Leveraging Human-Based Organoid Models to Decipher Disorders of Kidney Development

Naomi Pode Shakked

Did you know that Kidney development ceases near the end of pregnancy and no new functional kidney units (nephrons) are formed thereafter? This means that the kidney reserve one is born with needs to sustain them throughout life. Since the majority of these nephrons are formed in the third trimester of human pregnancy, preterm birth and other insults to kidney development during pregnancy can lead to a lower kidney reserve, exposing the newborn to a higher risk for developing kidney disease later in life.

The renin–angiotensin–aldosterone system (RAAS) regulates blood volume and systemic vascular resistance in humans. Autosomal Recessive Renal Tubular Dysgenesis (AR-RTD) is a fatal genetic disorder of kidney development resulting from pathogenic variants in any of the four genes involved in RAAS, often leading to perinatal death. The underlying etiology of this devastating disease is still unclear, and this hampers any potential development of novel etiology-based therapeutic interventions.

To address this gap, we sought to utilize kidney organoids. Organoids are miniature, personalized organs that unlock unprecedented precision in studying diseases, tailored to the individual's genetic background. Specifically, human-induced pluripotent stem cells (hiPSCs)-derived kidney organoids, mimic kidney development without an effective circulation, thereby providing a controlled system to study RAAS effects on kidney development. We induced null mutations in either of two AR-RTD-causing genes (*ACE* or *AGTR1*) in hiPSCs. These hiPSC lines and their isogenic-controls, along with hiPSCs derived from an AR-RTD patient, were differentiated to kidney organoids under standard (21%O_2) or hypoxic (2%O_2) conditions and grown in vivo under the kidney capsule of immunodeficient mice. While renal vesicle stage (d14) control organoids engrafted and differentiated well, d14 RAAS-mutant organoids failed to engraft due to insufficient pro-angiogenic VEGF-A expression. When grown under hypoxic conditions, VEGF-A expression was stimulated, and RAAS-mutant organoids were able to engraft and complete their differentiation in vivo.

Using this model we were able to uncover the underlying mechanism for this fatal disease, showing that RAAS-modified kidneys fail to recruit sufficient blood supply for their nourishment at a critical time during embryonic development. These human-based organoid models accurately replicate the disease phenotype, bringing us a significant step closer to understanding and combating developmentally-rooted renal diseases.

Our next big challenge is to determine which metabolites, capable of passing through the placenta, can aid and rescue renal development in affected fetuses. This holds the potential to revolutionize the way we approach kidney diseases in newborns.