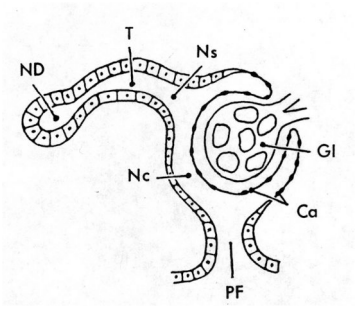
The Nephron


T
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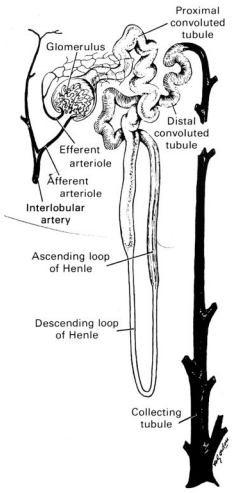
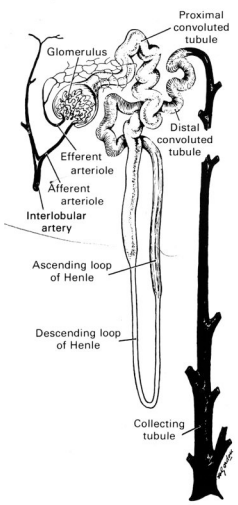
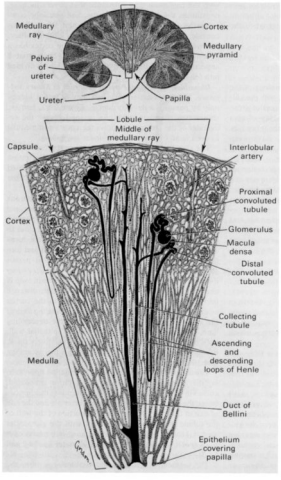
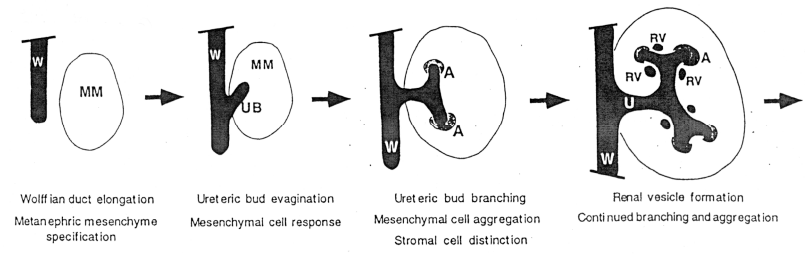
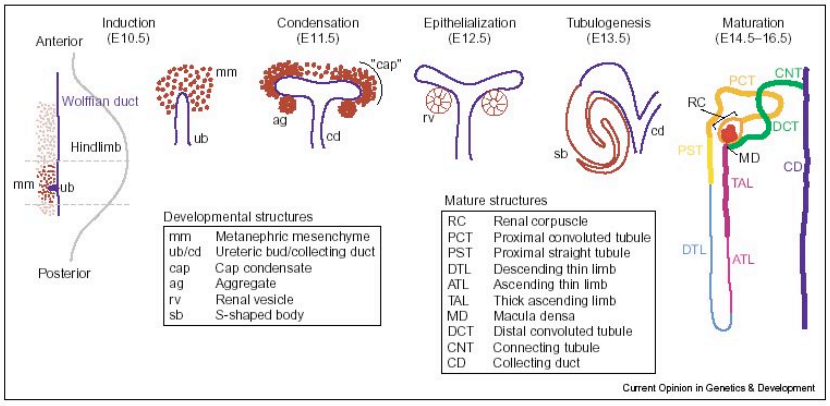
ND
Gl
Nc
Ca
PF


Proximal convoluted tubule
Glomerulus
Distal convoluted tubule
Efferent arteriole
Afferent arteriole
Interlobular artery
Ascending loop of Henle
Descending loop of Henle
Collecting tubule


Proximal convoluted tubule
Glomerulus
Distal convoluted tubule
Efferent arteriole
Afferent arteriole
Interlobular artery
Ascending loop of Henle
Descending loop of Henle
Collecting tubule

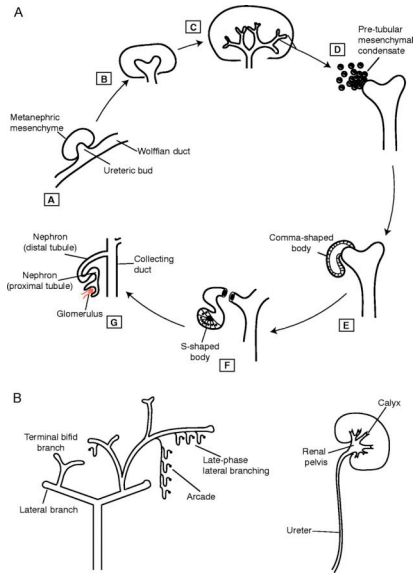

Medullary ray
Cortex
Medullary pyramid
Pelvis of ureter
Ureter
Papilla
Lobule
Middle of medullary ray
Capsule
Interlobular artery
Proximal convoluted tubule
Cortex
Glomerulus
Macula densa
Distal convoluted tubule
Collecting tubule
Ascending and descending loops of Henle
Medulla
Duct of Bellini
Epithelium covering papilla



