Progressive Recruitment of Mesenchymal Progenitors Reveals a Time-Dependent Process of Cell Fate Acquisition in Mouse and Human Nephrogenesis.

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Authors: Nils O Lindstrom, Guilherme De Sena Brandine, Tracy Tran, Andrew Ransick, Gio Suh, Jinjin Guo, Albert D Kim, Riana K Parvez, Seth W Ruffins, Elisabeth A Rutledge, Matthew E Thornton, Brendan Grubbs, Jill A McMahon, Andrew D Smith, Andrew P McMahon

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Public Summary:
Mammalian nephrons, the functional unit of the kidney, arise from a limited nephron pool of progenitor cells. The pool gives rise to around 14,000 nephrons over an 11-12 period in the mouse and a million nephrons over a 30-week period in man. In this study, we demonstrate a relationship between the time a nephron progenitor embarks on a program of nephron formation and the cell types it generates in the forming nephron in the mouse and human kidney. Progressive recruitment predicted from high-resolution image analysis and three-dimensional reconstruction of human nephrogenesis was confirmed through direct analysis of mouse kidneys developing in the tissue culture dish. Examining gene activity in single cells predicts pathways to the development of regional cell diversity essential for normal nephron function in the kidney.

Scientific Abstract:
Mammalian nephrons arise from a limited nephron progenitor pool through a reiterative inductive process extending over days (mouse) or weeks (human) of kidney development. Here, we present evidence that human nephron patterning reflects a time-dependent process of recruitment of mesenchymal progenitors into an epithelial nephron precursor. Progressive recruitment predicted from high-resolution image analysis and three-dimensional reconstruction of human nephrogenesis was confirmed through direct visualization and cell fate analysis of mouse kidney organ cultures. Single-cell RNA sequencing of the human nephrogenic niche provided molecular insights into these early patterning processes and predicted developmental trajectories adopted by nephron progenitor cells in forming segment-specific domains of the human nephron. The temporal-recruitment model for nephron polarity and patterning suggested by direct analysis of human kidney development provides a framework for integrating signaling pathways driving mammalian nephrogenesis.