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FOXOs modulate proteasome activity in human-induced pluripotent stem cells of Huntington's disease and their derived neural cells

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FOXOs modulate proteasome activity in human-induced pluripotent stem cells of Huntington's disease and their derived neural cells

Liu, Y., Qiao, F., Leiferman, P. C., Ross, A., Schlenker, E. H., Wang, H.

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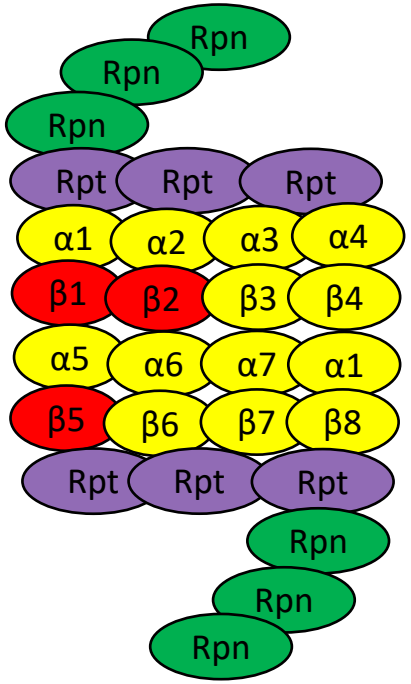
Abstract Abstracted

- Pluripotent stem cells with Huntington’s disease break down more protein than normal pluripotent stem cells
- However, pre-neurons with Huntington’s disease break down less protein
- Lastly, neurons with Huntington’s disease break down even less protein
- However, a transcription factor which increases how much proteasomes (complexes which break down proteins) act increases how much total protein is broken down

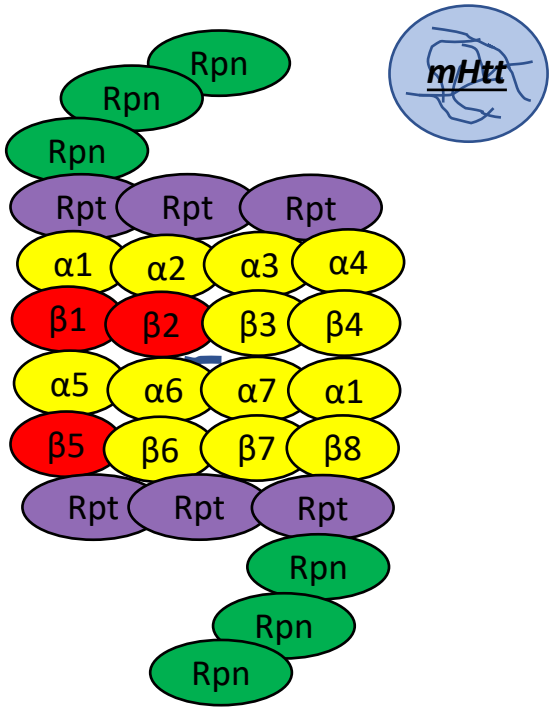
Introduction



30S proteasome

- Proteasomes break down misfolded proteins
- Protein degradation is important to maintain proteasis

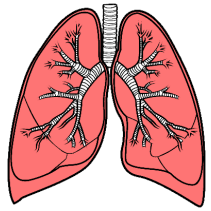
Introduction



30S proteasome

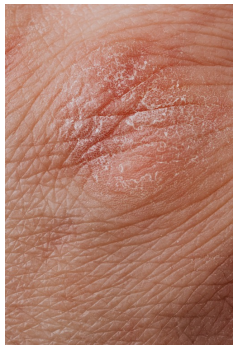
- Huntington's disease is a proteinopathy (caused by abnormal protein: mHtt)
- Proteasis is disrupted
- Proteasomes degrade the cytotoxic mHtt aggregates

Introduction

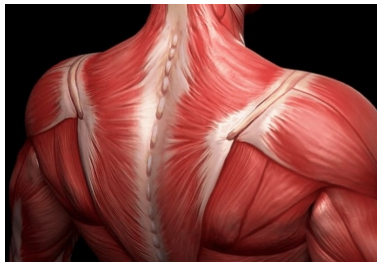


Endoderm
- Glands that form secretions in digestive tract
- Epithelium of the bladder