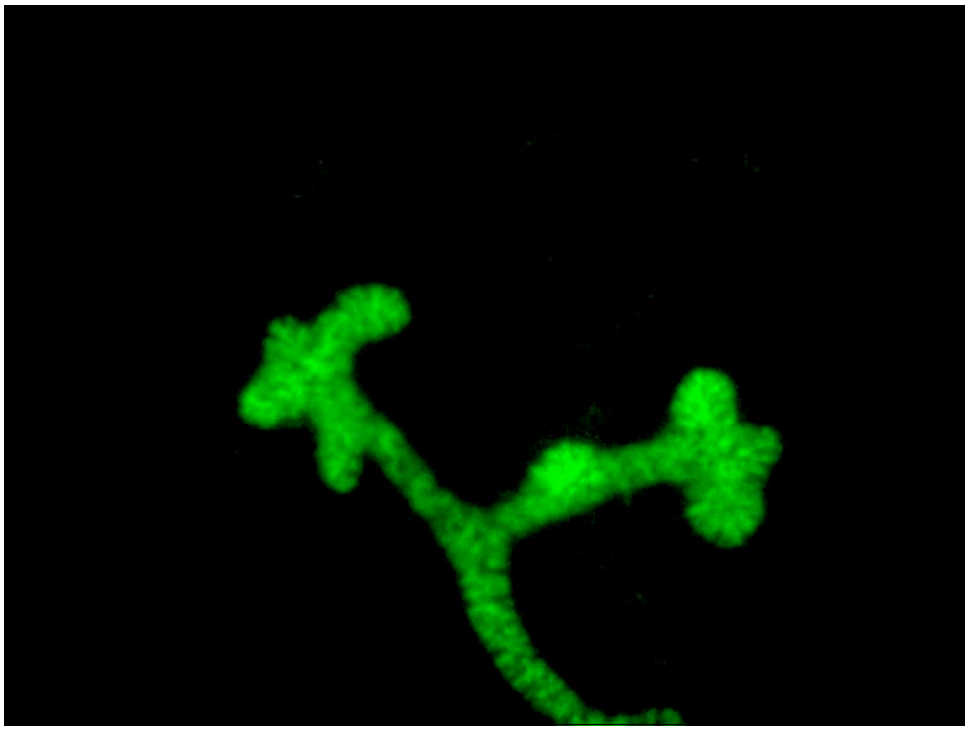


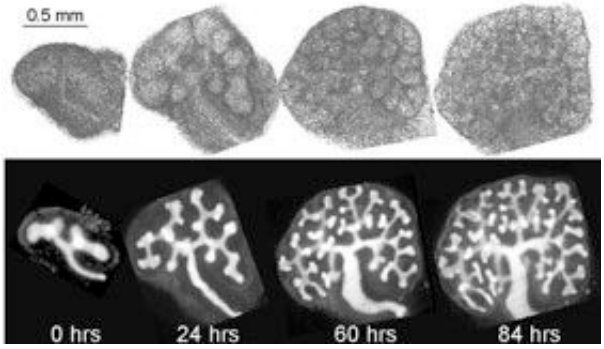
Stages of nephron formation. After the initial induction of the metanephric mesenchyme, reciprocal interactions produce new UB tips. At each tip a cap condensate produces a renal vesicle, that eventually forms an individual nephron. The approximate time-point of the first occurrence of each step is in parantheses.

Yu et al., Curr. Opin. Gene. Dev. 14:550-7, 2004



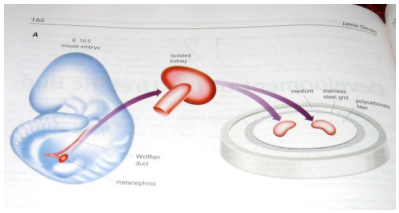
Shah, M. M. et al. Development 2004;131:1449-1462





HoxB7:GFP (ureteric bud expression)

Kidney Induction in Vitro



	Branching Duct ?	Tubules?
Ureteric Bud Alone	No	N.A.
Metanephric Mesenchyme Alone	N.A.	No
Combination	Yes	Yes

Grobstein, 1955

Many heterologous tissues can induce metanephric mesenchyme to form tubules

Table 3.2. *The inductive action of certain tissues tested in combination with the metanephric mesenchyme of 11-day mouse embryos*

Tissue	Active	Inactive
Embryonic epithelia		
Ureter	+	
Submandibular	+	
Pulmonary		–
Gastric		–
Pancreatic		–
Neural tissues		
Embryonic spinal cord	+	
Embryonic medulla	+	
Embryonic brain	+	
Embryonic spinal ganglia		–
Embryonic spinal cord[a]	+	
Adult brain		–
Neural teratoma	+	
Embryonic mesenchymes		
Salivary	+	
Jaw	+	
Head	+	
Tail		–
Limb bud		–
Developing bone	+	
Embryonic and adult liver		–
Adult retina and iris		–
Adult kidney tubules		–

[a] Chick origin, other tissues are murine.
Data from Grobstein, 1955*a*; Unsworth & Grobstein, 1970; Lombard & Grobstein, 1969; Auerbach, 1972; Saxén *et al.*, unpublished data.

But only the metanephric mesenchyme can form tubules in response to inducers

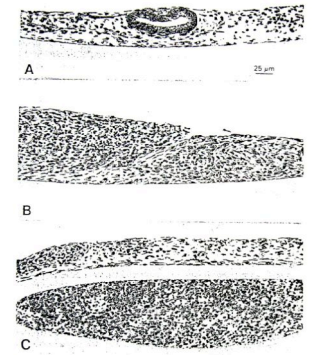


Fig. 3.2. Micrographs of heterologous mesenchymes combined with a kidney tubule inductor and cultivated for four days. No response can be detected in the mesenchyme (Saxén, 1970*a*). A. Isolated ureteric bud in combination with salivary gland mesenchyme. B. Direct combination of pulmonary mesenchyme (left) and spinal cord. C. Transfilter combination of salivary gland mesenchyme and spinal cord.

