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Iron deficiency in pregnancy is the most common micronutrient deficiency in the world, affecting as many as 2 billion people. Iron deficiency in pregnancy increases the risk for embryonic mortality, a preterm delivery and low birth weight baby, which highlights the importance of understanding how the required quantity of iron is delivered to the embryo for the prevention of birth defects.

The developing kidney requires sufficient iron for optimal organogenesis during pregnancy and in the early postnatal period. Iron is required throughout kidney morphogenesis, including during conversion of the metanephric mesenchyme into epithelia, during the branching of the ureteric bud, and during the postnatal completion of glomerulogenesis. Iron deficiency reduces nephron number and results in hypoplasia and hypertension, which increases the risk of renal failure and cardiovascular diseases in adult life. However, the mechanism by which iron traffics from the placenta to different cell lineages in developing organs including kidney has been a “black box” and as a result there have been few advances and almost no literature in understanding the impact of iron deficiency on organogenesis.

The current paradigm of iron trafficking derives from studies in the adult. These studies have revealed the molecular mechanisms underlying the so-called iron cycle, but surprisingly the deletion of its main components (transferrin, transferrin receptor1[Tfr1], divalent metal transporter 1[DMT1], Steap3, TIM) has produced much more limited phenotypes in the embryos than might have been predicted by the ubiquity of these proteins, and their conservation among species. Hence it remains unclear whether the ureteric bud and mesenchyme in the developing kidney obtain iron from different sources, whether iron delivery is “cell autonomous” or does reciprocal induction also include the exchange of iron between compartments, and whether iron deficiency dysregulates organogenesis of different cell lineages differently?

In this proposal, we identify iron trafficking processes that induce renal growth and development by genetically dissecting the functions of the central iron delivery pathway, Tf-Tfr1, in the developing kidney. The initial data unexpectedly suggested the following hypotheses, which we test here: these are (1) a cell specific, and (2) a temporally specific requirement for Tf-Tfr1, (3) a classical cell autonomous mechanism mediated by Tfr1, but additionally the possibility of a cell non-autonomous pathway as well, (4) the activity of non-Tf iron donors, including a novel pathway involving ferritin and (5) the activity of a unique iron transporter that is both sufficient and necessary to transfer Tf iron to the cytosol of the developing kidney. These hypotheses identify and test novel, tissue specific, and stage specific mechanisms of iron delivery, implicating that complex and highly regulated mechanisms synchronize cell need with iron capture. We suggest that these pathways are likely to be the target of iron deficiency in pregnancy, which is known to limit kidney growth and development.