**Supplemental Data**

# Failed mitochondrial import and impaired proteostasis trigger SUMOylation of mitochondrial proteins

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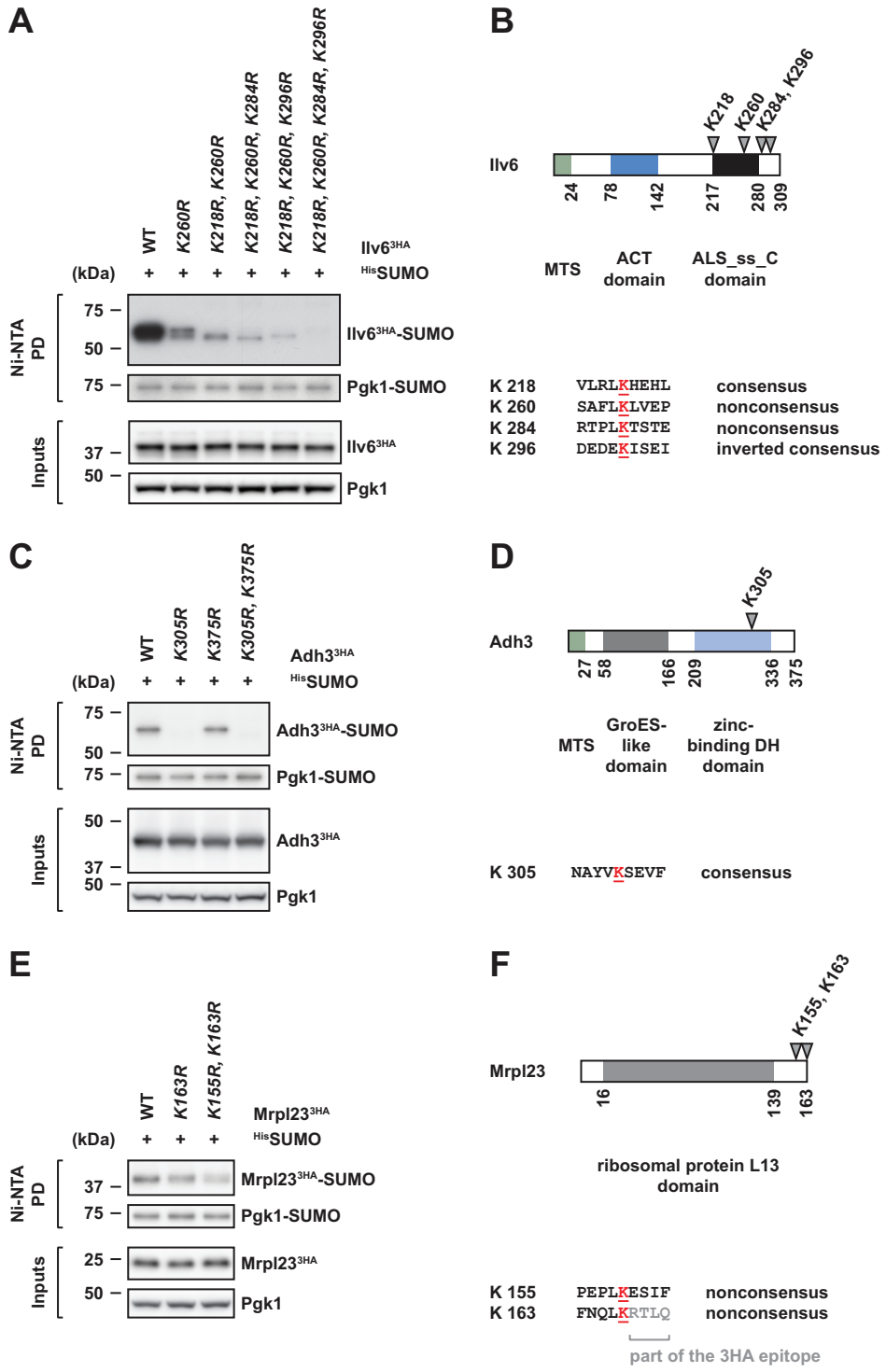


**Figure S1. Mapping of SUMO acceptor sites of mitochondrial proteins.**
(A, C, E) Identification of SUMO acceptor sites in Ilv6, Adh3 and Mrpl23. Denaturing $^{His}$SUMO Ni-NTA pull-downs from cells harboring plasmids that express 3HA-tagged versions of Ilv6 (A), Adh3 (C) and Mrpl23 (E) or corresponding lysine-to-arginine mutants as indicated. Expression of 3HA-tagged proteins is under control of endogenous promoter (A), *GAL1* promoter (C) or *ADH1* promoter (E).

