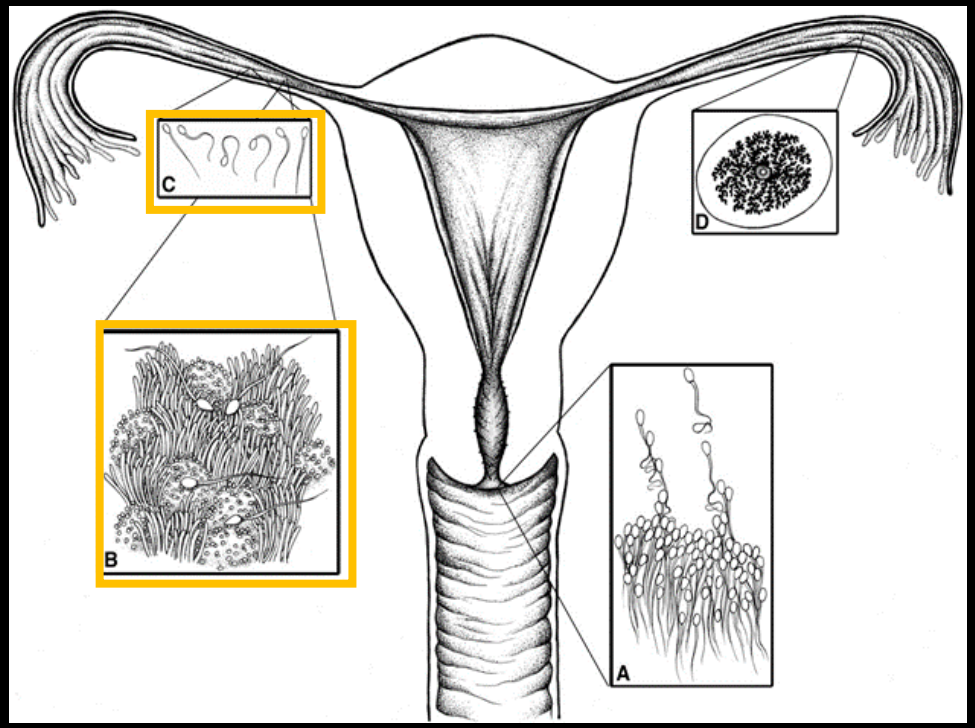
Spermatozoan Metabolism as a Non-traditional model for the study of Huntington Disease

Meghan Lawlor, Michal Zigo, Karl Kerns, Peter Sutovsky

Spermatozoan Capacitation

- Grants fertilizing ability
- Accelerates sperm metabolism and induces hyperactivated movement
- HD-related gene products activated in capacitated spermatozoa
- Non-traditional model for HD study and treatment testing



