Redefining the in vivo origin of nephron progenitors enables generation of three-dimensional kidney structures from pluripotent stem cells in vitro

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Recapitulating three-dimensional structures of the kidney in vitro is a major challenge for developmental biology and regenerative medicine. Adult kidney derives from embryonic metanephros, which develops by the reciprocal interaction between the metanephric mesenchyme and the ureteric bud. Here, we define the developmental origins of the nephron progenitors, which reside in the metanephric mesenchyme and generate most nephron components such as glomeruli and renal tubules. While nephron progenitors are believed to originate from the intermediate mesoderm that expresses a transcription factor Osr1, we unexpectedly find that nephron progenitors are derived from posteriorly located T (Brachyury)-positive population at the post-gastrulation stage, which is developmentally distinct from Osr1-positive ureteric bud precursors. We also identify phasic Wnt stimulation and stage-specific growth factor addition as molecular cues that promote the development of T-positive precursors into the nephron progenitors. We then use this information to derive nephron progenitors, via the newly identified T-positive precursors, from mouse embryonic stem cells and human induced pluripotent stem cells. Upon Wnt4 stimulation, the induced nephron progenitors readily reconstitute the three-dimensional structures of the kidney in vitro, including glomeruli with podocytes and renal tubules with clear lumina. Furthermore, mouse glomeruli are efficiently vascularized upon transplantation, because glomerular podocytes express vasculogenic factors including VEGF. Thus, by redefining the developmental origin of nephron progenitors, we have revealed the molecular cascades of kidney specification in vivo and succeeded in generating the three-dimensional nephrons in vitro from pluripotent stem cells both in mice and humans.

References

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