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The temporal dynamics of mild hypothermia response: from thermogenesis to protein synthesis

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Targeted temperature management

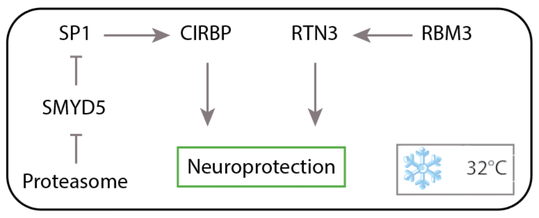
1. Benefits:
   → Reduces brain damage after hypoxic events as neonatal asphyxia, cardiac arrest or drowning.

2. Potential risks:
   → Systemic Inflammatory Response Syndrome (SIRS)
   → Bradycardia, Hypotension, Coagulopathies, Pneumonia

Thermogard XP®

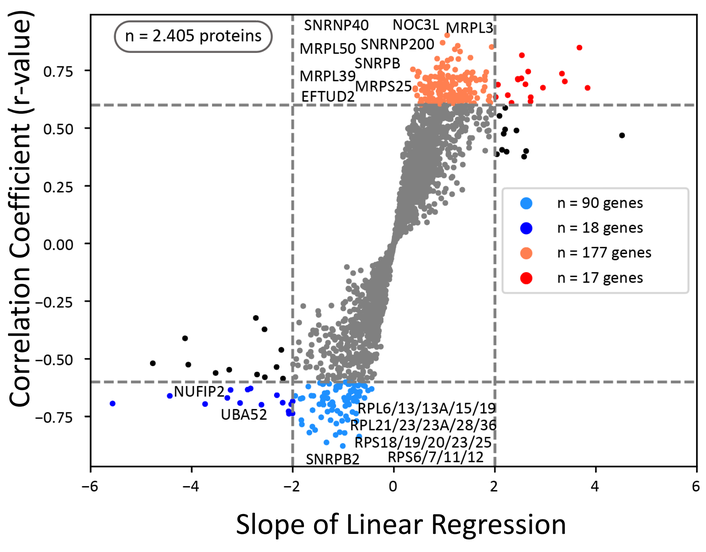
3. Understanding the pathways affected by TTM could:
   → Reveal the mechanisms behind its benefits and side effects
   → Help identify new targets for neurodegenerative treatments
   → Enable the use of drugs to activate these pathways instead of cooling

4. Only a few cold shock proteins are known
   a. RBM3: RNA Binding Motif Protein induced
   b. RTN3: Reticulon protein
   c. SP1: Transcription factor
   d. CIRBP: RNA Binding protein induced
   e. SMYD5: Histone methyltransferase



Ribosomal related proteins during hypothermia in HEK293 cells

On the 302 targeted proteins
31 are ribosome related:



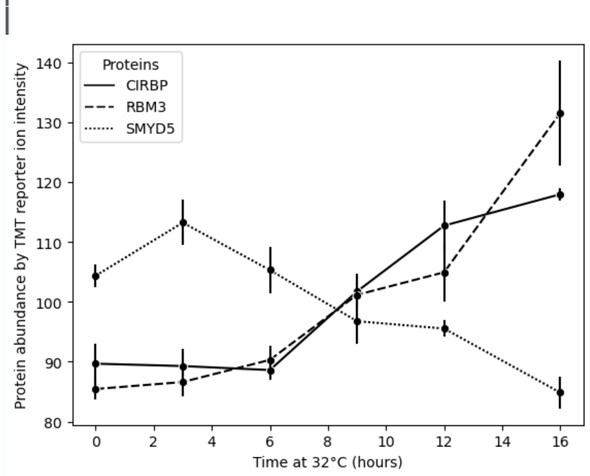
Cytoplasmic ribosomes
RPL proteins (60S component):
RPL6, RPL19, RPL21, RPL13, RPL23, RPL23A, RPL13A, RPL36, RPL15, RPL28, RPL40/UBA52

