Effects of Physiological Glucose and Oxygen Conditions On Human Neural Organoid Development

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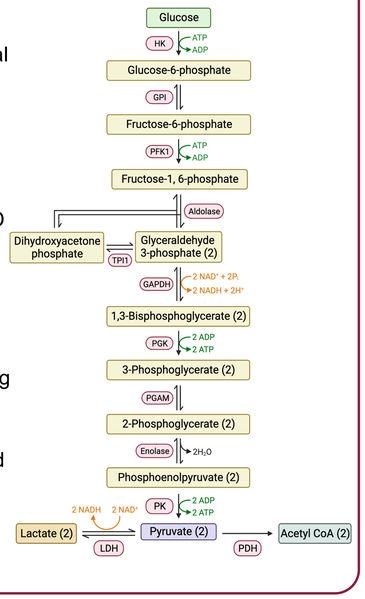
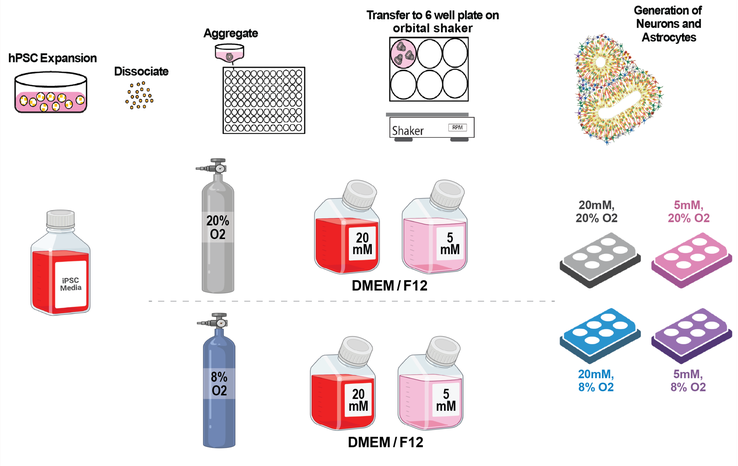
Introduction

- The mammalian brain undergoes significant metabolic shifts during development that actively shape neural cell fate and organization
- Neural progenitors transition from primarily glycolytic metabolism to oxidative phosphorylation as they differentiate into mature neurons [1]
- Cortical organoids provide valuable 3D models of human brain development but are limited by non-physiological culture conditions [2]
- Standard culture media use non-physiological glucose (20-25mM) and oxygen (20%) levels, potentially limiting organoid development [3]
- Neural stem cells respond strongly to metabolic cues during proliferation and differentiation [4]
- We hypothesize that physiological conditions (5mM glucose, 8% oxygen) will enhance organoid development

