

LINEAGE STUDY OF THE GDNF-EXPRESSING CELLS IN THE NEPHROGENIC MESENCHYME AND ANALYSIS OF THEIR SELF-RENEWAL POTENTIAL DURING KIDNEY DEVELOPMENT

Cristina Cebrián¹, Naoya Asai², Vivette D'Agati¹, Frank Costantini¹.

1.Columbia University Medical Center, New York, New York.

2.Nagoya University, Nagoya, Japan.

Kidney development initiates when an outgrowth of the Wolffian duct, the ureteric bud, invades the metanephric mesenchyme (MM), inducing discrete clusters of mesenchymal cells to condense around the UB tips, epithelialize and differentiate into nephrons. GDNF, which is expressed in the MM, is a critical factor for renal development and signals to the UB tips via Ret receptors. We have generated a mouse line for inducible Cre-mediated recombination in GDNF-expressing cells, and have used it to ask if these cells are nephron progenitors. In these GDNF-Cre-ER^{T2} animals, the expression of *Cre* recombinase is under control of the GDNF promoter and its activity is controlled by Tamoxifen. GDNF-Cre-ER^{T2} males were mated with ROSA^{26YFP} females, which were injected with Tamoxifen to induce recombination at different time-points during gestation, irreversibly labeling the GDNF-expressing cells. We found that GDNF-positive MM cells self-renew while they also give rise to the condensing mesenchyme, proximal and distal tubule, Henle's loop, connecting segment, Bowman's capsule and podocytes. No labeling was observed in blood vessels or cortical or medullary stroma. To test the role of the nephron progenitor cells in determining kidney size, GDNF-expressing cells were depleted by mating GDNF-Cre-ER^{T2} and ROSA^{26DTA} mice, followed by Tamoxifen injection at different times. In these animals, recombination induced the expression of the Diphtheria Toxin A resulting in apoptotic death of the targeted cell. At birth, these animals presented a significant reduction in kidney size and nephron induction with nearly absent nephrogenic zone and fibrous outer cortex.

In summary, we show that GDNF-positive cells are indeed nephron progenitors that maintain the population of renal stem cells and give rise to cells in the tubules of the nephron but not stroma. However, their self-renewal potential is limited and depletion of this population critically impairs nephron induction and renal growth.