HD Pathogenesis

(1) Aggregation of mutant huntingtin

(2) Transcriptional dysfunction

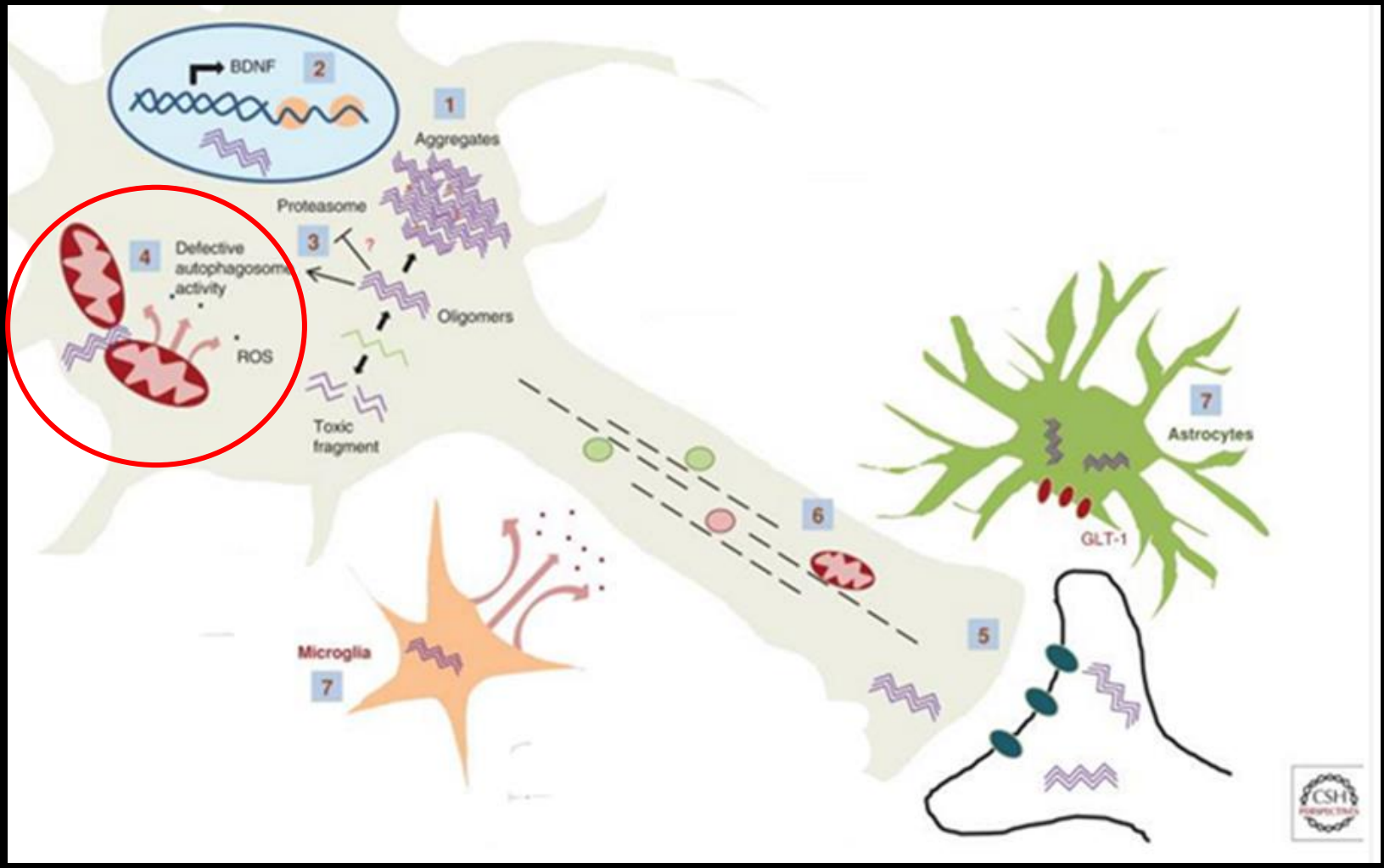
(3) Proteasome dysfunction

(4) Mitochondrial dysfunction

(5) Alteration of synaptic plasticity

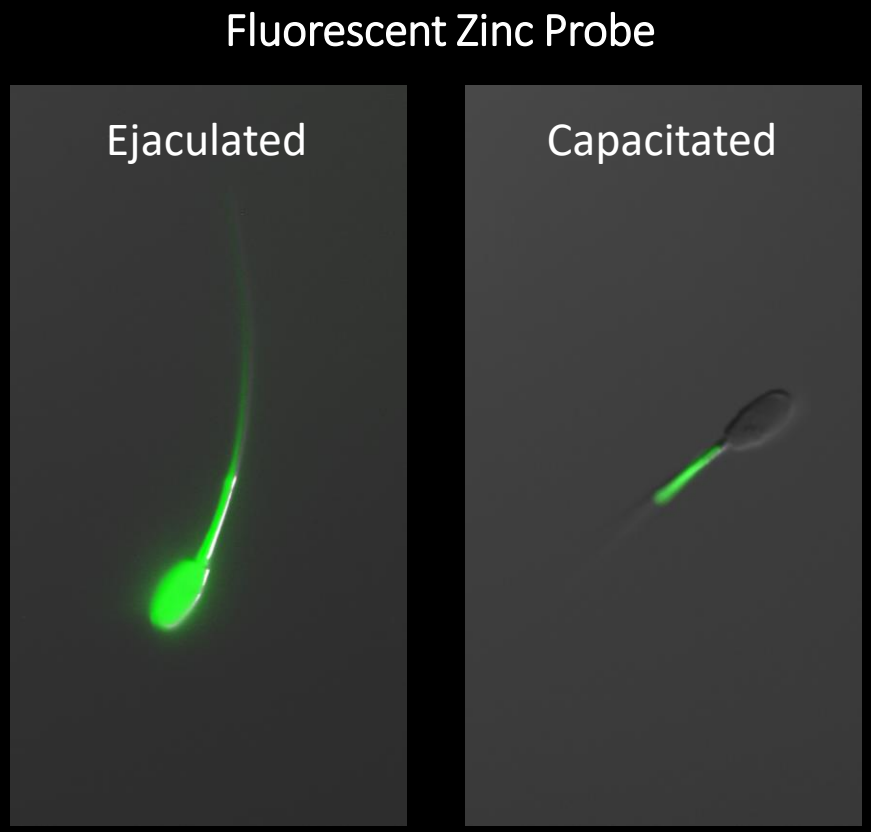
(6) Defective axonal transport

(7) Microglial dysfunction



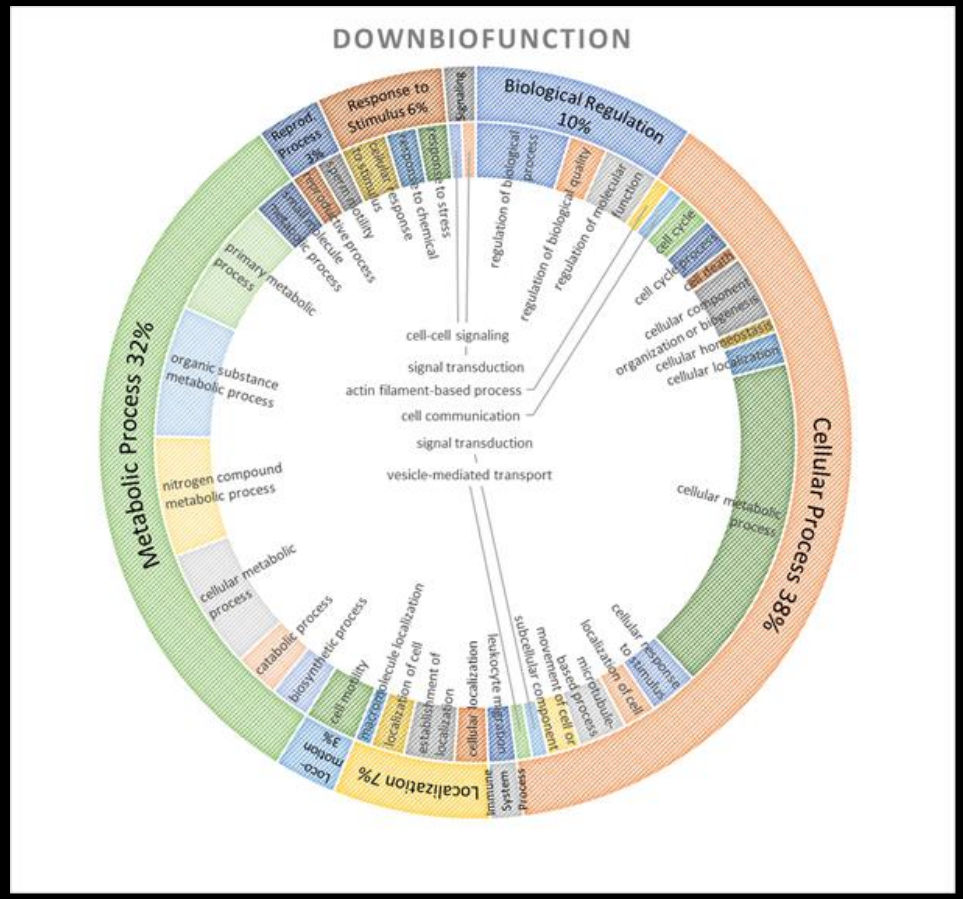
Role of Zinc in Capacitation & HD

- Essential for neuronal function & spermatozoan capacitation
- Dysregulation in HD →
  - Mitochondrial dysfunction
  - Oxidative stress (ROS)
  - Reduced ZnT3 expression



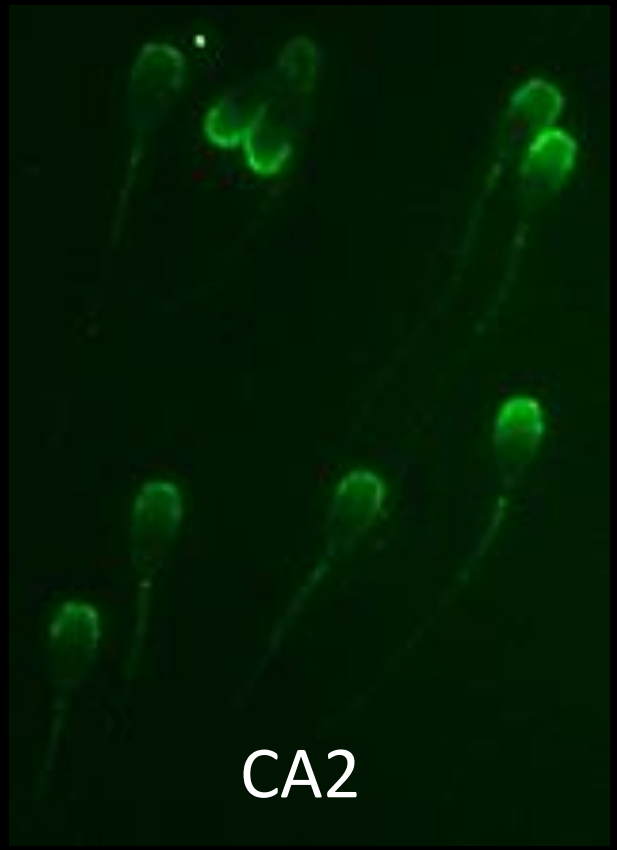
Implications of HD in Spermatozoa
mitochondrial dysfunction

- *Downregulation* of mitochondrial genes:
  - COX5, COX6, COX7, COX8
  - ATP5A, ATP5H, and ATP5G
  - NDUFA, NDUF5
  - SDHA, SDHB
  - SLC25A4, SLC24A5
- Mitochondrial metabolism related biomarkers:
  - Pyruvate
  - Complex-I-dependent respiration



Implications of HD in Spermatozoa:
transcriptional dysfunction

- *Upregulation* of transcriptional genes:
  - MAP2K6
- *Downregulation* of transcription factors:
  - TBP
  - SP1
  - PPARGC1A
- Dysregulated zincoproteins:
  - ARF1
  - CRYZ
  - GAPDHS
  - VAT1
  - CA2



Conclusion / ideas for future study

- Spermatozoa as “neurons with tails” – unique model for HD studies
- Targeting zinc ion dysregulation as therapeutic remedy
- Mitochondrial biomarkers could be used for diagnosis
- Investigation of mitochondrial & transcriptional proteins expressed in spermatozoa
  - Could be used to monitor disease progression & efficacy of therapeutic treatments

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