Hence, the metanephric mesenchyme is highly patterned before being induced to form tubules

Induction of the Ureteric Bud: C-ret and GDNF

C-ret: TK receptor expressed in the nephric duct and ureteric bud

C-ret -/- mice: No metanephros (although mesonephros is normal)

Branching of the ureteric bud in tissue recombinations of c-ret -/- and wild type tissues:

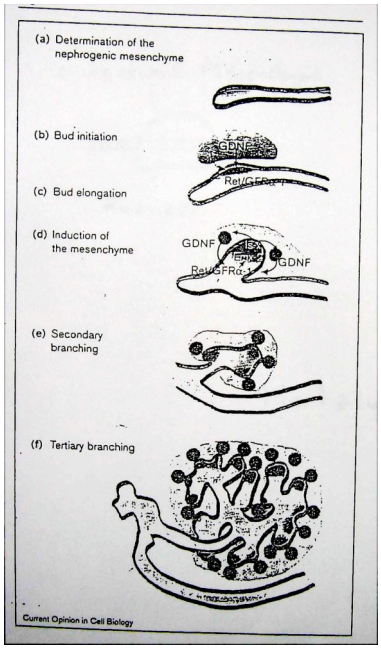
		Bud	
		+/+	-/-
Mesenchyme	+/+	+	-
	-/-	+	-

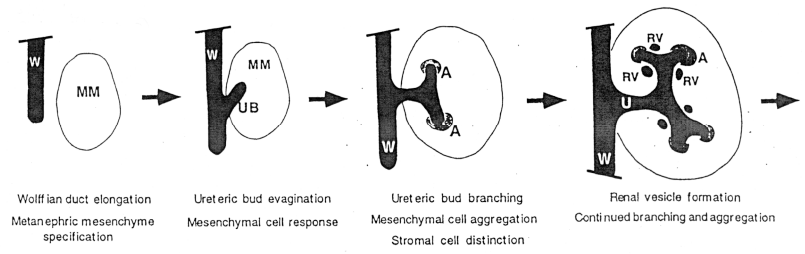
Schuchardt et al. Development 122, 1919-1929 (1996)

GDNF is a ligand for c-ret

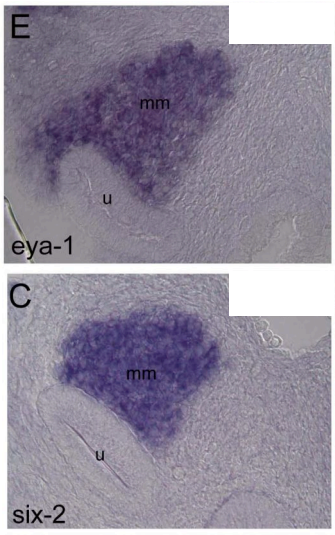
GDNF -/- mice have no kidneys or ureter

GDNF is expressed in the kidney mesenchyme around the ureteric bud branchpoints, and can induce ureteric bud branching and outgrowth in vitro (Sainio et al, Development 124, 4077-4087, 1997)

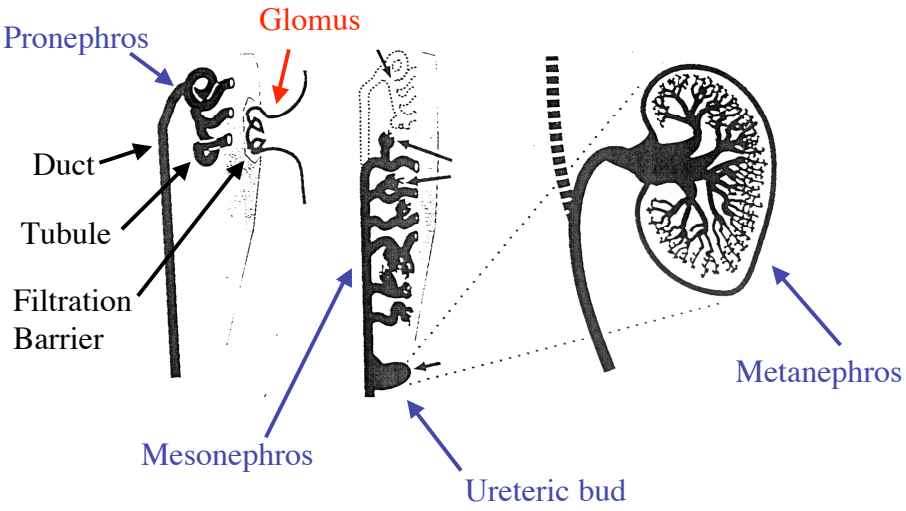




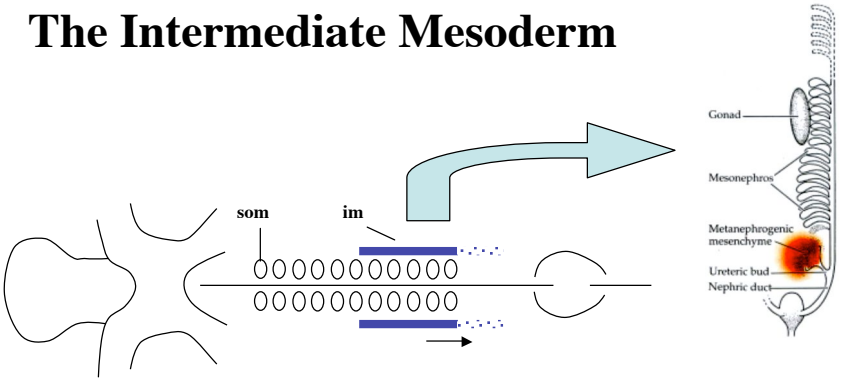
Tissue-specific genes are expressed in the kidney mesenchyme prior to its ineteraction with the duct