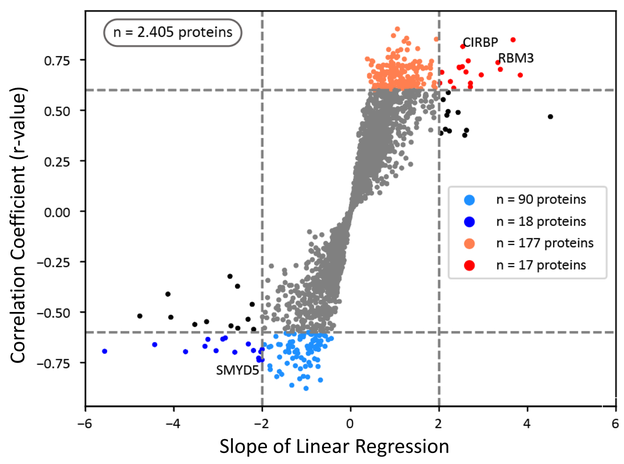
RPS proteins (40S component):
RPS6, RPS7, RPS11, RPS12, RPS18, RPS19, RPS20, RPS23, RPS25.

Mitochondrial ribosomes:
MRPS and MRPL proteins :
MRPS25, MRPL3, MRPL39, MRPL50.

Factors:
Ribosome biogenesis factors or splicing factors:
NOC3L, NUFIP2, EFTUD2, SNRPB, SNRPB2, SNRNP40, SNRNP200

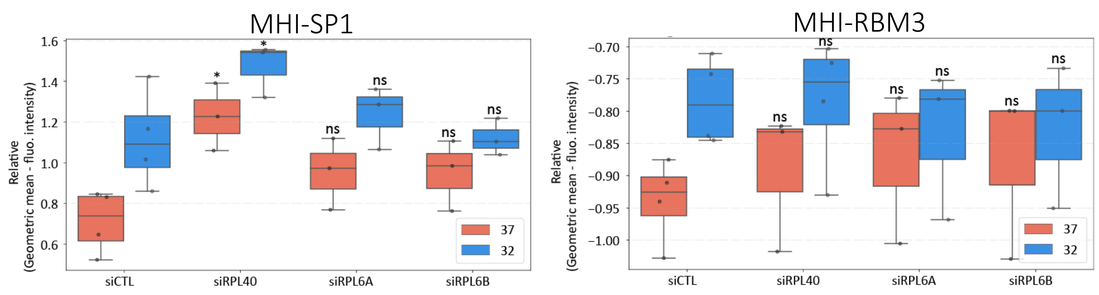
Unbiased proteomic study: target proteins detected in HEK293 cells