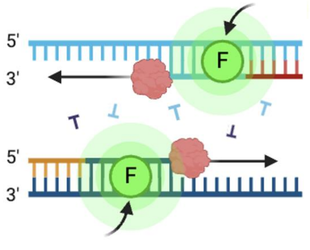


Methods

Glucose and Oxygen Perturbation



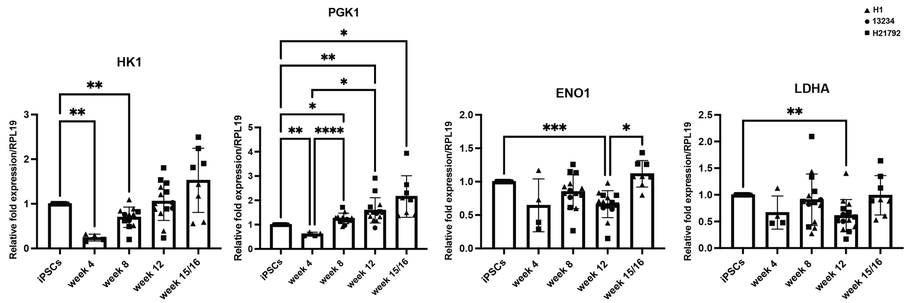
Quantitative Polymerase Chain Reaction



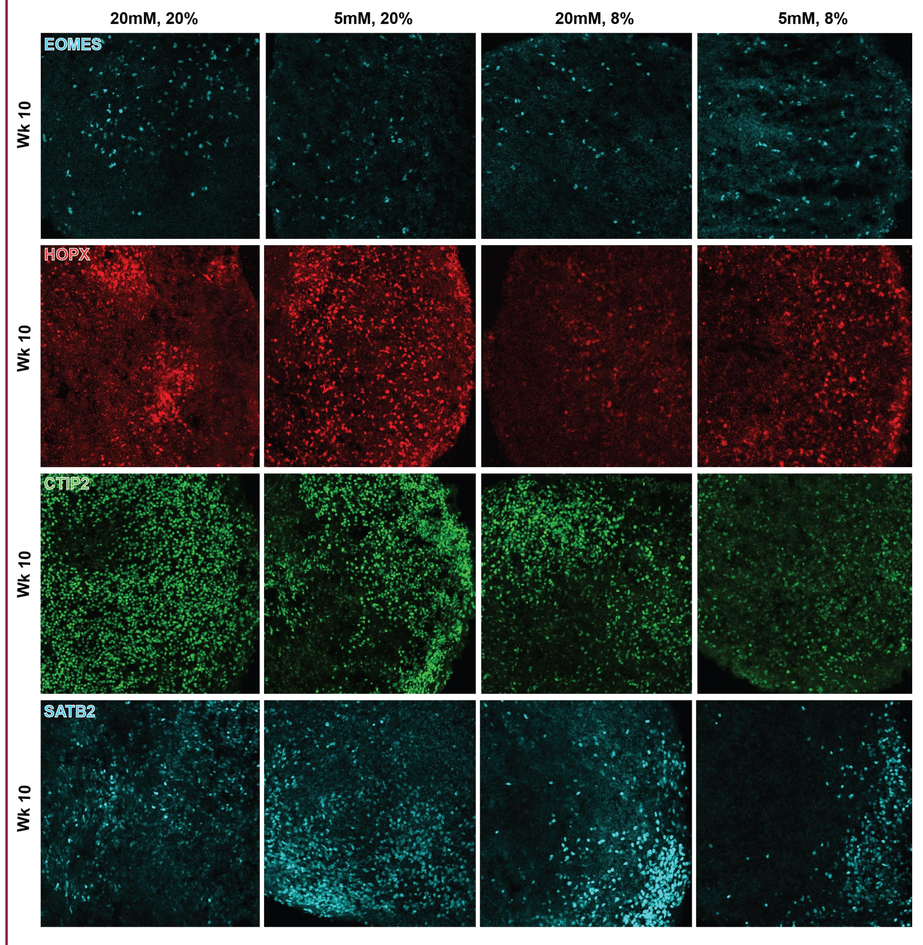
Immunohistochemistry

Results

Temporal Metabolic Regulation: Glycolytic Genes Show Dynamic Expression Patterns During Organoid Development

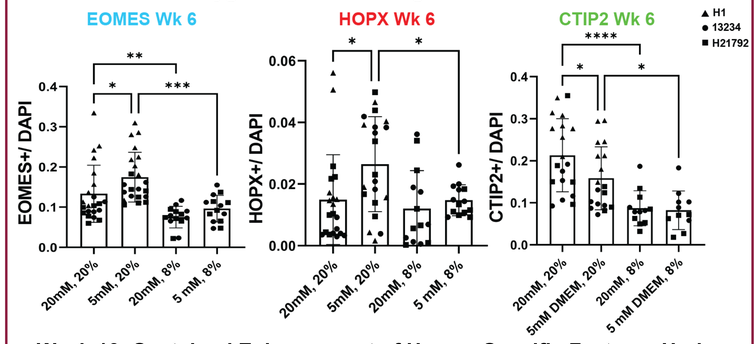


Physiological Metabolic Conditions Reveal Cell Type Specific Responses Across Developmental Stages

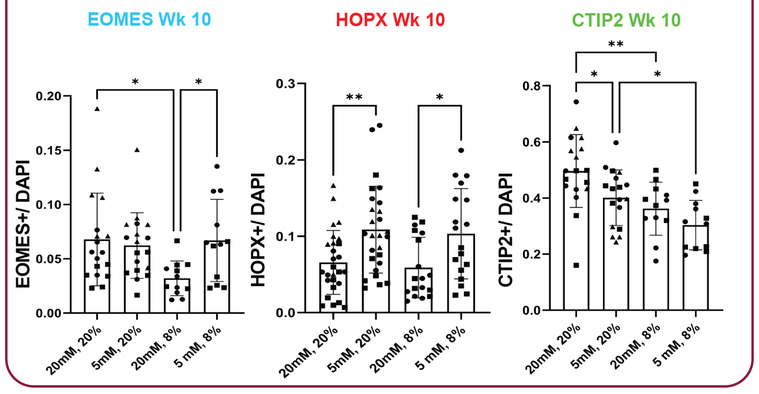


Results

Week 6: Physiological Glucose Promotes Outer Radial Glia While Oxygen Modulates Progenitor Balance



Week 10: Sustained Enhancement of Human Specific Features Under Physiological local Conditions



Summary, Conclusions and Future Directions

Our study demonstrates that physiological glucose and oxygen conditions significantly impact neural organoid development by promoting human specific features of cortical development. We found that physiological glucose (5mM) consistently enhances outer radial glia expansion, while physiological oxygen (8%) exerts stage specific effects on progenitor populations. These metabolic changes translate to increased upper-layer neurogenesis and decreased deep-layer neurogenesis, reflecting human specific cortical patterning. Future work will employ single-cell RNA sequencing to comprehensively characterize cell type specific transcriptional responses to metabolic conditions, revealing molecular mechanisms linking metabolism to cell fate determination. This approach will allow identification of metabolic gene networks that regulate neural progenitor identity and differentiation trajectories. These findings establish metabolism as an instructive signal in human cortical development and highlight the importance of physiologically relevant culture conditions for accurate brain modeling.

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References

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2. M. A. Lancaster *et al.*, "Cerebral organoids model human brain development and microcephaly," *Nature*, vol. 501, no. 7467, pp. 373–379, Sep. 2013, doi: 10.1038/nature12517.
3. A. Bhaduri *et al.*, "Cell stress in cortical organoids impairs molecular subtype specification," *Nature*, vol. 578, no. 7793, pp. 142–148, Feb. 2020, doi: 10.1038/s41586-020-1962-0.
4. N. Shyh-Chang and H.-H. Ng, "The metabolic programming of stem cells," *Genes Dev*, vol. 31, no. 4, pp. 336–346, Feb. 2017, doi: 10.1101/gad.293167.116.