The Vertebrate Kidney

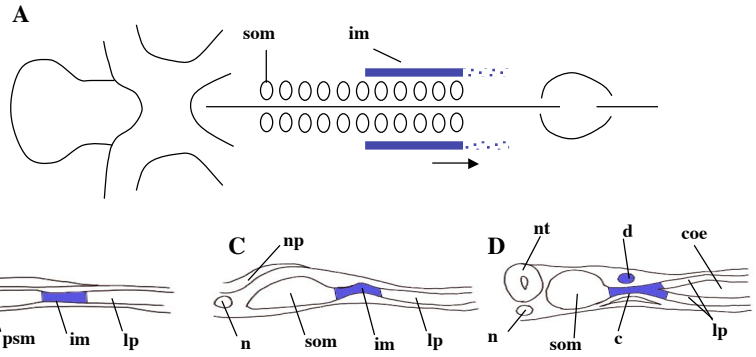


The Intermediate Mesoderm



Partial List of Intermediate Mesoderm Derivatives

Kidney, Somatic Gonad, Hematopoietic Tissue, Aorta, Adrenal Glands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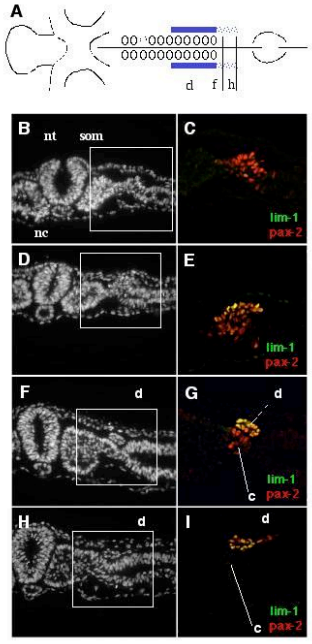
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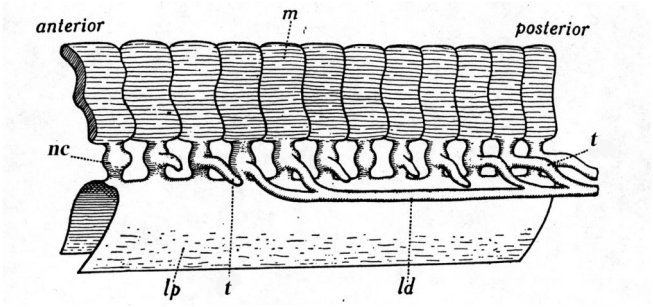
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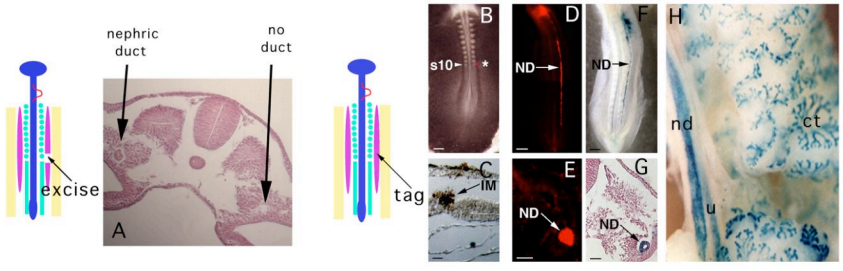
nephric duct
no duct
excise
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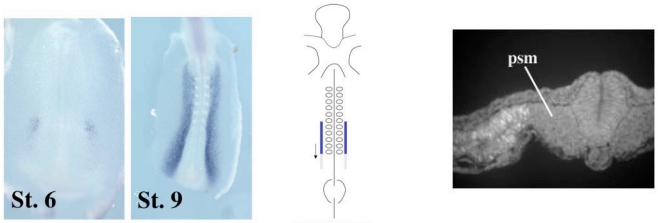
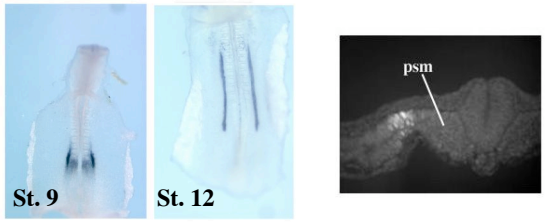
Gene expression during intermediate mesoderm formation