(B, D, F) Schematic representations of Ilv6 (B), Adh3 (D) and Mrpl23 (F) showing the positions of SUMO acceptor site lysines. Abbreviations: MTS (matrix-targeting sequence), ACT domain (named after aspartate kinase, chorismate mutase, TyrA), ALS_ss_C domain (acetolactate synthase, small subunit, C-terminal domain), zinc-binding DH domain (zinc-binding dehydrogenase domain).

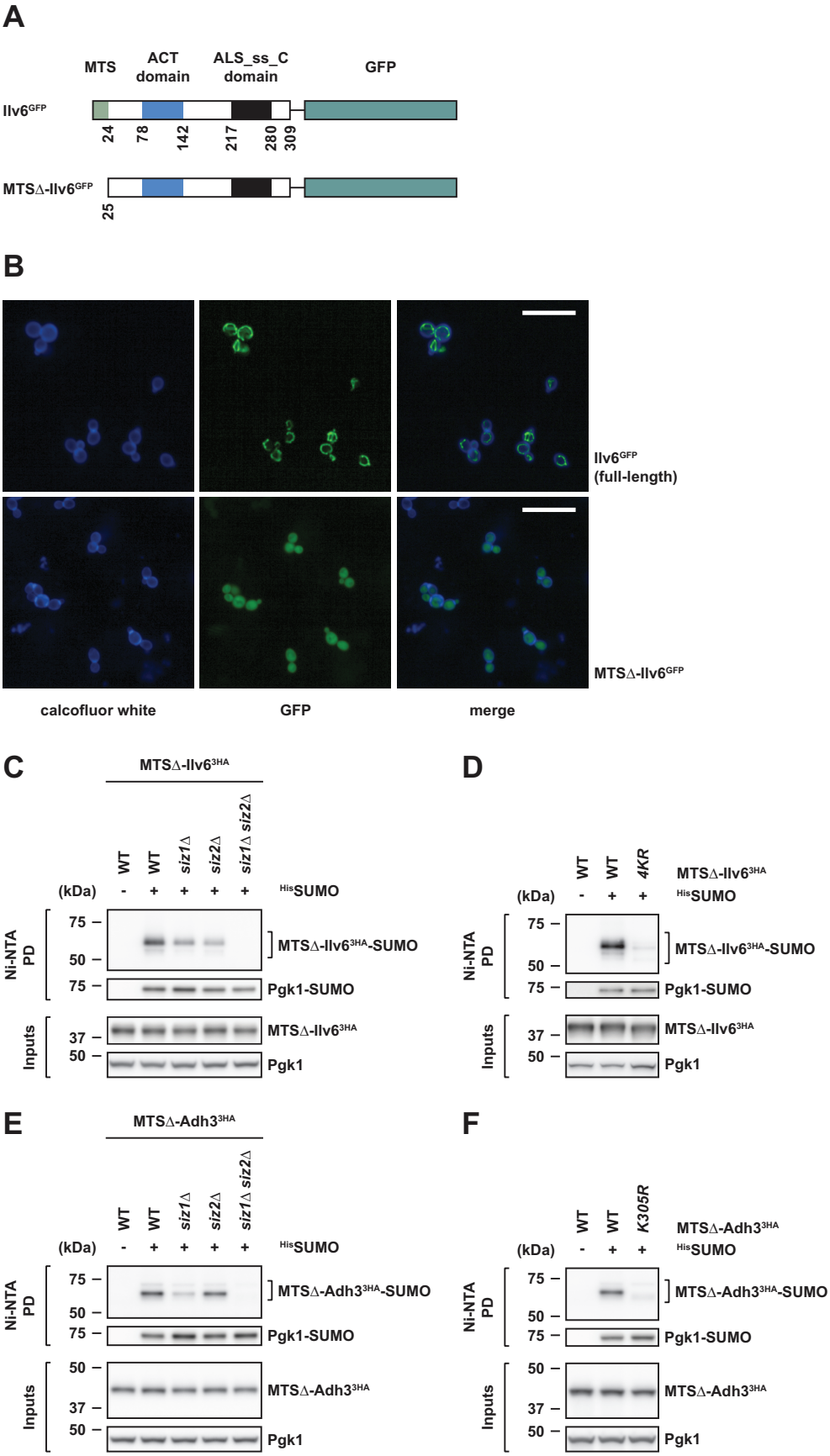
A
MTS
ACT domain
ALS_ss_C domain
GFP
Ilv6GFP
24
78
142
217
280
309
MTSΔ-Ilv6GFP
25
B
Ilv6GFP (full-length)
MTSΔ-Ilv6GFP
calcofluor white
GFP
merge
C
MTSΔ-Ilv6 3HA
WT
WT
siz1Δ
siz2Δ
siz1Δ siz2Δ
(kDa)
HisSUMO
Ni-NTA PD
75
50
75
MTSΔ-Ilv6 3HA-SUMO
Pgk1-SUMO
Inputs
37
50
MTSΔ-Ilv6 3HA
Pgk1
D
WT
WT
4KR
MTSΔ-Ilv6 3HA
(kDa)
HisSUMO
Ni-NTA PD
75
50
75
MTSΔ-Ilv6 3HA-SUMO
Pgk1-SUMO
Inputs
37
50
MTSΔ-Ilv6 3HA
Pgk1
E
MTSΔ-Adh3 3HA
WT
WT
siz1Δ
siz2Δ
siz1Δ siz2Δ
(kDa)
HisSUMO
Ni-NTA PD
75
50
75
MTSΔ-Adh3 3HA-SUMO
Pgk1-SUMO
Inputs
50
37
50
MTSΔ-Adh3 3HA
Pgk1
F
WT
WT
K305R
MTSΔ-Adh3 3HA
(kDa)
HisSUMO
Ni-NTA PD
75
50
75
MTSΔ-Adh3 3HA-SUMO
Pgk1-SUMO
Inputs
50
37
50
MTSΔ-Adh3 3HA
Pgk1

