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

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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 cell types. The description uses DEFINED TIME SLOTS (from Theiller 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

Early development of the urogenital system in the mouse

