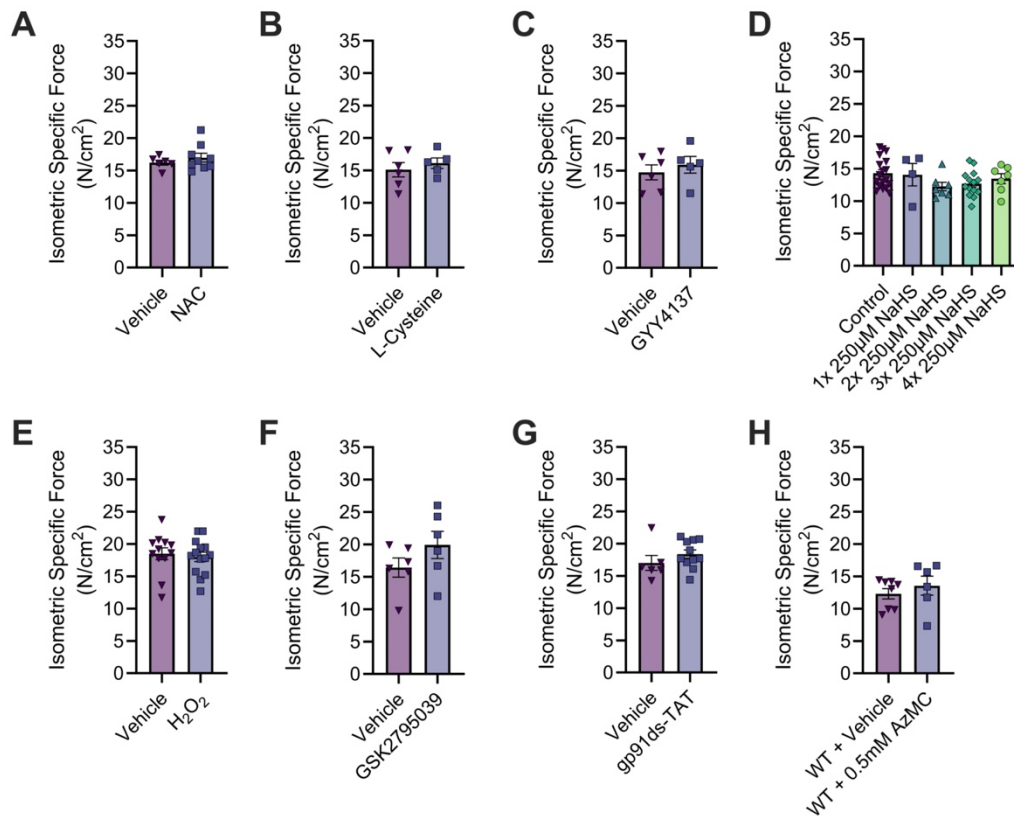
**Fig. S2. Illustration of the methodology used for chemo-proteomic sample preparation.**

(A) Following ECCs, EDLs from all groups were flash frozen and stored in -80C. Frozen EDLs were homogenized and divided into two fractions: oxidized (ox) and total. Screen 1 a 5 plex assay with 6 channels in each plex containing ox and total samples from WT control, WT+ECC, and *mdx* control EDLs. Screen 2 was identical to screen 1 except for the samples which were *mdx*, *mdx*+ECC, and *mdx*+ECC+NaHS. Free thiols were blocked/alkylated in the ox fraction. Reversibly oxidized thiols were reduced, and all free thiols were labeled with iodoTMT tags. Protein samples were digested and enriched for TMT-labeled peptides. Samples were processed using liquid chromatography/tandem mass spectrometry (LC-MS/MS) and relative levels of oxidation between groups for a given cysteine were calculated. (B) Schematic showing additional details of the blocking/alkylating, reducing, and labeling processing steps for ox and total fractions.



**Fig. S3. Model illustrating the three elements driving ECC force loss in *mdx* skeletal muscle.**

(A) Wild type (WT) skeletal muscle has a largely reduced proteome (large green circle) at baseline due to minimal basal reactive oxygen species (ROS) production. This, combined with normal levels of hydrogen sulfide (H<sub>2</sub>S), preserves the function of the cysteine proteome redox buffer through persulfidation, allowing adequate buffering of excess ROS during ECCs. (B) Dystrophin-deficient (*mdx*) muscle has elevated levels of ROS and baseline proteome oxidation, which is compounded by a lack of persulfidation-mediated protection due to a deficit in H<sub>2</sub>S. As a result, *mdx* muscle has a compromised redox buffer that is overwhelmed with excess ROS during ECCs ultimately leading to irreversible oxidation and loss of protein function and muscle force. (C) Treatment of *mdx* muscles with NaHS effectively bypasses the defective H<sub>2</sub>S-producing enzymes GOT1 and MPST and protects the redox buffer from irreversible oxidation, thereby preserving protein function and ECC force. Created with BioRender.com. Green circles = reduced (-SH) or persulfide-protected thiol (-SSH, SSOH, etc.); Yellow circles = oxidized thiol (-SOH); red circles = irreversibly oxidized thiol (-SO<sub>2</sub>H, -SO<sub>3</sub>H).



**Fig. S4. Effects of various *in vitro* pharmacological treatments on *mdx* EDL muscle isometric specific force production.**

(A-H) EDL muscles were isolated from *mdx* mice, suspended in an *in vitro* bath, and incubated with (A) vehicle or 20mM N-Acetyl Cysteine (NAC), (B) vehicle or 40mM L-Cysteine, (C) vehicle or 100µM GYY4137, (D) vehicle, 1x, 2x, 3x, or 4x doses of 250µM NaHS, (E) vehicle or 0.5mM H<sub>2</sub>O<sub>2</sub>, (F-G) vehicle or the NOX2 inhibitors (F) 50µM GSK2795039 or (G) 5µM gp91ds-TAT, (H) vehicle or 0.5mM of the H<sub>2</sub>S scavenger 7-Azido-4-methylcoumarin (AzMC). Results are presented as mean ± SEM.

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