The Era of Human Developmental Nephrology

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In this issue of the *Journal of the American Society of Nephrology*, Lindström et al.1–3 published three milestone papers on human embryonic kidney development. Our current understanding of human kidney development as well as the textbooks of embryology used for learning at medical schools are mostly on the basis of classic examinations of histologic sections performed 50–100 years ago. However, developmental biology has made significant advances since then owing to rapid progress in techniques for molecular biology, imaging, and generation of genetically engineered animals. We now know that the kidney is derived from at least three precursor populations: nephron progenitors that give rise to glomeruli and renal tubules, the ureteric bud that forms the collecting ducts and ureter, and stromal progenitors that produce interstitial cells. Signature genes of these precursor populations as well as markers for their descendant nephron segments have been identified. Many of these genes have been knocked out in mice, and their functions have been studied in detail. Moreover, various mouse strains expressing Cre recombinase or fluorescent reporters have been generated, and the gene expression profiles of many kidney cell lineages have been elucidated by microarray and RNA-sequencing analyses. Despite these advances in mice, little information is available on human kidney development.

In the milestone studies in this issue, Lindström et al.1–3 applied modern technologies, including three-dimensional imaging and RNA sequencing, to the human embryonic kidney. They collected as many as 135 human kidneys ranging from 4 to 23 weeks of gestation (counting from fertilization) and provide a modernized framework for human kidney development. According to their reports, the ureteric bud invades into the metanephric mesenchyme, which contains nephron progenitors, at approximately 4 weeks after fertilization (Carnegie stage 13 [CS13]) compared with embryonic day 11.5 in mice. S-shaped bodies, representing the transition state to nascent glomeruli, are first observed at 6–7 weeks (CS18–CS19), and the kidney structures from 8 weeks (CS23) to 16 weeks are somewhat similar to those in mice at embryonic day 15.5, although the human kidney has multiple lobes. There are many conserved features between the two species, including the overall structures, distinct cell lineage markers, and nascent nephron patterning. However, species-specific differences also exist. For example, some of the marker genes for nephron segments in mice are differentially expressed in humans. Furthermore, human nephron progenitor–specific genes are identified.2 Meanwhile, Foxd1, the most representative marker for stromal progenitors in mice, is expressed equally in stromal and nephron progenitors in humans, and thus, we may need to reconsider the molecular differences between these two precursor populations. Some of the most informative data for developmental nephrologists are provided by single-cell RNA sequencing of the cortical nephrogenic zone in the 16-week human kidney.2 On the basis of the gene expression patterns, 2750 cells are classified into multiple clusters representing nephron progenitors, ureteric bud, interstitial cells, vasculature cells, and many others. The nephron progenitors are separated into three subpopulations (naive, primed, and differentiating cells), and the gene profiles in these subpopulations are elucidated. Although not studied in detail in these reports, other lineages, such as interstitial cells, are also separated into multiple fractions, and further analyses could reveal heterogeneity within these lineages. Examinations at different time points will further accelerate our understanding of the maturation process of the human embryonic kidney.

The above data will serve as useful references for in vitro kidney organogenesis. Several groups, including ours, have shown the generation of kidney tissues from human induced pluripotent stem cells (iPSCs).4–6 These tissues reflect significant advances, and it is exciting to see human glomeruli and renal tubules in a dish. However, it remains unknown which stage of the in vivo kidney the organoids correspond to and how similar they are. The culture periods required for kidney induction from human iPSCs range from 16 to 22 days depending on the protocols used. If we assume that human iPSCs represent 2-week embryos on the basis of a transcriptome analysis of monkey embryonic stem cells7 and if iPSCs follow the same developmental clock as that observed in vivo, it would take 2 weeks to form nephron progenitors (CS13) and 2 more weeks to give rise to nascent glomeruli (CS18–CS19). Thus, the in vitro nephrogenesis is accelerated or the in vitro nephrons are more immature than expected. Lindström et al.1 report that the Hox11 expression observed in human embryonic kidneys in vivo is higher than that previously detected in kidney organoids in vitro5 and propose the importance of
discriminating metanephros induction from mesonephros induction. Therefore, it is imperative to optimize the induction protocols by comparing the gene expression levels in organoids with the in vivo levels as references. At present, single-cell RNA sequencing has only been performed at 16 weeks in vivo. Data at 4 weeks (CS13), when nephron progenitors are initially formed, would serve as better references to improve the induction protocols, because nephron progenitors have distinct expression profiles depending on their developmental stages, at least in mice.8 This should also hold true for the other lineages. We recently reported the generation of branching ureteric buds from human iPSCs,9 but it remains to be determined how similar these buds are to their in vivo counterparts. Stromal progenitors would also be required for genuine higher-order kidney organogenesis, and thus, the expression profiles of this lineage need to be elucidated. Meanwhile, information on later embryonic stages will be needed to achieve further maturation of organoids.

Currently, we have entered the era of human developmental biology. Many researchers have started to analyze human embryos, and research on other organs is becoming more advanced. For example, human embryonic brains have been sequenced at the single-cell level, and even time-lapse imaging after fluorescence labeling has been performed.10 Of course, ethical issues need to be carefully addressed when dealing with human embryos, because just one case of careless handling could hamper the scientific progress of the entire research community. Because accessibility to human embryos varies from country to country, sharing of any obtained information on a unified platform is important and will also help to avoid redundant usage of human embryos. With these points in mind, further analyses of human kidney development will accelerate the progress of kidney organogenesis in vitro, and gene manipulation of organoids by Clustered Regularly Interspaced Short Palindromic Repeat-Cas9 technology will in turn deepen our understanding of human kidney development in vivo. This cycle will lead to modeling and drug discovery for human kidney diseases and eventually, rebuilding of a genuine kidney applicable for transplantation therapy.

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DISCLOSURES

None.

REFERENCES


See related articles, “Conserved and Divergent Features of Human and Mouse Kidney Organogenesis,” “Conserved and Divergent Features of Mesenchymal Progenitor Cell Types within the Cortical Nephrogenic Niche of the Human and Mouse Kidney,” and “Conserved and Divergent Molecular and Anatomic Features of Human and Mouse Nephron Patterning,” on pages 785–805, 806–824, and 825–840, respectively.

Evolution and Kidney Development: A Rosetta Stone for Nephrology

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This issue of the Journal of the American Society of Nephrology contains three interrelated papers from the laboratory of Andrew McMahon, providing a comprehensive analysis of sequential human and mouse kidney development at