CARO Use Case: The early development of the mouse urogenital system

Jonathan Bard
University of Edinburgh
j.bard@ed.ac.uk

This informal text description of the early urogenital system tries to link the developmental anatomy (tissues) with their associated cell types to (1) the underlying processes underpinning development and (2) the changes in differentiation that give rise to new cells types. The description uses defined time slots (from Theiler stages (TS) = 12h here, partly for standardization and partly as this is the granularity of GXD, the mouse gene-expression database). A simplified graphical version is given at the end.

I should emphasise that this description, even if it has no explicit errors, is almost certainly an oversimplification, but it will do as a use case for considering the problems in handling complex developmental phenomena.

It is also worth noting that, in principle at least, each time-dependent tissue, cell type and developmental process can be assigned an EMAP, CL or GO ID, and the tissues can be linked to the GXD database to give gene expression data. It is thus relatively straightforward to produce a complete systems description of the molecules, cell types, tissues and processes that enable the intermediate mesenchyme to produce the gonad and the metanephros.

**The developmental anatomy**

**At the beginning of TS13 (E8.5)**, the intermediate mesoderm, now known as the nephrogenic or nephric cord, is located in the urogenital ridge, is restricted to the future thoracic region, and is composed of early mesenchymal cells. This tissue proliferates and extends caudally.

**During TS 14 (E9)**, this tissue partitions, with one part differentiating (to epithelium that will become the nephric duct):

**By TS 15 (E9.5)**, the cord has extended, and comprises

1. The rostral pronephros (epithelial vesicle [?] and mesenchyme) – this is rapidly subject to apoptosis and is lost.

2. **Intermediate mesoderm** (mesenchymal cells) that is subject to the processes of proliferation, caudal extension and patterning/epithelialisation: the earliest epithelial vesicles are now visible within that part of the tissue that is separating out into the mesonephros

3. The **nephric duct**, an epithelial tubule that forms from the aggregation of cells in the nephrogenic (nephric) cord that have undergone an M->E transition. It is subject to the processes of growth, caudal extension and the initiation of branching into the mesoderm (to form the mesonephros), and this may involve a signalling interaction.

**By TS 16 (E10)**, the system comprises

The mesonephros: this is composed of mesenchymal cells into which extend epithelial tubules that are branches from the nephric duct and which also contains epithelial vesicles that are not branches off the nephric duct (the mesonephros is still forming from the same processes extant in TS15). Further patterning of the mesonephros now occurs so that its medial part becomes the presumptive gonad, although it is not known whether this involves a
change in cell type, apart from its colonisation by primary germ cells (to which it presumably secretes a chemotactic signal).

The (meso)nephric duct: this epithelial tissue continues to proliferate and extend caudally, but the bifurcation process into the mesonephros ceases.

Non-mesonephric nephrogenic cord: this proliferates and extends caudally towards the presumptive bladder. Within this cord a small area is patterned to become condensed metanephric mesenchyme that signals to the nearby (meso)nephric duct

BY TS 17 (E10.5), the system comprises
The mesonephros: this contains mesenchymal cells into which extend epithelial branch tubules from the nephric duct and epithelial vesicles that are not branches off the nephric duct (the mesonephros is still enlarging via the same processes extant in TS16).

The attached gonad: this contains mesenchymal and primary germ cells and proliferates.

The metanephric mesenchyme (MM) condenses (and so becomes apparent) and signals to the spur from the duct that is approaching it.

The (meso)nephric duct: this epithelial tissue branches to send a spur (the ureteric bud) which extends towards and into the MM and which will bifurcate soon after it has invaded it.

Non-meso/metanephric nephrogenic cord: this mesenchyme appears to be less important and is either proliferating less or apoptosing.

BY TS 18 (E11), the system comprises
The mesonephros: its morphology remains unchanged but, while extending at its caudal part, it is starting to regress through apoptosis of mesenchyme at its rostral region.

The attached gonad: this contains mesenchymal and primary germ cells and proliferates.

The nephric duct (now called the mesonephric or Wolffian duct): this tubule has extended to the presumptive bladder area and there are two sets of tubules that emerge from it.

1: The epithelial tubules to the mesonephros/gonad
2: The epithelial spur to the metanephros whose proximal region becomes the presumptive ureter while the more distal region now invades:

The metanephros: this is now composed of the metanephric mesenchyme together with the distal region of the duct (known as the ureteric bud) which now undergoes a primary bifurcation.

Non-meso/metanephric cord: this mesenchyme appears to be less important and is either proliferating less or apoptosing.

AT THE BEGINNING OF TS 19 (E11.5), the system comprises
The mesonephros: this has stopped extending and its mesenchyme is regressing at its rostral end through apoptosis to leave the epithelial tubules that will link to the gonad.

The attached gonad: this contains mesenchymal and primary germ cells and is enlarging

The (meso)nephric duct: this tubule has two sets of tubules that extend from it.

1: The rostral epithelial tubules to the mesonephros/gonad
2: The caudal epithelial presumptive ureter that extends to:
The **metanephros**: this is now composed of the metanephric mesenchyme together with the distal region of the epithelial duct. This tubule is starting its **secondary bifurcation** and **signalling** to the MM to initiate nephron formation.

**Non-meso/metanephric nephrogenic cord**: this is now much diminished.

**Definitions**
- **Apoptosis**: programmed cell death
- **Bifurcation/branching**: the process by which a spur comes off an epithelial tubule
- **Caudally**: towards the tail
- **Epithelium**: cells that make side-to-side adhesions and so form 2D sheets, vesicles + tubes
- **Mesenchyme**: tissue containing (mesenchymal) cells that packs in 3D, often have a lot of extracellular matrix and usually differentiate further
- **Mesoderm**: one of the original germ layers that partitions to give paraxial, intermediate and lateral mesoderm that in turn form muscles, dermis, the bones of the body (and a few of the head), cartilage, joints and the urogenital system.
- **Rostrally**: towards the head
- **Vesicles**: hollow balls of epithelial cells