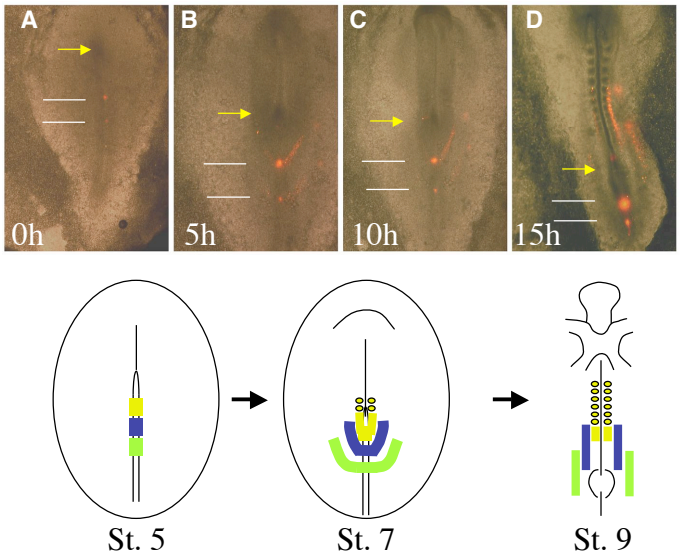
Phase I:
Osr1



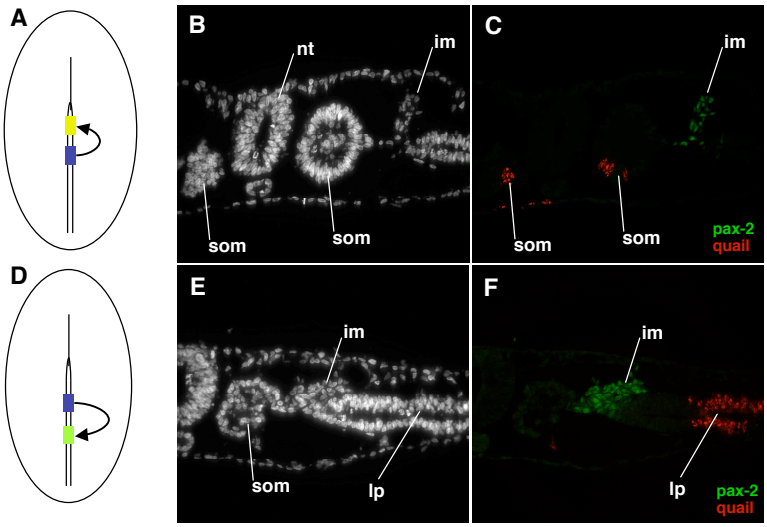
Phase II:
Pax2, lim1, wt1



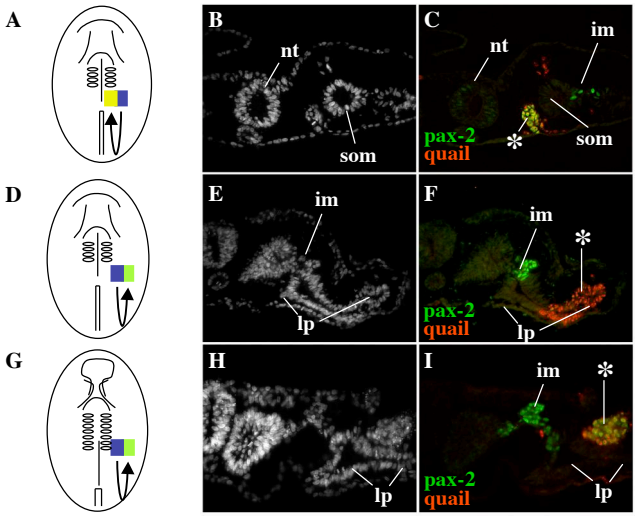
Fate Map of the Avian Intermediate Mesoderm



IM is not specified in the primitive streak



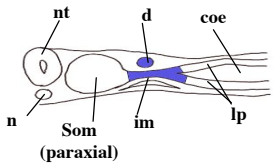
IM becomes progressively specified as it migrates from the primitive streak

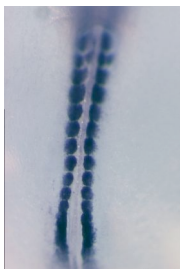
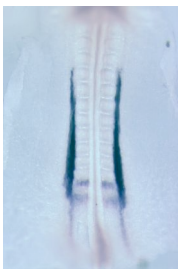
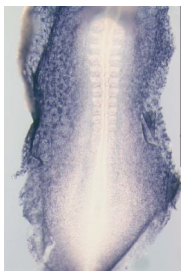


IM is determined with respect to transplantation into paraxial tissues by St. 8

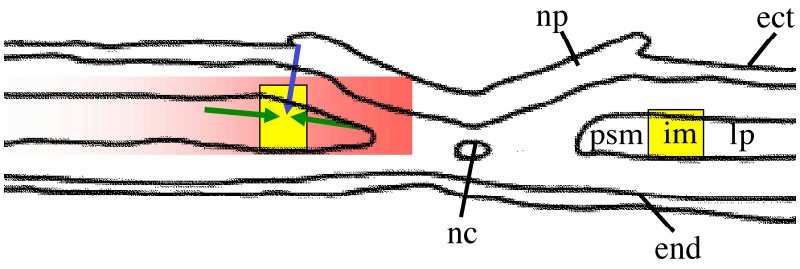
IM is NOT determined with respect to transplantation into lateral tissues at St. 8, but becomes determined by St. 9

Transcription Factors in the mesoderm



Paraxial	Paraxial/IM	IM	IM/LP	LP
				
Paraxis (Mesogenin, Meox, Tbx6)	**FoxC2**	**Pax-2** (Lim1, Wt1)	**Osr1**	**Cytokeratin**

Models of Intermediate Mesoderm Patterning: The Medio-lateral Axis



Mediolateral gradient

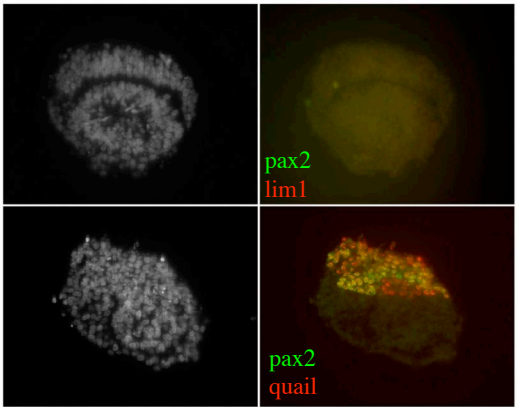
Interaction between two already specified tissues

Vertical signaling

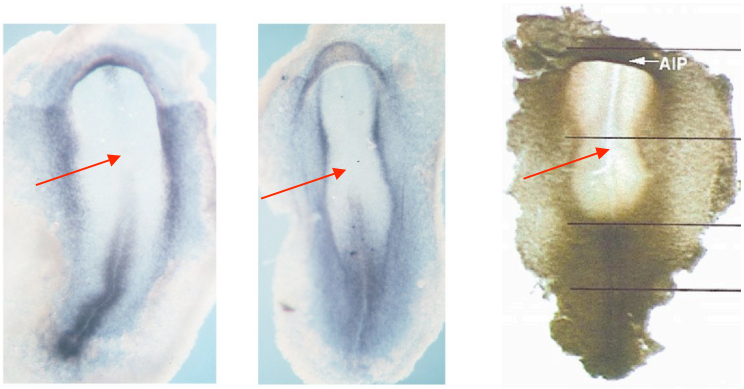
A property in the lateral plate which can induce IM genes in the somite

