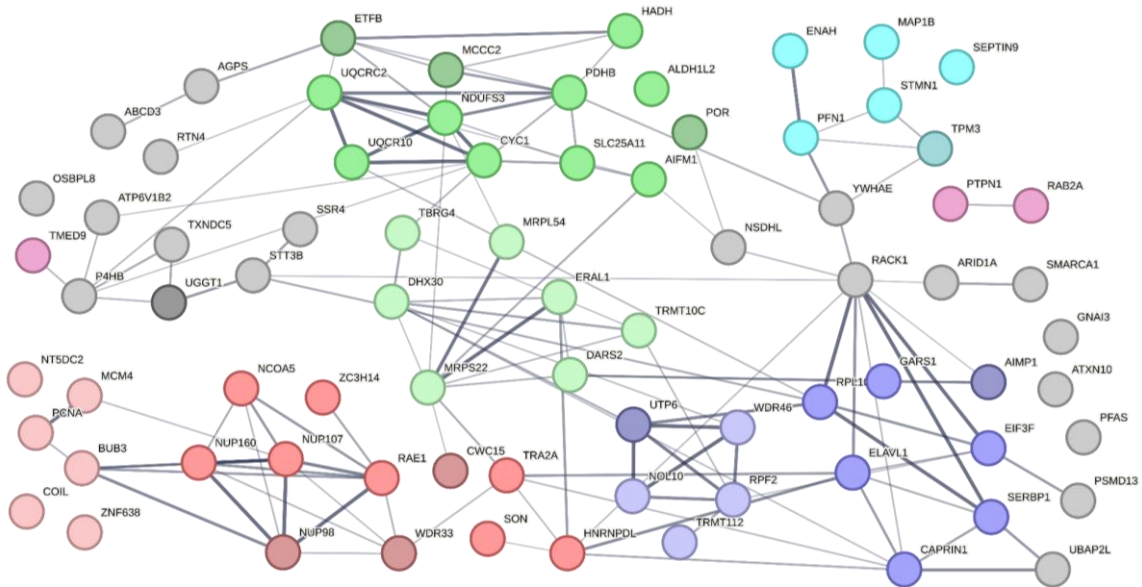


A

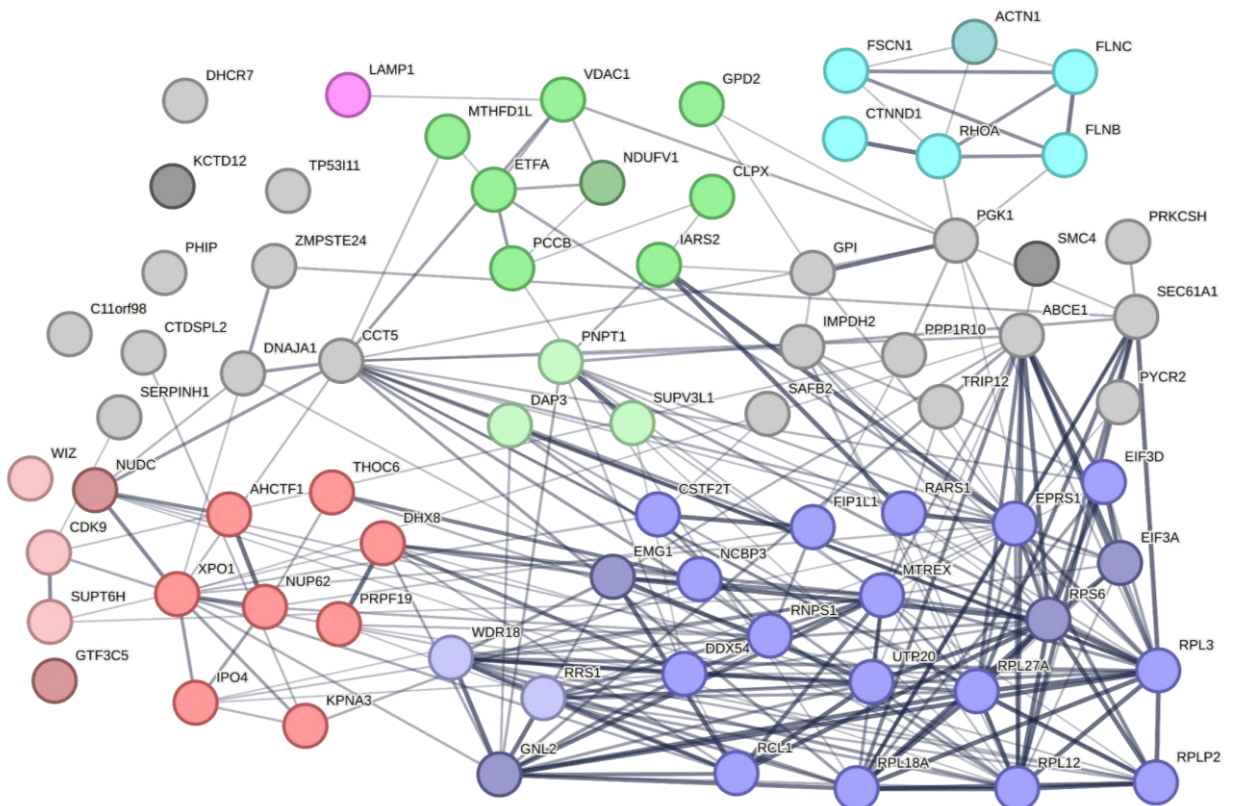
STRING analysis of stabilized proteins upon PepA (early differentiation)