**Figure S2. SUMOylation of import-incompetent mutant variants of mitochondrial proteins.**
(A, B) Generation and localization of an import-incompetent Ilv6 mutant variant. (A) Schematic representation of GFP fusion proteins of Ilv6 ($Ilv6^{GFP}$) and an import-incompetent variant lacking the N-terminal 24-amino-acid matrix-targeting sequence ($MTS\Delta\text{-}Ilv6^{GFP}$). (B) Subcellular localization of wild type and import-incompetent versions of $Ilv6^{GFP}$ using GFP fluorescence. Yeast cell walls were stained with calcofluor white. Scale bars: 20 µm.
(C-F) SUMOylation of Ilv6 and Adh3 variants lacking an MTS is mediated by the SUMO E3 ligases Siz1 and Siz2 and occurs at similar sets of SUMO acceptor sites as in wild type proteins. (C, E) Denaturing $^{His}$SUMO Ni-NTA pull-downs from wild type (WT) cells and cells lacking the indicated SUMO E3 ligases. All strains harbor plasmids that express 3HA-tagged import-incompetent Ilv6 ($MTS\Delta\text{-}Ilv6^{3HA}$) or Adh3 ($MTS\Delta\text{-}Adh3^{3HA}$) from the *GAL1* promoter. (D, F) Denaturing $^{His}$SUMO Ni-NTA pull-downs from cells expressing import-incompetent Ilv6 ($MTS\Delta\text{-}Ilv6^{3HA}$) (D) or Adh3 ($MTS\Delta\text{-}Adh3^{3HA}$) and corresponding lysine-to-arginine mutants as indicated from the *GAL1* promoter.