Quail somite

Quail somite + Chick lateral plate mesoderm



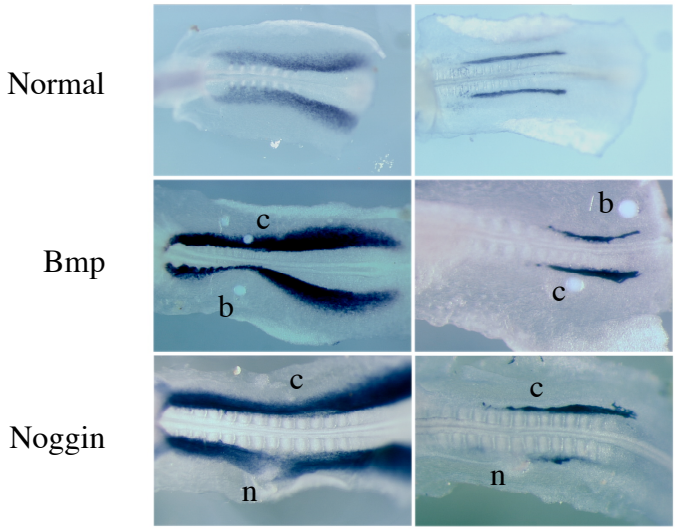
Bmp signaling at the time of initial Intermediate Mesoderm formation



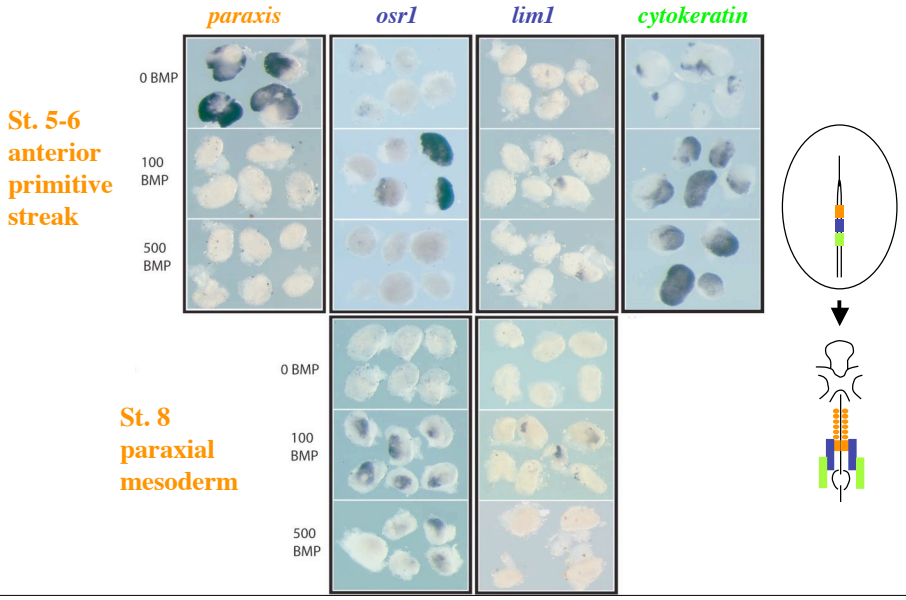
Bmp-2 ***Bmp-4*** ***P-Smad1***

P-Smad1 from Faure et al., Dev. Biol. 244:44 (2002)

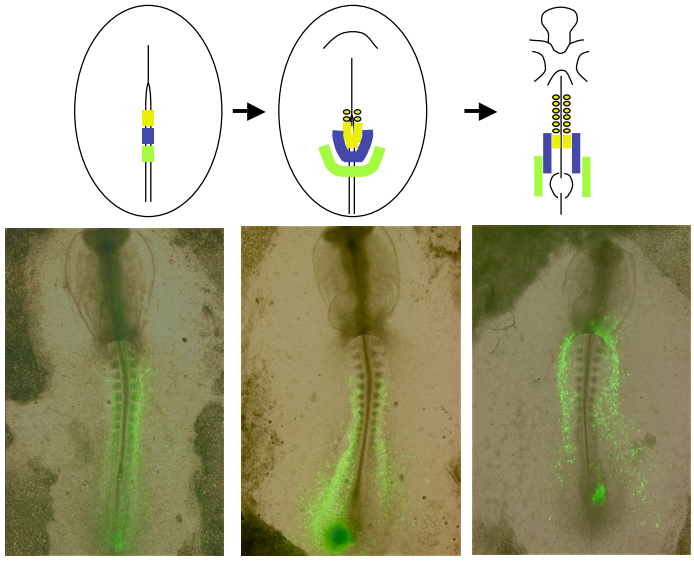
Alterations in IM gene expression by manipulation of Bmp signaling in vivo



Bmp-2 can generate IM from paraxial mesoderm in a dose-responsive manner

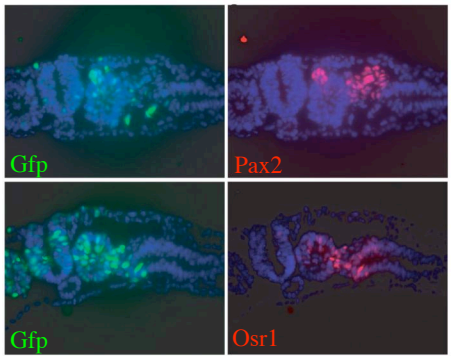


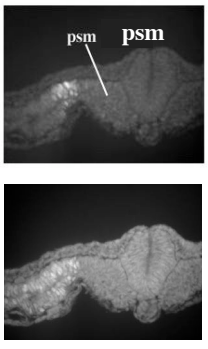
Does BMP regulate IM gene expression cell-autonomously?