Legend: Nucleus Transcription Nucleolus Translation Mitochondrial transcription
Mitochondria Cytoskeleton Other organelles Other proteins

B

STRING analysis of destabilized proteins upon PepA (early differentiation)

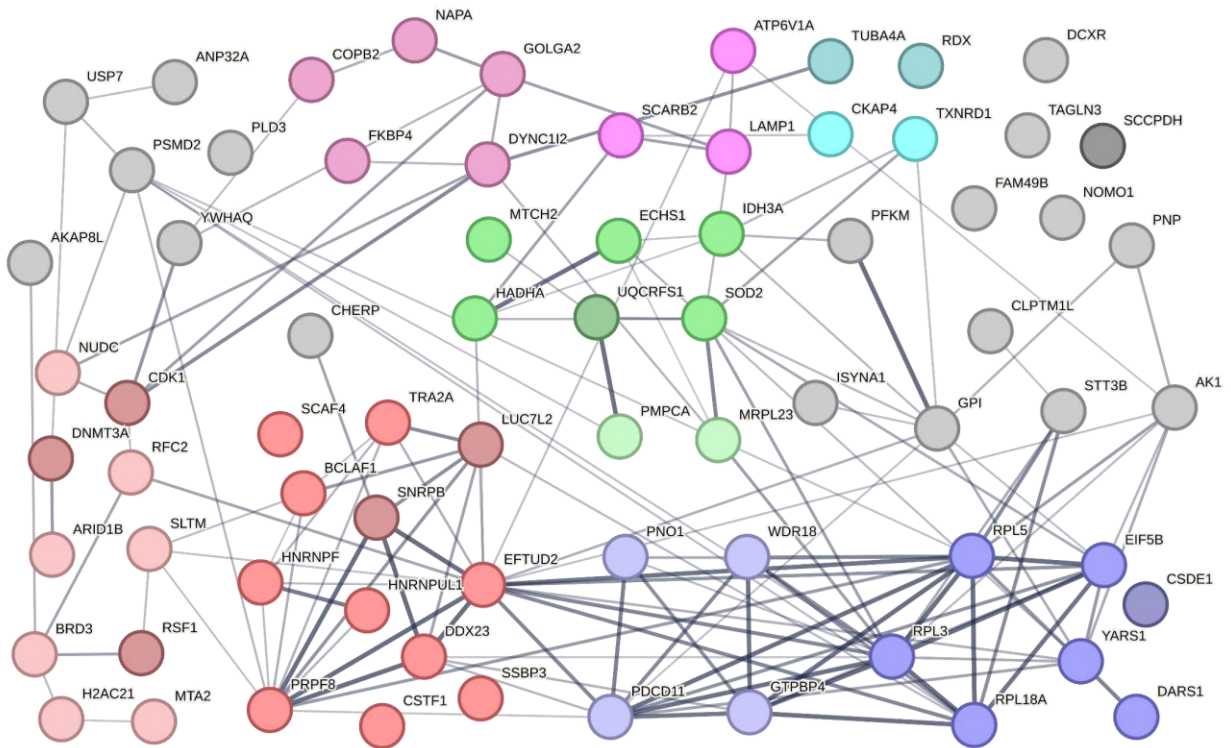


Legend: Nucleus Transcription Nucleolus Translation Mitochondrial transcription
Mitochondria Cytoskeleton Other organelles Other proteins

Supplementary Fig. S1. (A-B) STRING analysis with stabilized (A) and destabilized proteins (B) in LUHMES cells upon Pepstatin A treatment during early neuronal differentiation averaged over 12h, 24h and 48h after label switch (n=3 independent experiments).