PSCs



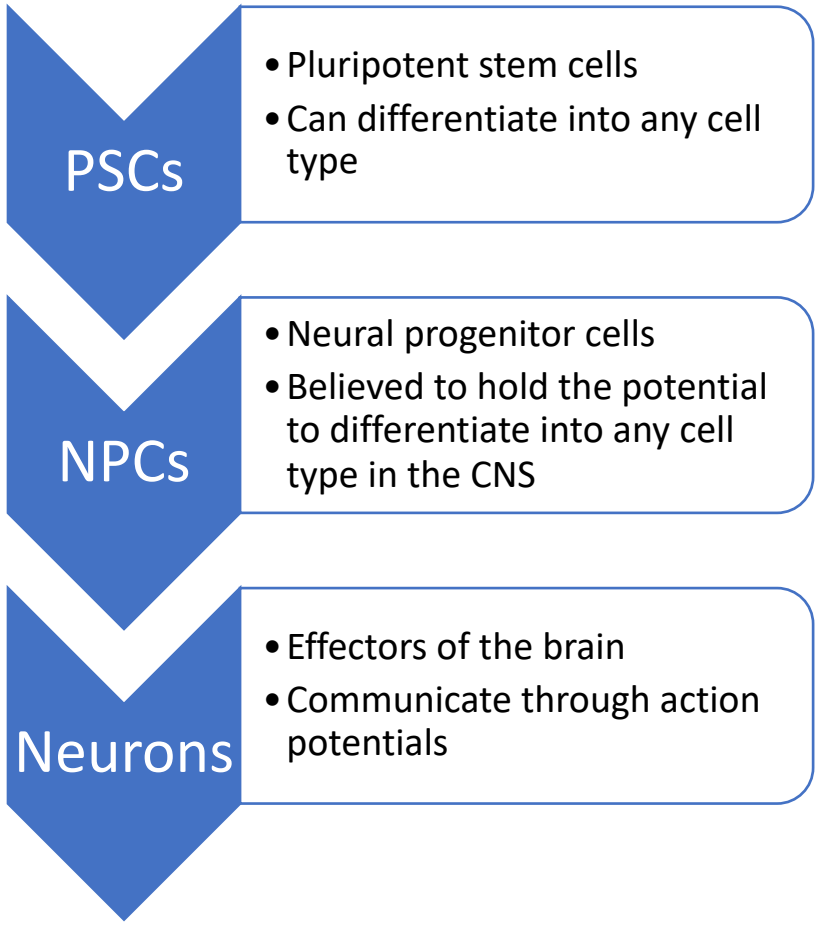
Ectoderm
- Some epithelial tissue
- Nerve tissue
- Salivary glands



Mesoderm
- Muscles
- Bone and cartilage
- Blood cells

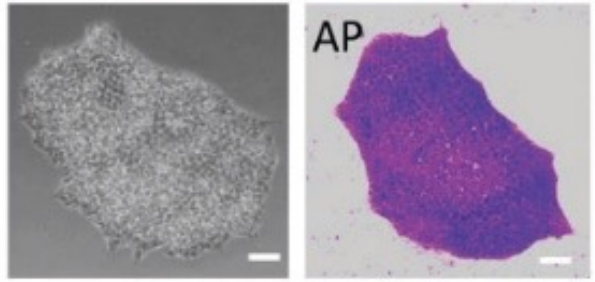
- Pluripotent stem cells can differentiate into any type of cell in the body
- To maintain pluripotency, maintenance of proteasis is important
- Environmental factors can stimulate PSCs to differentiate specifically