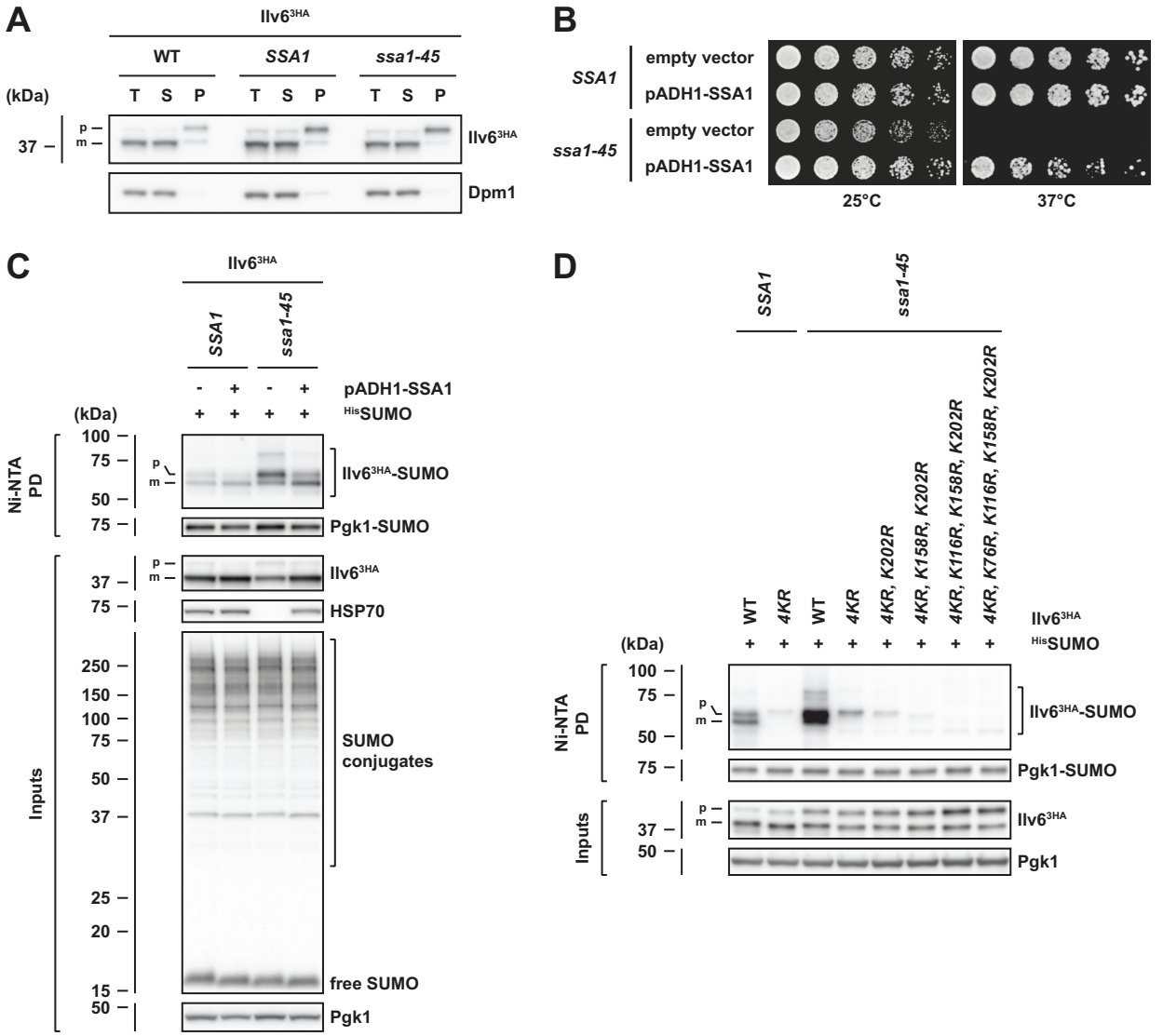


**Figure S3. The SUMOylation pattern of Ilv6 is specifically altered in *SSA* mutant cells.**
(A) Levels of the Ilv6 precursor are elevated in *SSA* mutant cells and show an increased propensity to fractionate as insoluble. Total (T) cell lysates of wild type (WT), *SSA1* and *ssa1-45* cells were separated into soluble (S) and insoluble pellet (P) fractions and analyzed by western blotting using HA epitope-specific, Dpm1-specific and Smt3-specific antibodies (fractions were loaded in a T:S:P ratio of 1:1:60). All strains express 3HA-tagged Ilv6 from the endogenous promoter and $^{His}$SUMO from the *ADH1* promoter. Bands corresponding to the precursor protein (p) or mature form (m) are labeled.
(B, C) Ectopic expression of Ssa1 promotes growth of *ssa1-45* cells at restrictive temperature and reduces Ilv6 precursor SUMOylation in *SSA* mutants. (B) *SSA1* and *ssa1-45* cells were complemented with an empty vector or plasmids expressing wild type Ssa1 from the *ADH1* promoter. 5-fold serial dilutions of cells were spotted on SC agar plates and grown at 25°C for 2 days or 37°C for 3 days. (C) Denaturing $^{His}$SUMO Ni-NTA pull-downs from *SSA1* and *ssa1-45* cells harboring plasmids that express wild type Ssa1 from the *ADH1* promoter. All strains express 3HA-tagged Ilv6 from the endogenous promoter. Bands corresponding to the unmodified or monoSUMOylated precursor protein (p) or mature form (m) are labeled.
(D) SUMOylation of multiple sites in the Ilv6 precursor is detectable in *SSA* mutant cells. Denaturing $^{His}$SUMO Ni-NTA pull-downs from *SSA1* and *ssa1-45* cells harboring plasmids that express 3HA-tagged

wild type (WT) Ilv6 or one of multiple *KR* mutant variants from the *ADH1* promoter. Bands corresponding to the unmodified or monoSUMOylated precursor protein (p) or mature form (m) are labeled.