Bmp signaling can induce IM gene expression cell-autonomously

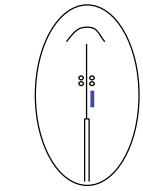
pCS2-c.a. Alk3-IRES-GFP



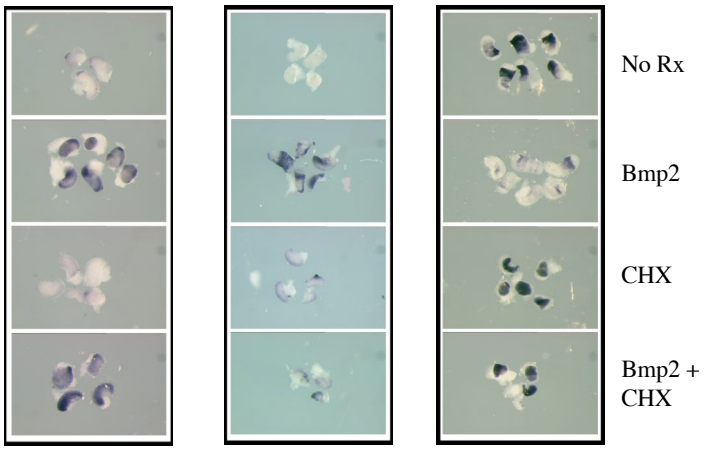


Control

Direct responders to Bmp signaling ?



St. 8 PSM cultured for 3 hours

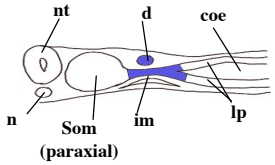


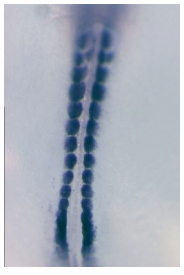
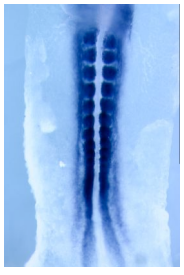
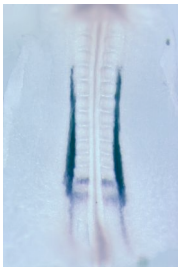
Directly activated

Not directly activated; Under negative regulation?

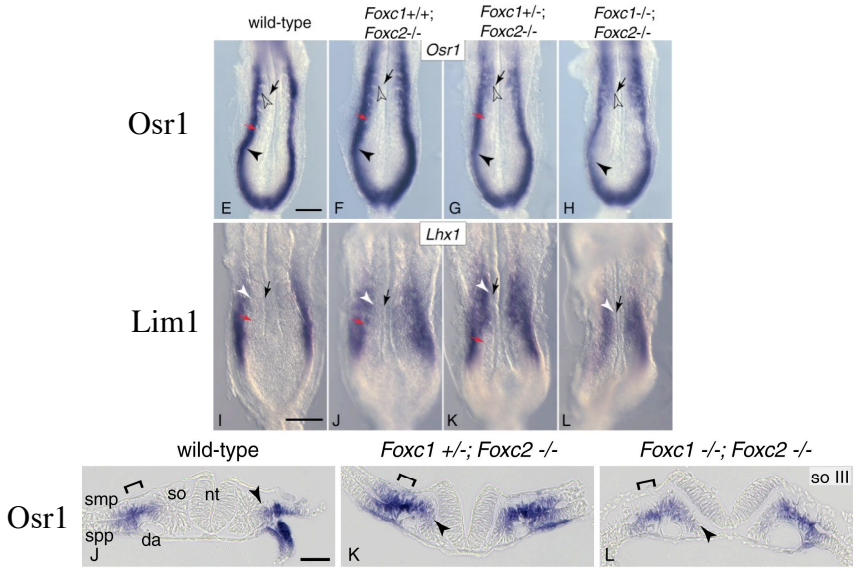
Not directly repressed

Transcription Factors in the mesoderm

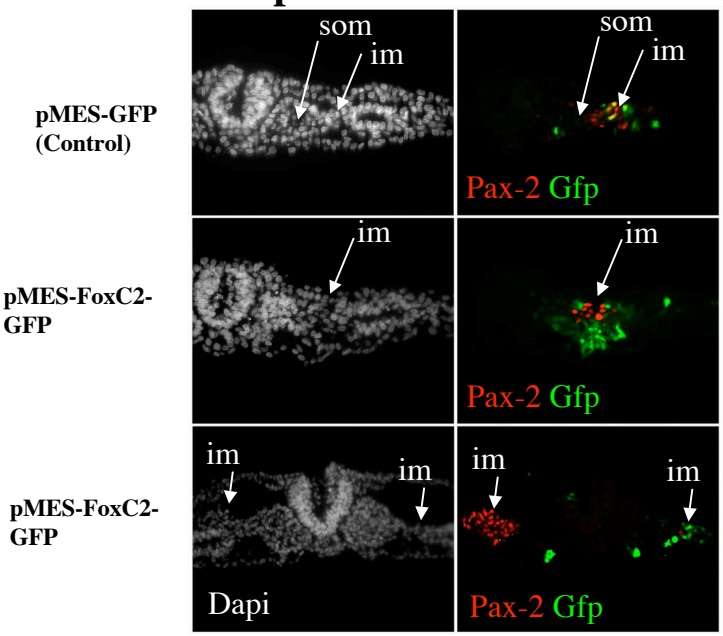


Paraxial	Paraxial/IM	IM	IM/LP	LP
				
Paraxis (Mesogenin, Meox, Tbx6)	**FoxC2**	**Pax-2** (Lim1, Wt1)	**Osr1**	**Cytokeratin**

