Preface

Metanephric kidney has been a traditional model for inductive tissue interactions for many decades. Until recently, only few groups were working with it, but now, suddenly, several developmental biologists are becoming fascinated by its possibilities. This rapidly enhanced interest is not driven by the belatedly realized value of a useful experimental model, but mainly because of the availability of transgenic mice. Many knockout mouse strains have unexpectedly had difficulties in their kidney morphogenesis (for instance DARPP-32-deficient mice, see Svennilson and Aperia this issue; Avner *et al.,* this issue), and these "sudden hits" have spread the interest in kidney morphogenesis to scientists previously outside the field. On the other hand, the elucidation of the genetic background and pathogenesis of several renal diseases and developmental disorders have facilitated our understanding of renal development (see Avner *et al.*, this issue; Davies *et al.,* this issue; Fleming, this issue; Tryggvason *et al.,* this issue). Accordingly, whereas the physiology of kidney epithelia has been carefully characterized over several decades, unravelling of the molecular basis of their functional differentiation has been rapid only during the last few years (Lehtonen *et al.,* this issue). Not only the metanephric kidney is in fashion, but several key findings have been recently made from pro- and mesonephrogenesis (see Brändli, this issue; Sainio and Raatikainen-Ahokas, this issue).

The organotypic kidney cultures, developed principally by Clifford Grobstein during the 50's (see Saxén, this issue), are fortunately rather easy to perform and even, without great experience in microdissection, investigators are able to experimentally approach renal defects in their transgenic mice. Such experiments are typically done as recombinant cultures between wild type and transgenic tissues. For example, Emx-2 -deficient mice lack kidneys, but show initially a kidney rudiment with a histologically normal nephrogenic mesenchyme and ureteric bud (M. Yoshida, Y. Suda, I. Matsuo, N. Miyamoto, N. Takeda, S. Kuratani and S. Aizawa. *Emx1 and Emx2 functions in development of dorsal telencephalon.* Development 124: 101-111; 1997). In order to identify the site of primary renal defects in these mice, Miyamoto and colleagues (N. Miyamoto, M. Yoshida, S. Kuratani, I. Matsuo and S. Aizawa. *Defects of urogenital development in mice lacking Emx2.* Development 124: 1653-1664; 1997) recombined mutant ureteric buds with wild-type nephrogenic mesenchyme and vice versa. The result was clear. The mutant buds could not induce differentiation of the wild-type nephrogenic mesenchyme, but the nephrogenic mesenchyme from Emx-2-null mice induced differentiation of the wild-type ureteric buds. The experimental result fits well with the distribution of Emx-2 in the kidney, where it is expressed only by the ureteric bud.

Sometimes, however, it has been difficult to resolve the pathogenesis of the kidney phenotype. Such was the case of BF-2-deficient mice (V. Hatini, S.O. Huh, D. Herzlinger, V.C. Soares and E. Lai. *Essential role of stromal mesenchyme in kidney morphogenesis revealed by targeted disruption of Winged Helix transcription factor BF-2.* Genes Dev. 10: 1467-1478; 1996). BF-2 is a Forkhead/Winged Helix transcription factor with an expression pattern restricted to the stromal compartment of the embryonic kidney. BF-2-deficient mice show renal hypodysplasia as well as retarded growth and differentiation of the kidneys. The mutant kidneys are fused longitudinally and rotated 90 degrees. This phenotype challenges the scientist in several ways. First, stromal cells are not possible to dissect out from the kidney rudiment as they, at early stages, look like other nephrogenic mesenchymal cells. Second, the origin of these cells is not clear. Third, the developmental function of the renal stroma is poorly established and still debatable. Furthermore, because BF-2 is also expressed by other embryonic organs, it is not evident that the primary defect resides in the mutant kidney itself. The authors did exactly what they could do. They faithfully mapped the distribution of BF-2 during kidney morphogenesis, analyzed morphologically several stages of embryonic kidneys, quantified the growth parameters of mutant ureteric buds, nephrons and whole kidneys, analyzed expression patterns of cell lineage markers and key regulators of kidney morphogenesis, and finally discussed the data elegantly. However, the pathogenesis of renal hypodysplasia in BF-2-null mice is still unresolved. In this case, we obviously lack basic information about the histogenesis of stromal cells.

In spite of all recent progress, many questions concerning the biology and molecular control of nephrogenesis are still amenable to attack and can be reduced to four key problems: i) the nature of inductive signals of the nephrons (see Vainio *et al.,* this issue), ii) the multiple signaling events in the ureteric branching (see Godin *et al.,* this issue;

Sariola and Saarma, this issue), iii) the origin and developmental functions of renal stromal cells (H. Sariola, E. Aufderheide, H. Bernhard, S. Henke-Fahle, W. Dippold and P. Ekblom. *Antibodies to cell surface ganglioside GD3 perturb inductive epithelial-mesenchymal interactions.* Cell 54: 235-245, 1998; H. Sariola, K. Holm-Sainio and S. Henke-Fahle. *The effect of neuronal cells on kidney differentiation.* Int. J. Dev. Biol. 33: 149-155, 1989; J. Bard. *A new role for the stromal cells in kidney development.* BioEssays 18: 705-707; 1996), and iv) the commitment of the nephrogenic mesenchyme. The three first problems have been eagerly attacked during this century, but the last, and perhaps most important problem has remained an enigma. The title of Lauri Saxén's article in this issue hints to the present confusing situation: "What is needed for kidney morphogenesis and how do we find it?" A lot of molecular data is accumulating and has been catalogued in an Internet database (J.A. Davies and A.W. Brändli. *The Kidney Development Database.* http://www.ana.ed.ac.uk/anatomy/database/kidbase/kidhome.html. 1997; Bard, this issue). More than 30 transgenic mouse strains show renal defects ranging from total aplasia to minimal hyperplastic nodules. Several pieces in the puzzle have been located correctly, but the picture is still not forthcoming. It is possible that we have a default image of the final biological landscape. Maybe we are too closely looking at the interaction between the nephrogenic mesenchyme and the ureteric bud, and neglect other cell lineages participating in nephrogenesis, like stromal cells, neuronal cells, vessels and smooth muscle cells. They may receive signals from the developing nephrons for an orderly controlled patterning. Why should they not reciprocally communicate with nephrons, and influence nephron formation when even the foetal environment does it (see Merlet-Bénichou, this issue)?

Two decades ago scientists working with embryonic kidney were frustrated about the lack of molecular data, and now they are frustrated about their excess. This has been the motivation for this nephrogenesis issue and for the recent Princess Lilian symposium held last autumn in Brussels (entitled "Kidney Development has Clinical Impact"). It is time for a critical re-evaluation of the biology of kidney differentiation and morphogenesis, and it is indispensable to include the perspectives of different disciplines such as developmental biology, pathology, oncology and genetics. The editors thank the authors for producing excellent reviews, and acknowledge the support of Dr. Juan Aréchaga, the editor-in-chief of this journal, for providing us the opportunity to bring these puzzle pieces together.

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