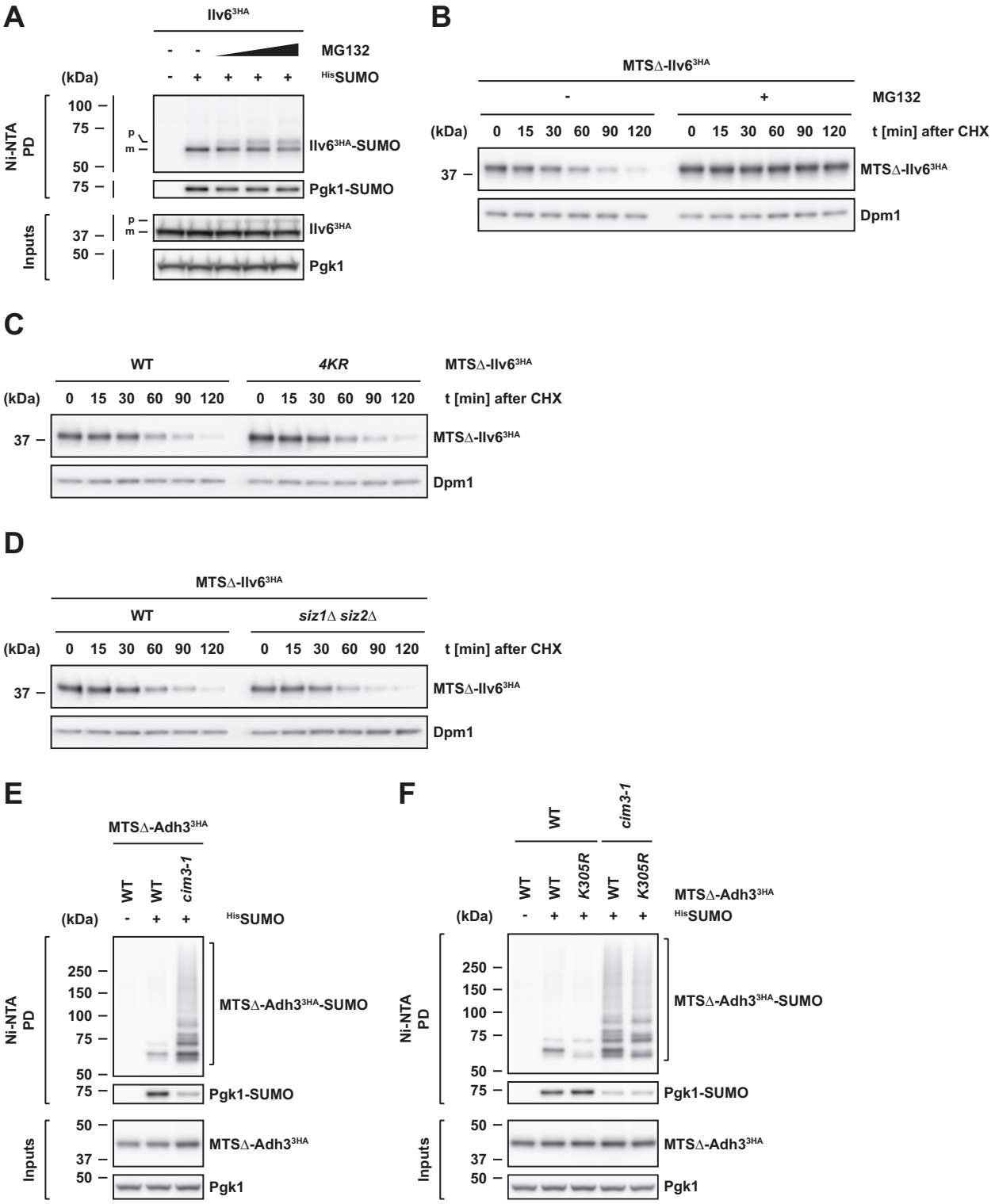


**Figure S4. Enhanced SUMOylation of mitochondrial proteins in proteasome mutant cells.**
(A) SUMOylation of the Ilv6 precursor is enhanced upon proteasome inhibition by MG132. Yeast cells (*pdr5Δ*) expressing C-terminally 3HA-tagged Ilv6 were treated with 10 µM, 20 µM or 50 µM MG132 for 2 h and denaturing Ni-NTA pull-downs were performed to isolate $^{His}$SUMO conjugates. Bands

corresponding to the unmodified or monoSUMOylated precursor protein (p) or mature form (m) are labeled.

(B) Import-incompetent Ilv6 is degraded in a proteasome-dependent manner. Yeast cells (*pdr5Δ*) expressing import-incompetent Ilv6 (MTSΔ-Ilv6$^{3HA}$) from the *GAL1* promoter were incubated with MG132 for 1 h, treated with 0.5 mg/ml cycloheximide (CHX) and collected at the indicated time points. Mutant HA-tagged Ilv6 and Dpm1 were detected by western blotting using HA tag- and Dpm1-specific antibodies.

(C, D) Lack of Ilv6 SUMOylation does not noticeably affect the degradation of import-incompetent Ilv6. Experimental setup as in (B) but with cells expressing wild type (WT) or the *4KR* variant of import-incompetent Ilv6 (C) and wild type (WT) cells or cells lacking the SUMO E3 ligases Siz1 and Siz2 (*siz1Δ siz2Δ*) (D).