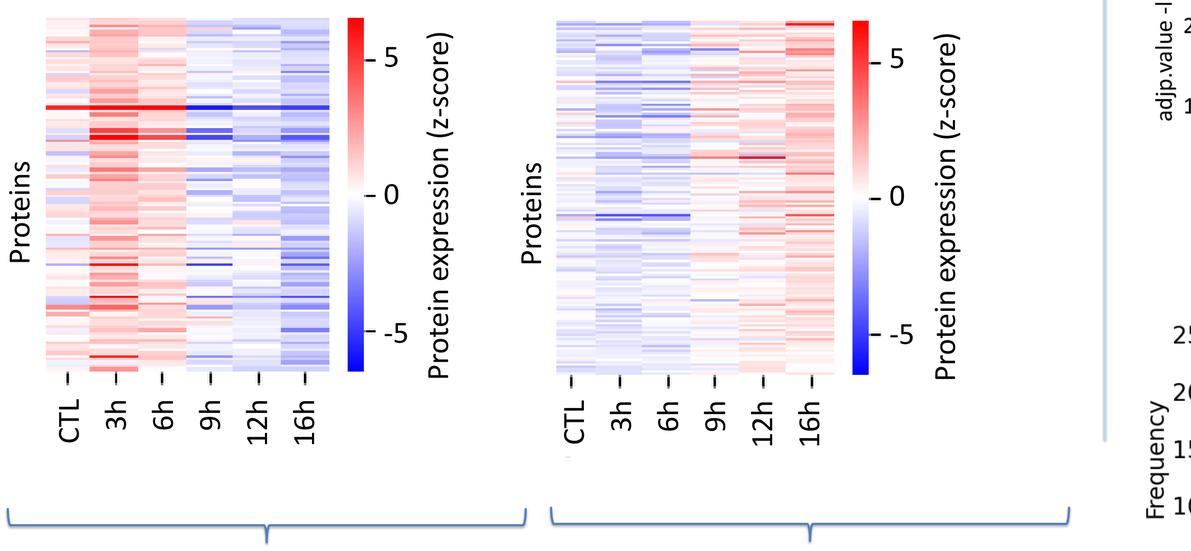


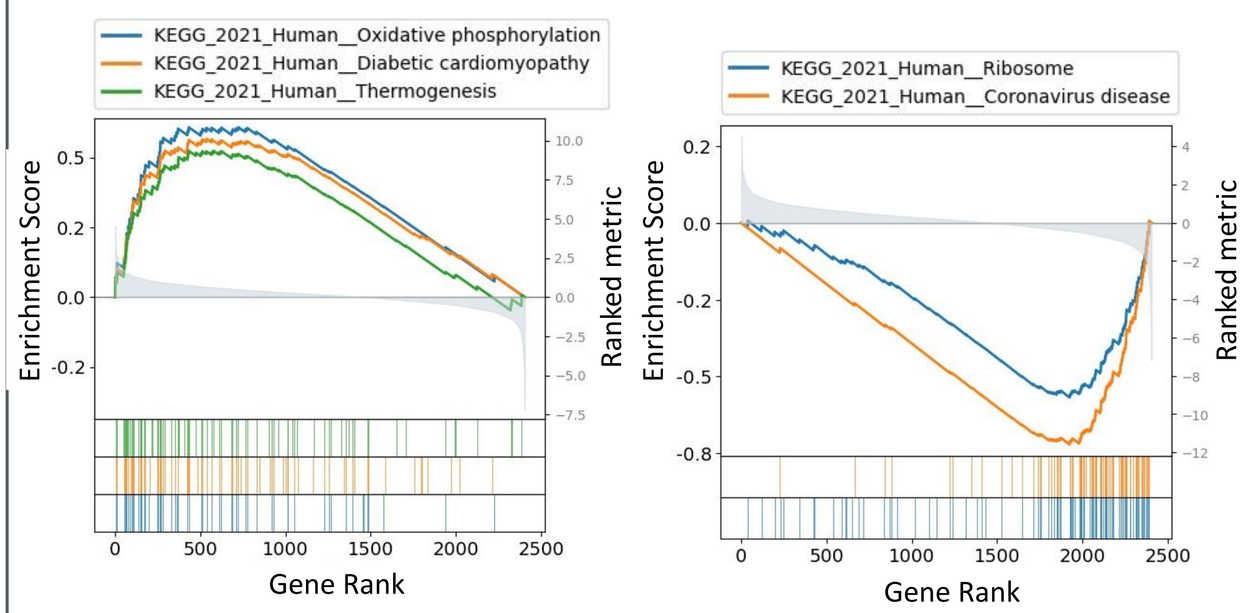
RPL40/UBA52 is a repressor of SP1

Flow cytometry approach using a fluorescent indicator to map promoter usage in HEK293 cells