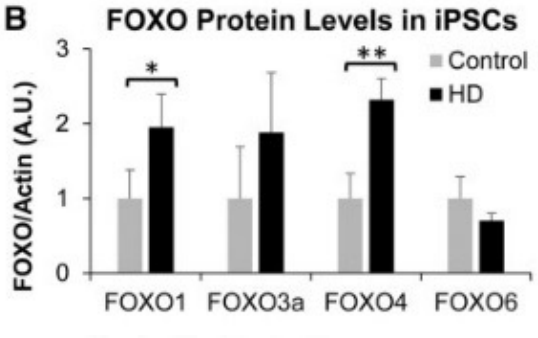
Methods

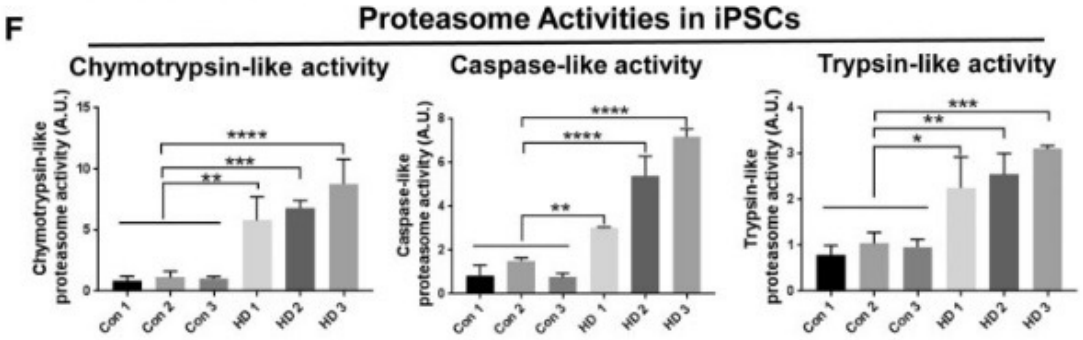


- Liu et al. transfected the PSCs with HD-inducing (high CAG repeat length) plasmids
- The proteasome activity in each cell type (HD + control)
- FOXO levels were also measured
  - FOXO1
  - FOXO3a
  - FOXO4
  - FOXO6

Results



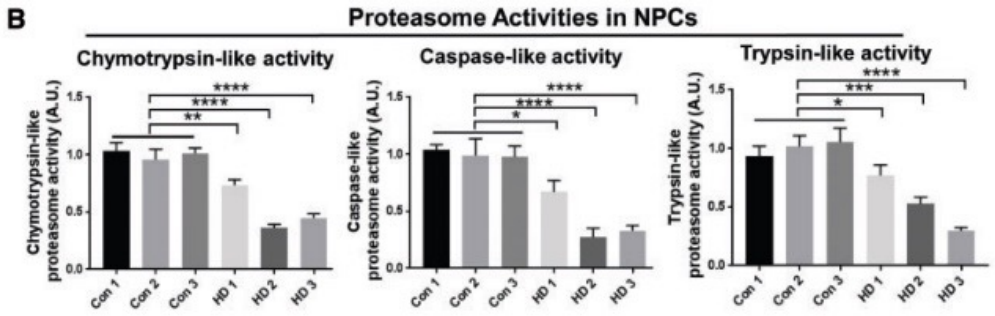




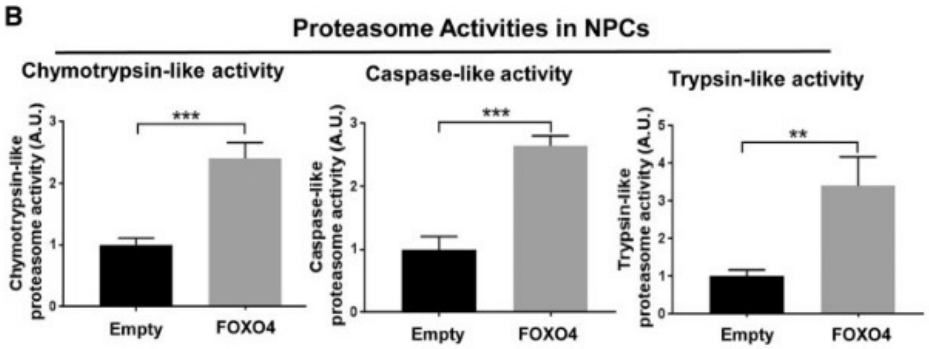
- HD iPSCs maintained normal morphology and pluripotency
- HD iPSCs exhibited greater FOXO1 and FOXO4 expression
- Knockdown of FOXO4 only lowered proteasomal function