A

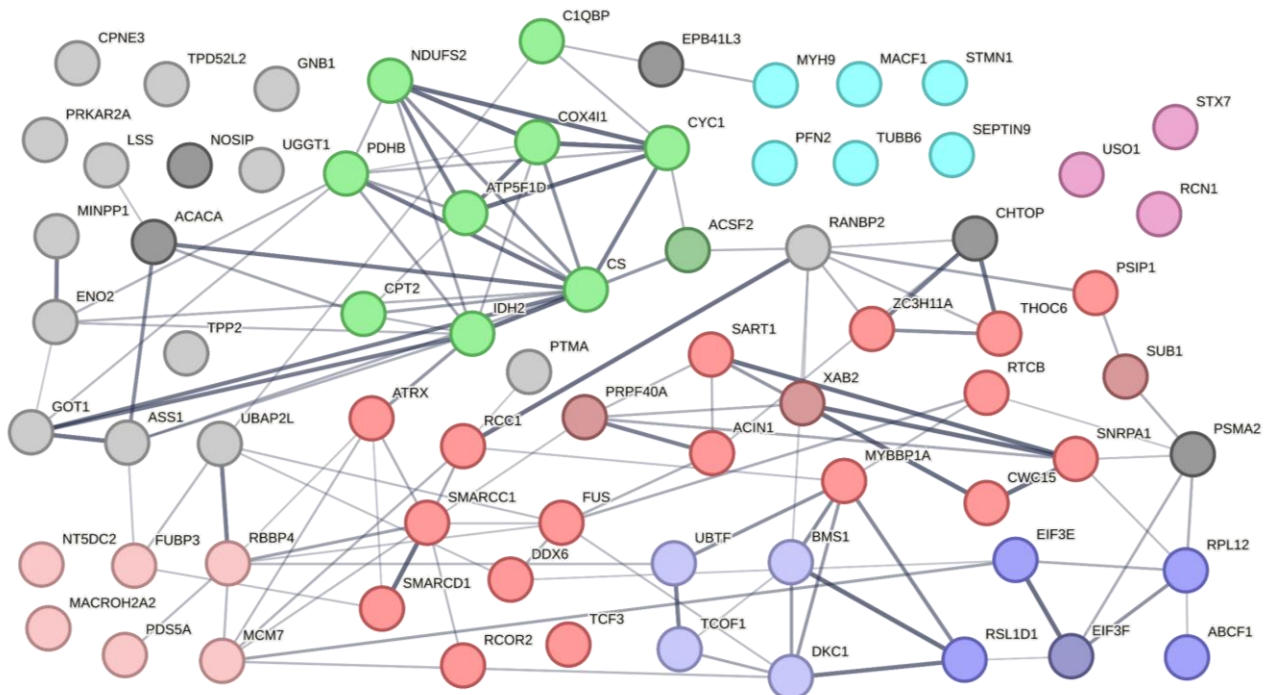
STRING analysis of stabilized proteins upon PepA (late differentiation)



Legend: Nucleus (red) Transcription (red) Nucleolus (blue) Translation (blue) Mitochondrial transcription (green)
Mitochondria (green) Cytoskeleton (cyan) Other organelles (magenta) Other proteins (grey)

