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Abstract Title

How Much Is Enough? Modeling Epigenetic Regulator Dosage in Human Kidney Organoids to Understand Development, Health, and Pediatric Cancer

Authors

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Background

While many adult malignancies emerge after decades of genetic and environmental triggers, most pediatric cancers arise from disruptions of developmental programs. This includes altered activity of epigenetic regulators that organize chromatin and control gene expression. The essential role of these regulators in embryogenesis has been determined primarily through complete loss-of-function studies. This approach overlooks how development responds to the naturally graded, inter-individual variability in protein abundance, and how regulator dosage rather than presence or absence shapes cell fate. Kidney development is well-suited to address this topic, since the nephron progenitor pool is finite and exhausted as nephrogenesis ends. Persistent embryonic kidney tissue, known as nephrogenic rests, is associated with Wilms tumor. Our initial focus will be TRIM28, a chromatin-associated scaffold essential for gene silencing, whose reduced function is linked to these rests.

Objective

To overcome limitations of fetal tissues, we are establishing and optimizing a human induced pluripotent stem cell (hiPSC)-derived kidney organoid platform. This will enable accurate modeling of early development and mechanistic studies into the role of epigenetic regulator dosage, with Wilms tumor as our first target disease.

Methods

We are directing hiPSCs to three-dimensional kidney organoids through intermediate mesoderm and nephron progenitor stages. Degron-tagged TRIM28 will permit rapid, reversible, dose-controlled protein

depletion at defined developmental windows. This will allow us to vary the timings and magnitude of perturbation across organogenesis and to test whether altered dosage shifts the balance from normal differentiation to persistent progenitor states associated with Wilms tumor.

Results

N/A

Conclusion

This platform will provide a mechanistic framework for determining how epigenetic regulator dosage shapes developmental outcomes and disease susceptibility. Although Wilms tumor is our proof-of-principle, the underlying strategy can be adapted to other cancers arising from disrupted developmental programs, including hepatoblastoma, and more broadly, to questions of organ patterning, tissue composition, and developmental health.