Results

Before FOXO4 overexpression

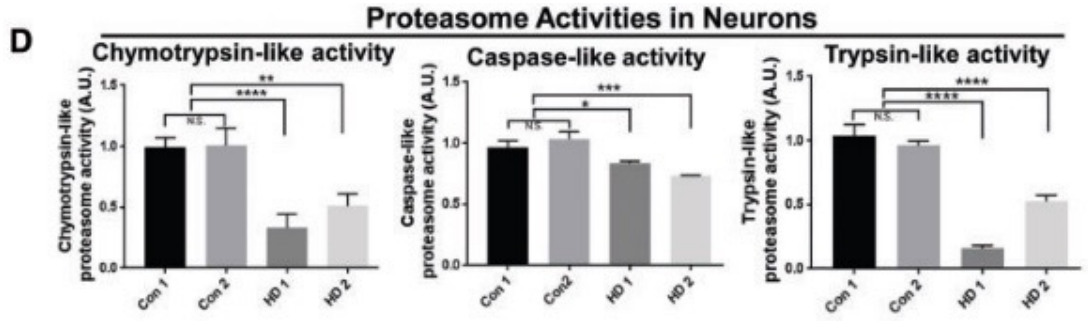


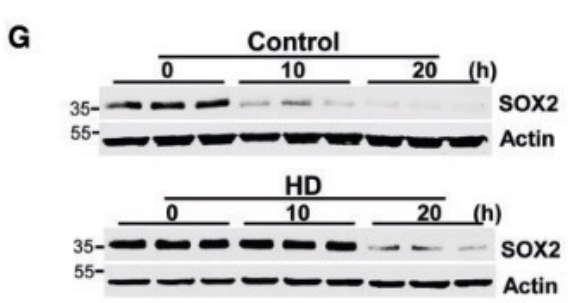
After FOXO4 overexpression

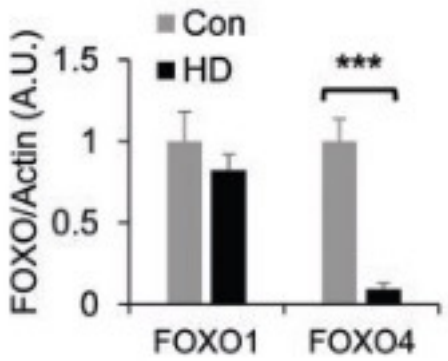


- NPC (control + HD) exhibited lower proteasomal function and FOXO1 and FOXO4 expression
- HD cells now experienced lower proteasomal function than their control counterparts
- FOXO4 overexpression rescued proteasomal function in HD NPCs

Results







- Proteasomal function in HD iPSC-derived neurons was lower than control neurons
- SOX2 degradation rate was significantly lower in the HD neurons
- FOXO4 expression significantly differed between control and HD mice

Conclusions

- HD iPSCs maintained pluripotency
- FOXO4, but not FOXO1, mediates proteasomal function in HD
- FOXO4 overexpression rescued proteasomal function in HD NPCs

HD cells compared to controls

Stage: [Condition]	FOXO1 expression	FOXO4 expression	Proteasomal activity
iPSC	↑	↑	↑
NPC	↓	↓	↓
Neuron	-	↓	↓
iPSCs: FOXO4 knockdown	-	↓	↓
NPCs: FOXO4 overexpression	-	↑	↑

Reference

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Discussion Questions

1. What would you like to see in stem cell research?

2. Gene therapy (HD iPSC generation, FOXO1/FOXO4 knockdown, FOXO4 overexpession) was used. What potential do you see in gene therapy?

3. Do you think we should explore more disease-manipulating treatments, or should we quench the issue before solving it?