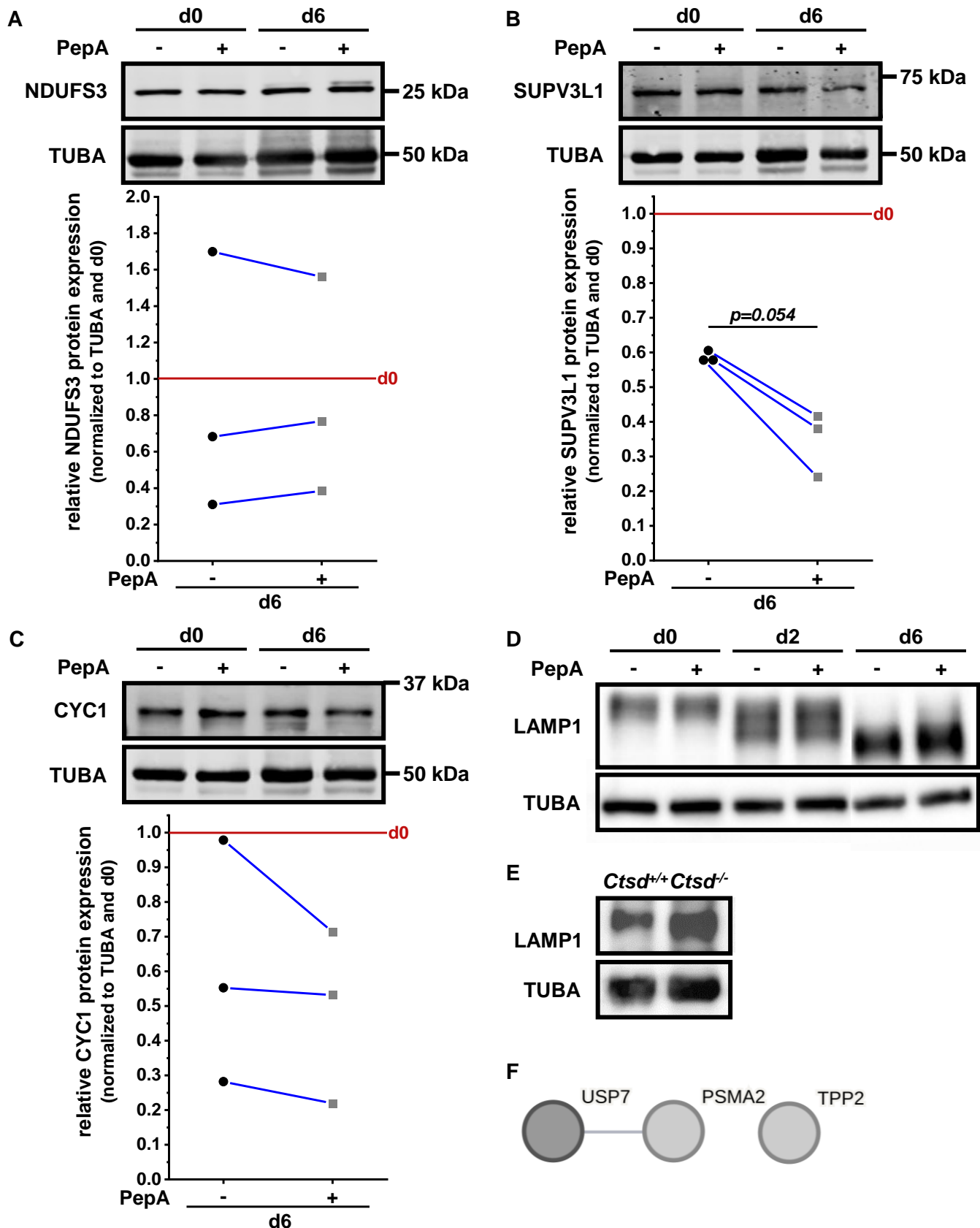
B

STRING analysis of destabilized proteins upon PepA (late differentiation)



Legend: Nucleus (red) Transcription (red) Nucleolus (blue) Translation (blue) Mitochondrial transcription (green)
Mitochondria (green) Cytoskeleton (cyan) Other organelles (magenta) Other proteins (grey)

Supplementary Fig. S2. (A-B) STRING analysis with stabilized (A) and destabilized proteins (B) in LUHMES cells upon Pepstatin A treatment during late neuronal differentiation averaged over 12h, 24h and 48h after label switch (n=3 independent experiments).



Supplementary Fig. S3. (A-C) Western Blot of SUPV3L1 (A), CYC1 (B) and NDUFS3 (C) of LUHMES cell lysates \pm Pepstatin A treatment during neuronal differentiation (n=3 independent experiment; two-sided paired-sample t-test). (D) Western Blot of LAMP1 of LUHMES cell lysates \pm Pepstatin A treatment during neuronal differentiation (n=1 independent experiment). (E) Western Blot of LAMP1 of whole brain lysates of a *Ctsd*^{+/+} and *Ctsd*^{-/-} mouse (n=1 independent experiment). (F) STRING analysis with stabilized (USP7) and destabilized proteins (PSMA2; TPP2) of the Ubiquitin-Proteasome System (UPS) in LUHMES cells upon Pepstatin A treatment during late neuronal differentiation averaged over 12h, 24h and 48h after label switch (n=3 independent experiments). Diagrams show all data points with paired connection per biological replicate and p -values.