(E, F) SUMOylation of import-incompetent Adh3 is strongly enhanced in proteasome mutant cells. Denaturing $^{His}$SUMO Ni-NTA pull-downs from wild type (WT) and *cim3-1* cells harboring plasmids that express MTSΔ-Adh3$^{3HA}$ or the corresponding *K305R* variant from the *GAL1* promoter.

**Table S1. Excel file containing a compiled list of potential mitochondrial SUMO substrates identified by multiple mass spectrometry experiments.**

**Table S2. Yeast (*Saccharomyces cerevisiae*) strains used in this study, related to Experimental procedures.**

| Strain | Genotype | Reference |
|---|---|---|
| DF5 | *his3-Δ200 leu2-3,112 lys2-801 trp1-1 ura3-52* | (1,2) |
| W303 (*RAD5*) | *ade2-1 can1-100 his3-11,15 leu2-3,112 trp1-1 ura3-1 RAD5* | (3) |
| *SSC1* | *Matα, his4-713 lys2 ura3-52 trp1Δ leu2-3,112 SSC1* | (4) |
| *ssc1-3* | *Matα, his4-713 lys2 ura3-52 trp1Δ leu2-3,112 ssc1-3::LEU2* | (4) |
| JN516 | *Matα, his3-11,15 leu2-3,112 his3-11 ura3-52 trp1Δ lys2 SSA1 ssa2Δ::LEU2 ssa3Δ::TRP1 ssa4Δ::LYS2* | (5) |
| *ssa1-45 (ΔU)* | *Matα, his3-11,15 leu2-3,112 his3-11 ura3-52 trp1Δ lys2 ssa1-45 ssa2Δ::LEU2 ssa3Δ::TRP1 ssa4Δ::LYS2* | (5,6) |
| CMY826 | *Mata, ura3-52 leu2Δ1 his3Δ-200 trp1Δ63 lys2-801 ade2-101 bar1Δ::HIS3* | (7) |
| CMY726 | *Matα, cim3-1 ura3-52 leu2Δ1* | (7) |
| Y0002 | DF5, *Matα* | (2) |
| YFPX4-3A | DF5, *Matα, pADH-$^{His}$SMT3::URA3* | this study |
| YFPX10-5C | DF5, *Matα, ADH3$^{3HA}$::kanMX4* | this study |
| YFPX12-9B | DF5, *Matα, ILV6$^{3HA}$::kanMX4* | this study |
| YFPX14-1C | DF5, *Matα, pADH-$^{His}$SMT3::URA3 ADH3$^{3HA}$::kanMX4* | this study |
| YFPX16-6C | DF5, *Matα, pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::kanMX4* | this study |
| YFPX244-5C | DF5, *Matα, pADH-$^{His}$SMT3::URA3 siz1Δ::hphNT1* | this study |
| YFPX245-7C | DF5, *Matα, pADH-$^{His}$SMT3::URA3 siz2Δ::natNT2* | this study |
| YFPX248-2C | DF5, *Matα, pADH-$^{His}$SMT3::URA3 siz1Δ::hphNT1 siz2Δ::natNT2* | this study |
| YFPX149-12D | DF5, *Matα, pADH-$^{His}$SMT3::URA3 ADH3$^{3HA}$::kanMX4 siz1Δ::hphNT1* | this study |
| YFPX147-4B | DF5, *Matα, pADH-$^{His}$SMT3::URA3 ADH3$^{3HA}$::kanMX4 siz2Δ::HIS3MX6* | this study |
| YFPX153-2D | DF5, *Matα, pADH-$^{His}$SMT3::URA3 ADH3$^{3HA}$::kanMX4 siz1Δ::hphNT1 siz2Δ::HIS3MX6* | this study |
| YFPX150-7C | DF5, *Matα, pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::kanMX4 siz1Δ::hphNT1* | this study |
| YFPX164-3C | DF5, *Matα, pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::kanMX4 siz2Δ::natNT2* | this study |
| YFPX165-14B | DF5, *Matα pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::kanMX4 siz1Δ::hphNT1 siz2Δ::natNT2* | this study |
| Y2725 | W303, *Matα* | (3) |
| YFP339 | W303, *Matα, YIplac211-pADH-$^{His}$SMT3::URA3* | this study |
| YFP406 | W303, *Matα, pdr5Δ::HIS3MX6* | this study |
| YFPX118-13C | W303, *Matα, siz1Δ::hphNT1 siz2Δ::HIS3MX6* | this study |
| YFP582 | W303, *Matα, ILV6$^{3HA}$::TRP1 pdr5Δ::kanMX4* | this study |
| YFP522 | W303, *Matα, YIplac211-pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::TRP1 pdr5Δ::kanMX4* | this study |
| YFPX212-7D | W303, *Matα, YIplac211-pADH-$^{His}$SMT3::URA3 siz1Δ::hphNT1* | this study |
| YFPX213-7D | W303, *Matα, YIplac211-pADH-$^{His}$SMT3::URA3 siz2Δ::natNT2* | this study |
| YFPX220-20D | W303, *Matα, YIplac211-pADH-$^{His}$SMT3::URA3 siz1Δ::hphNT1 siz2Δ::natNT2* | this study |
| YFP627 | W303, *Matα, pRS306-pGAL-ADH3$^{3HA}$-tCYC1::URA3* | this study |
| YFP630 | W303, *Matα, pRS306-pGAL-adh3$_{28-375}$$^{3HA}$-tCYC1::URA3* | this study |
| YFPX251-15C | W303, *Matα, YIplac128-pADH-$^{His}$SMT3::LEU2 pRS306-pGAL-ADH3$^{3HA}$-tCYC1::URA3* | this study |
| YFPX256-9C | W303, *Matα, YIplac128-pADH-$^{His}$SMT3::LEU2 pRS306-pGAL-adh3$_{28-375}$$^{3HA}$-tCYC1::URA3* | this study |
| YFPX255-3B | W303, *Matα, YIplac128-pADH-$^{His}$SMT3::LEU2 pRS306-pGAL-adh3$_{28-375}$$^{3HA}$-K305R-tCYC1::URA3* | this study |
| YFPX254-6D | W303, *Matα, YIplac128-pADH-$^{His}$SMT3::LEU2 pRS306-pGAL-adh3$_{28-375}$$^{3HA}$-tCYC1::URA3 cim3-1* | this study |
| YFPX255-7D | W303, *Matα, YIplac128-pADH-$^{His}$SMT3::LEU2 pRS306-pGAL-adh3$_{28-375}$$^{3HA}$-K305R-tCYC1::URA3 cim3-1* | this study |
| YFPX271-19D | W303, *Matα, YIplac128-pADH-$^{His}$SMT3::LEU2 pRS306-pADH-ADH3$^{3HA}$-tCYC1::URA3* | this study |
| YFPX272-20A | W303, *Matα, YIplac128-pADH-$^{His}$SMT3::LEU2 pRS306-pADH-adh3$_{28-375}$$^{3HA}$-tCYC1::URA3* | this study |
| YFPX271-11D | W303, *Matα, YIplac128-pADH-$^{His}$SMT3::LEU2 pRS306-pADH-ADH3$^{3HA}$-tCYC1::URA3 cim3-1* | this study |
| YFPX272-19C | W303, *Matα, YIplac128-pADH-$^{His}$SMT3::LEU2 pRS306-pADH-adh3$_{28-375}$$^{3HA}$-tCYC1::URA3 cim3-1* | this study |