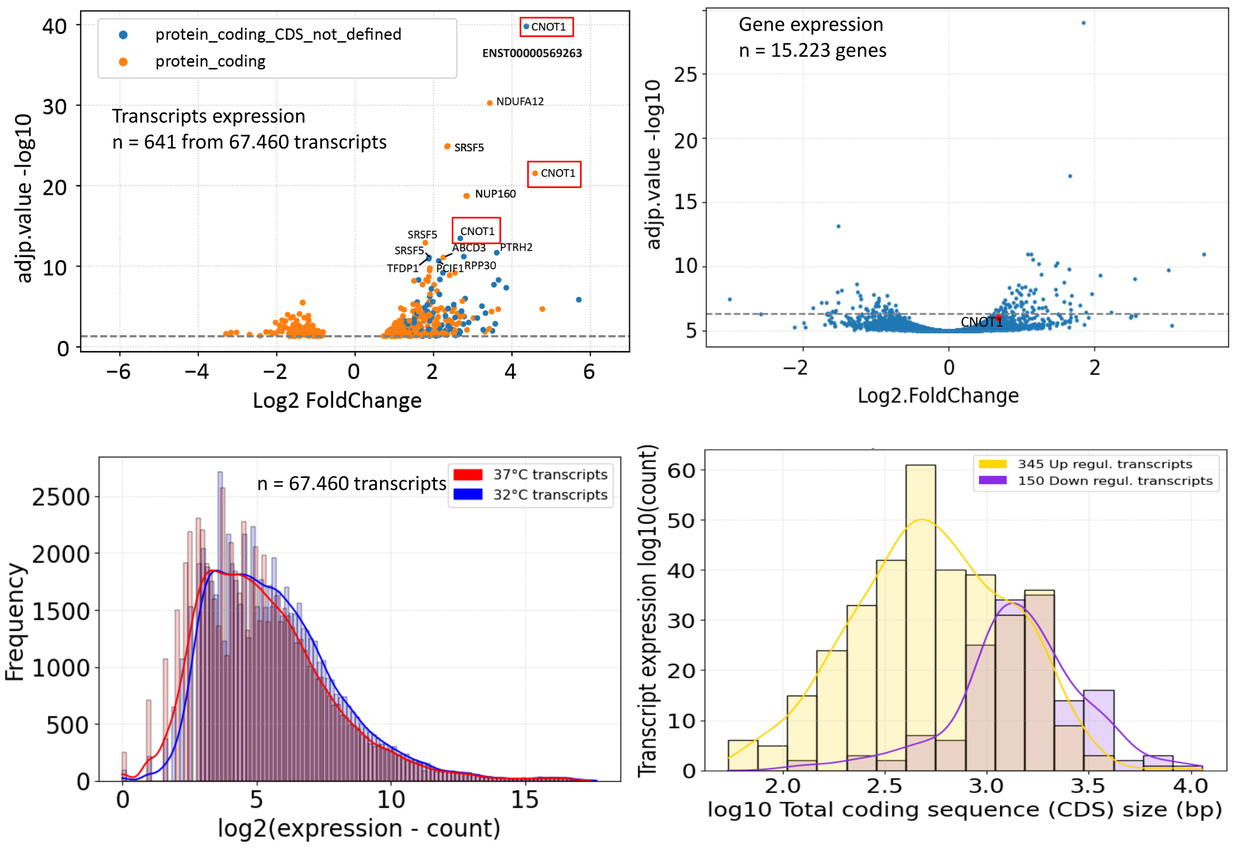


Two mild hypothermia responses in HEK293 cells: thermogenesis and translation control

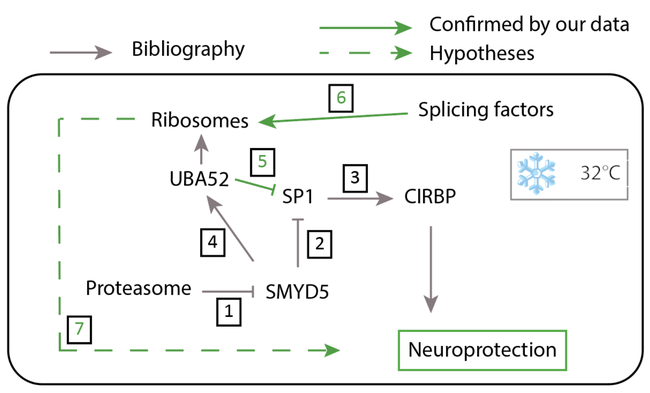




Isoform switch during mild hypothermia in HEK293 cells



Schematic summary



At 32°C:
1. SMYD5 protein is degraded
2. Lack of SMYD5 leads to SP1 expression
3. SP1 induces CIRBP expression
4. SMYD5 is unable to trimethylated UBA52
5. Lack of UBA52 activates SP1 expression
6. Isoform switch from long to short isoforms
7. Ribosomes appear key actors in MHR