Acute Innate immune Responses to Simulated Transplantation Surgery in Two HD Mouse Models.

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INTRODUCTION

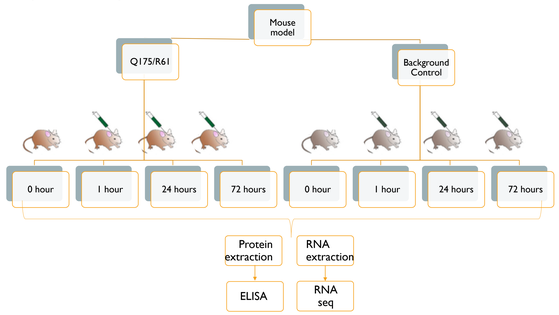
- Multiple studies provide proof-of-concept for the benefits of cell replacement therapy (CRT) in neurodegenerative conditions including Huntington's disease (HD)[1].
- Attaining a high survival rate of the cells post-transplantation has remained a significant challenge.
- Neuroinflammation is crucial in the onset and progression of HD[2].
- . Identification of key factors in the inflammatory process, may facilitate the translation of CRT into therapy for patients with neurodegenerative diseases.

OBJECTIVES

- We hypothesise that inflammatory response to CRT surgery might be exacerbated due to a primed intrinsic inflammatory environment, partly explaining cell death and graft failure
- This study aims to define innate immune responses to **simulated transplantation surgery** in two HD mouse models (^{HD}Q175 & ^{HD}R6/1).

METHODS

- Mice were either kept as Control (no surgery, time 0), or underwent bilateral stereotactic needle insertion to the striatum simulating CRT surgery and culled at 1hr, 24hrs or 72hrs post-surgery, as shown below.
- A 3mm^3 cube of tissue surrounding and including the injury site was collected for RNA sequencing and multiplex cytokine analysis.



- **Figure 1.** Design of simulated (mock) transplant surgery and subsequent experiments. (N:3 for cytokine analysis, N:4-6 for RNA sequencing. (Q175 anr R61 are transgenic HD mice strains).

RESULTS

- The introduction of a needle into mouse brain produced an amplified pro-inflammatory response in both HD models, compared with background controls as shown by increased **cytokine** levels.

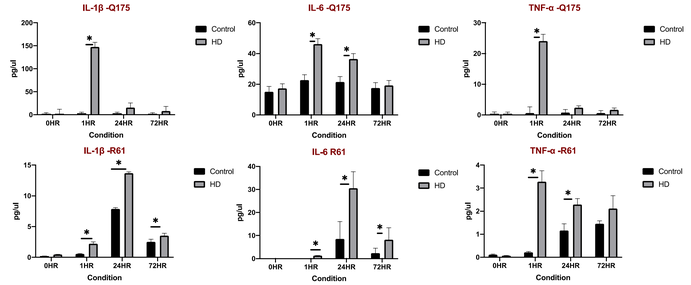


Fig 2. Brain tissue lysate concentration of **IL-1β,IL-6, TNF-α.** Concentrations are in pg/ul. HD: Q175 and R61 mice, Control: Wild background/litter mates, n:3, p<0.05, Error bar: Mean ±SEM, 2 way ANOVA.

- Proinflammatory **genes** upregulated in HD (at 1 hour in Q175, ar 1 hour, 24 hours & 72 hours in R61) after needle injury compared With HD no needle

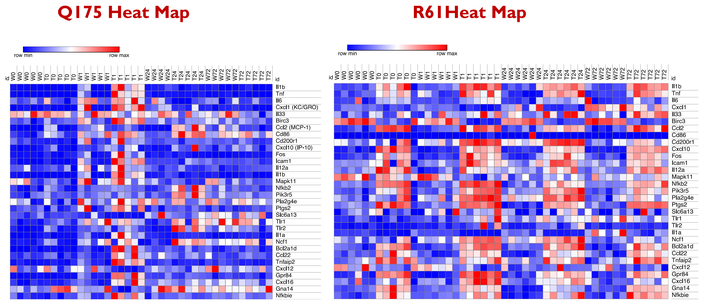


Fig 3. Heat map of row counts of **genes** involved in the **neuroinflammatory** pathway. Inflammatory genes upregulated at 1 hour post-surgery in the Q175 HD model, inflammatory genes upregulated at 1 hour, 24 hours & 72 hours in R61 HD model. Image obtained using Morpheus. (W: Wild, T: Transgenic/HD Red: Upregulation, Blue: Down regulation)

- Major biological changes at 1 hour post injury in the HD mice compared with background control included upregulation of IL-1B, TNF, TLR4 & NF-kB (in Q175), and IL-1B, TNF, IL-4, IGF1 (in R61).

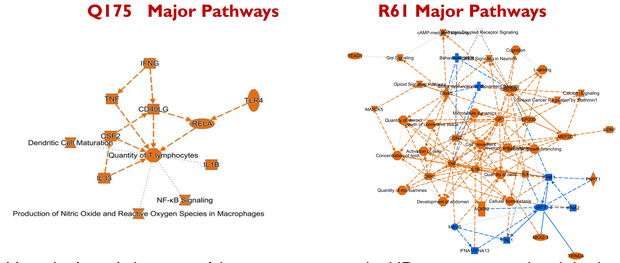


Fig 4. Major biological changes at 1 hour post injury in the HD mice compared with background control. (Orange: Upregulation, Blue: Down regulation)

CONCLUSIONS

- The amplified pro-inflammatory response to needle injury in HD brain compared to wild-type, reveals a state of enhanced basal pro-inflammatory activation.
- Thus the HD brain appears to be 'primed' to produce an enhanced immune response.
- The inflammatory reaction to surgical trauma post-CRT is likely to contribute to neural graft site hostility.
- Simultaneous modulation of these pro-inflammatory pathways during graft delivery may improve graft survival in CRT and advance the translation of direct intraparenchymal delivery of cells into neurosurgical therapeutic practice

REFERENCES

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- C. A. Ross and S. J. Tabrizi, "Huntington's disease: from molecular pathogenesis to clinical treatment," e *Lancet Neurology*, vol. 10, no. 1, pp. 83–98, 2011.

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