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| | | |
|---|---|---|
| YFP95 | *Matα, SSC1 YIplac211-pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::TRP1* | this study |
| YFP103 | *Matα, ssc1-3 YIplac211-pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::TRP1* | this study |
| YFP516 | *Matα, SSA1 ssa2Δ::LEU2 ssa3Δ::TRP1 ssa4Δ::LYS2 YIplac211-pADH-$^{His}$SMT3::URA3* | this study |
| YFP519 | *Matα, ssa1-45 ssa2Δ::LEU2 ssa3Δ::TRP1 ssa4Δ::LYS2 YIplac211-pADH-$^{His}$SMT3::URA3* | this study |
| YFP602 | *Matα, SSA1 ssa2Δ::LEU2 ssa3Δ::TRP1 ssa4Δ::LYS2 YIplac211-pADH-$^{His}$SMT3::URA3 ADH3$^{3HA}$::kanMX4* | this study |
| YFP606 | *Matα, SSA1 ssa2Δ::LEU2 ssa3Δ::TRP1 ssa4Δ::LYS YIplac211-pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::kanMX4* | this study |
| YFP612 | *Matα, ssa1-45 ssa2Δ::LEU2 ssa3Δ::TRP1 ssa4Δ::LYS2 YIplac211-pADH-$^{His}$SMT3::URA3 ADH3$^{3HA}$::kanMX4* | this study |
| YFP616 | *Matα, ssa1-45 ssa2Δ::LEU2 ssa3Δ::TRP1 ssa4Δ::LYS2 YIplac211-pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::kanMX4* | this study |
| YFP162 | CMY826, *Mata, YIplac211-pADH-$^{His}$SMT3::URA3* | this study |
| YFP140 | CMY763, *Matα, YIplac211-pADH-$^{His}$SMT3::URA3* | this study |
| YFP167 | CMY826, *Mata, YIplac211-pADH-$^{His}$SMT3::URA3 ADH3$^{3HA}$::kanMX4* | this study |
| YFP154 | CMY763, *Matα, YIplac211-pADH-$^{His}$SMT3::URA3 ADH3$^{3HA}$::kanMX4* | this study |
| YFP171 | CMY826, *Mata, YIplac211-pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::kanMX4* | this study |
| YFP156 | CMY763, *Matα, YIplac211-pADH-$^{His}$SMT3::URA3 ILV6$^{3HA}$::kanMX4* | this study |

