METANEPHRIC KIDNEY DEVELOPMENT is a complex process involving maturational changes and reciprocal signaling between epithelial and mesenchymal tissues. Over the last 15–20 years, the number of reports on kidney development has increased, with the vast majority focused on early events such as interactions between the ureteric bud and metanephric mesenchyme, ureteric bud branching morphogenesis, and induction of glomeruli and nephrons (1, 14). Although these events are clearly important, another critical process is the maturation and differentiation of distal portions of the ureteric bud into specialized collecting duct epithelia. In fact, failure of the normal maturation of the ureteric bud into collecting ducts is likely one of the causes of renal dysplasia in humans (12). The report by Saifudeen et al. (9) in this issue of American Journal of Physiology-Renal Physiology is another in a series of elegant reports from Dr. Samir El-Dahr’s laboratory that begin to dissect out the molecular control of collecting duct differentiation and maturation.

The ureteric bud arises as an outgrowth of the nephric duct at around 5 wk gestation in the human and embryonic day 11 (E11) in the mouse and E12 in the rat (6). Once it makes contact with the surrounding metanephric mesenchyme, it undergoes a series of dichotomous branchings. The terminal tips of the ureteric bud induce the formation of nephrons from the surrounding mesenchyme. Ultimately, the main trunk of the ureteric bud gives rise to the mature ureter, whereas the early branches become the renal pelvis and calices. The distal branches of the ureteric bud fuse with the developing nephrons (from the mesenchyme) and mature into the heterogeneous collecting duct epithelia to generate functional units in the kidney.

The genetic control of distal ureteric bud maturation has only just begun to be clarified. Markers of mature collecting duct principal cells such as the epithelial sodium channel, aquaporin-2 (AQP2), and Na-K-ATPase first appear at around E16 in deeper cortical regions of the rat kidney (8, 10, 11, 13). In addition, El-Dahr’s group noted that in rat kidneys, bradykinin B2 receptors were first expressed on the apical surface of terminal ureteric bud tissues (and in glomeruli) and continued to be found in mature tubular elements after birth (3). In a subsequent paper, El-Dahr’s laboratory demonstrated that the transcription factor p53 is coexpressed with and directly up-regulates expression of many of the markers of collecting duct differentiation, including the bradykinin B2 receptor, AQP2, and the Na-K-ATPase (7, 8). They also noted that p53 knockout mice develop renal dysplasia with hyperplastic foci, cystic changes, and aberrant expression of many of the aforementioned collecting duct genes including B2 receptors (8).

Despite the expression of the bradykinin B2 receptor in the early maturing collecting duct, B2 receptor null mice were not initially shown to have any renal structural abnormalities. El-Dahr et al. did observe that the B2 receptor null mice were prone to salt-sensitive hypertension after birth (2). Furthermore, when pregnant mice were subjected to high salt intake, B2 receptor knockout embryos developed severe cystic dysplasia in the renal collecting tubules, resulting in death shortly after birth (4). Importantly, this was the first time renal developmental abnormalities were induced by a combination of a genetic defect and an environmental stressor (4). As reported in a recent follow-up article by the El-Dahr group, the renal defects in the salt-loaded B2 receptor null mice are, in part, due to aberrant expression of p53 and subsequent decreases in E-cadherin levels (5).

Given the crucial role of bradykinin B2 receptors in kidney development, the El-Dahr group focused more extensively on the transcriptional control of B2 receptors in the developing kidney. Although p53 clearly upregulates expression of the B2 receptor, they determined that there was not only an activating but also a repressive p53 response element in the rat B2 receptor promoter (7). In this issue, they further clarify the positive regulation of the B2 receptor in the developing rat kidney. They show that in addition to p53, Kruppel-like factor 4 and cAMP response element-binding protein (CREB) have activating response elements in the B2 receptor promoter (9). Moreover, the aforementioned transcription factors appear to assemble into a complex on the B2 receptor promoter, a process requiring recruitment of CREB binding protein and histone hyperacetylation (9). As noted by the authors themselves, this report is important in that it reveals new details about transcriptional regulation of collecting duct maturation, a process that is crucial for normal kidney formation (9). It is also the first time a gene has been shown to require a complex of three transcription factors for its expression in the developing kidney (9). Finally, this report raises critical questions about whether other developmentally important renal genes require transcriptional factor complexes for normal expression.

REFERENCES


