Title:
Genetic Regulation of Nephron Progenitor Cells During Mammalian Kidney Development

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Abstract:
The functional unit of the kidney, the nephron, is repetitively generated during mammalian kidney development. Previously, our fate map analysis revealed that the Six2+ cap mesenchyme represents a multipotent, self-renewing nephron progenitor population throughout kidney development (Kobayashi et al., 2008, Cell Stem Cell). We further found that the nephron and interstitium form distinct compartments with a strict lineage boundary during kidney organogenesis. Currently, it is not well known how the nephron progenitor population is maintained during kidney organogenesis.

The paired-domain transcription factor Pax2 is expressed in multiple urogenital tissues including the cap mesenchyme. However, Pax2 function in the cap mesenchyme has not been examined in vivo. Therefore, we investigated Pax2 function in the cap mesenchyme using mouse genetic approaches, including tissue-specific inactivation and mosaic analysis.

In this study, we found that the Pax2 mutant mice fail to maintain the cap mesenchyme in the developing kidney. Surprisingly, fate map analysis in the mutants showed that cap mesenchyme-derived cells lacking Pax2 activity are not lost, but persist throughout kidney development. Detailed molecular marker analysis indicated that these cap mesenchyme-derived cells can trans-differentiate into medullary interstitial cells. Our mosaic analysis reveled a cell-autonomous requirement of Pax2 activity for cap mesenchyme cells.

Taken together, our observations suggest that Pax2 maintains a self-renewing nephron progenitor population by repressing interstitial cell fates. Thus, Pax2 activity establishes a lineage boundary between the nephron and non-nephron compartments during kidney organogenesis.

References:

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