**Table S3. Plasmids used in this study, related to Experimental procedures.**

| Plasmid | Description | Reference |
|---|---|---|
| p41XADH | pRS41X-pADH-tCYC1 | (8) |
| p41XGAL | pRS41X-pGAL-tCYC1 | (9) |
| D1374 | YIplac211-pADH-$^{His}$SMT3 | (10) |
| D1549 | YIplac128-pADH-$^{His}$SMT3 | (11,12) |
| pFP17 | YCplac22-pILV6-Ilv6$^{3HA}$ | this study |
| pFP38 | YCplac22-pILV6-Ilv6$^{3HA}$-K260R | this study |
| pFP41 | YCplac22-pILV6-Ilv6$^{3HA}$-K218, K260R | this study |
| pFP50 | YCplac22-pILV6-Ilv6$^{3HA}$-K218,K260R, K284R | this study |
| pFP51 | YCplac22-pILV6-Ilv6$^{3HA}$-K218,K260R, K296R | this study |
| pFP52 | YCplac22-pILV6-Ilv6$^{3HA}$-K218,K260R, K284R, K296R (4KR) | this study |
| pFP53 | p415GAL-Ilv6$^{3HA}$ | this study |
| pFP62 | p415GAL-Ilv6$_{25-309}$$^{3HA}$ | this study |
| pFP72 | p415GAL-Ilv6$_{25-309}$$^{3HA}$-K218R, K260R, K284R, K296R (4KR) | this study |
| pFP108 | p413ADH-Ilv6$^{3HA}$ | this study |
| pFP109 | p413ADH-Ilv6$^{3HA}$-K218R, K260R, K284R, K296R (4KR) | this study |
| pFP110 | p413ADH-Ilv6$^{3HA}$-4KR, K202R | this study |
| pFP111 | p413ADH-Ilv6$^{3HA}$-4KR, K158R, K202R | this study |
| pFP112 | p413ADH-Ilv6$^{3HA}$-4KR, K116R, K158R, K202R | this study |
| pFP113 | p413ADH-Ilv6$^{3HA}$-4KR, K76R, K116R, K158R, K202R | this study |
| pFP93 | pRS313-pILV6-Ilv6$^{GFP}$ | this study |
| pFP91 | p413GAL-Ilv6$_{25-309}$$^{GFP}$ | this study |
| pFP12 | p415GAL-Adh3$^{3HA}$ | this study |
| pFP23 | p415GAL-Adh3$^{3HA}$-K305R | this study |
| pFP24 | p415GAL-Adh3$^{3HA}$-K375R | this study |
| pFP25 | p415GAL-Adh3$^{3HA}$-K305R, K375R | this study |
| pFP13 | p415GAL-Adh3$_{28-375}$$^{3HA}$ | this study |
| pFP107 | p415GAL-Adh3$_{28-375}$$^{3HA}$-K305R | this study |
| pFP118 | pRS413-pTDH3-Adh3$^{3HA}$ | this study |
| pFP119 | pRS413-pTDH3-Adh3$^{3HA}$-K305R | this study |
| pFP120 | pRS413-pTDH3-Adh3$_{28-375}$$^{3HA}$ | this study |
| pFP121 | pRS413-pTDH3-Adh3$_{28-375}$$^{3HA}$-K305R | this study |
| pFP103 | pRS306-pGAL-Adh3$_{28-375}$$^{3HA}$ | this study |
| pFP106 | pRS306-pGAL-Adh3$_{28-375}$$^{3HA}$-K305R | this study |
| pFP114 | pRS306-pADH-Adh3$^{3HA}$ | this study |
| pFP115 | pRS306-pADH-Adh3$_{28-375}$$^{3HA}$ | this study |
| pFP97 | p415ADH-Mrpl23$^{3HA}$ | this study |
| pFP98 | p415ADH-Mrpl23$^{3HA}$-K163R | this study |
| pFP99 | p415ADH-Mrpl23$^{3HA}$-K155R, K163R | this study |
| pFP77 | p413ADH-Ssa1 | this study |

Plasmids encoding the import-incompetent mutant variant of Ilv6 (MTSΔ-Ilv6) encode a protein variant lacking the N-terminal 24 amino acids (Ilv6$_{25-309}$); plasmids encoding the import-incompetent mutant variant of Adh3 (MTSΔ-Adh3) encode a protein variant lacking the N-terminal 27 amino acids (Adh3$_{28-375}$).

**Supplemental references**


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