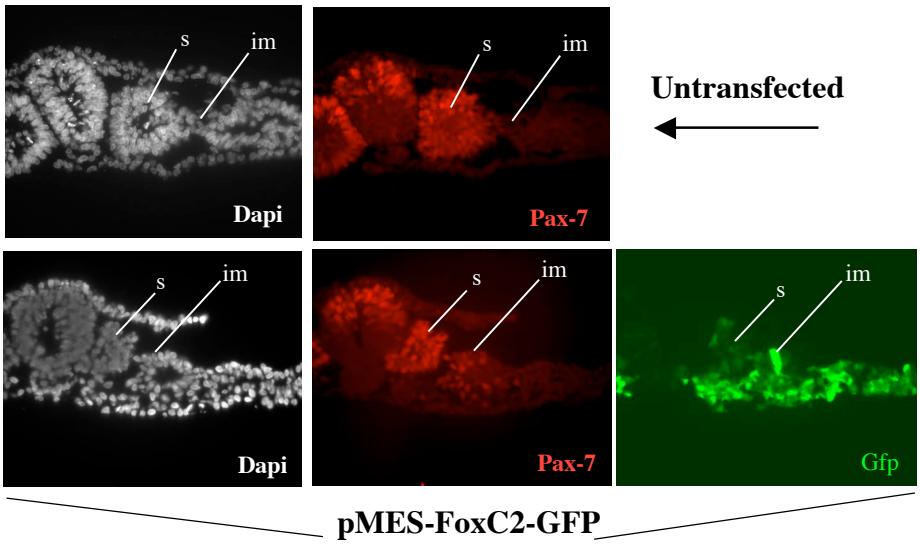
Intermediate Mesoderm markers are expanded medially in FoxC1/C2 mutants

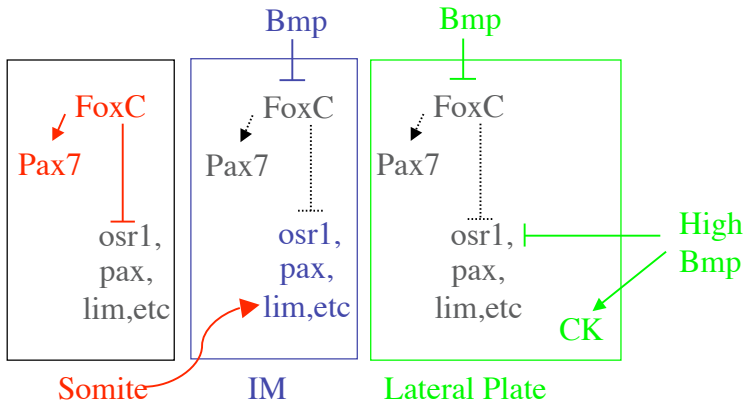


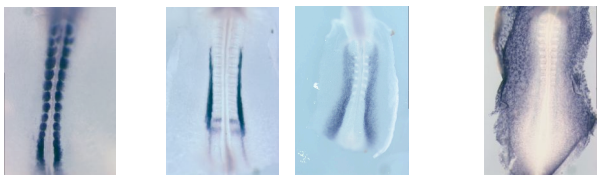
FoxC2 represses Pax-2 in the IM



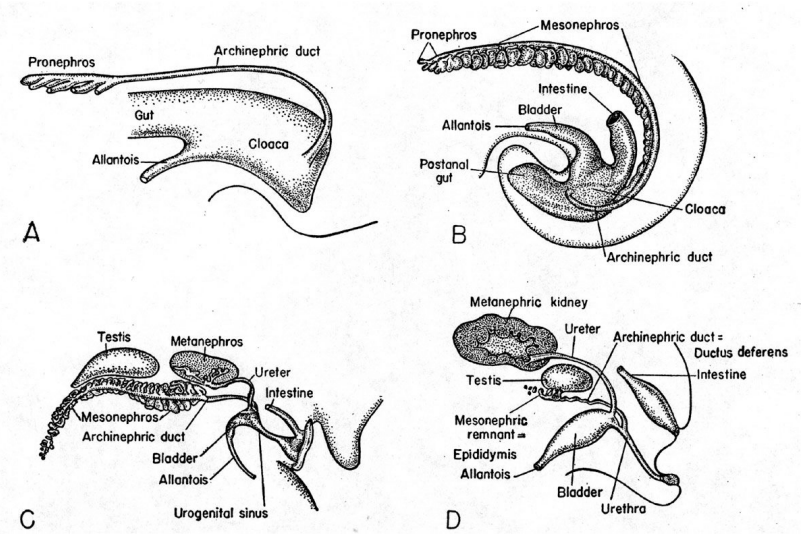
FoxC2 induces expression of the somite marker Pax-7 in the IM







Paraxis **Pax-2** **Osr1** **Cytokeratin**


Pronephros
Archinephric duct
Gut
Cloaca
Allantois
A
Pronephros
Mesonephros
Intestine
Bladder
Allantois
Postanal gut
Cloaca
Archinephric duct
B
Testis
Metanephros
Ureter
Intestine
Mesonephros
Archinephric duct
Bladder
Allantois
Urogenital sinus
C
Metanephric kidney
Ureter
Archinephric duct = Ductus deferens
Intestine
Testis
Mesonephric remnant
Epididymis
Allantois
Bladder
Urethra
D