

## V9: Cellular differentiation - development

In developmental biology, **cellular differentiation** is the process where a cell changes its **cell fate** from one cell type to another. Most commonly the cell changes to a **more specialized type**.

Differentiation occurs numerous times during the development of a multicellular organism as it changes from a simple zygote to a complex system of tissues and cell types.

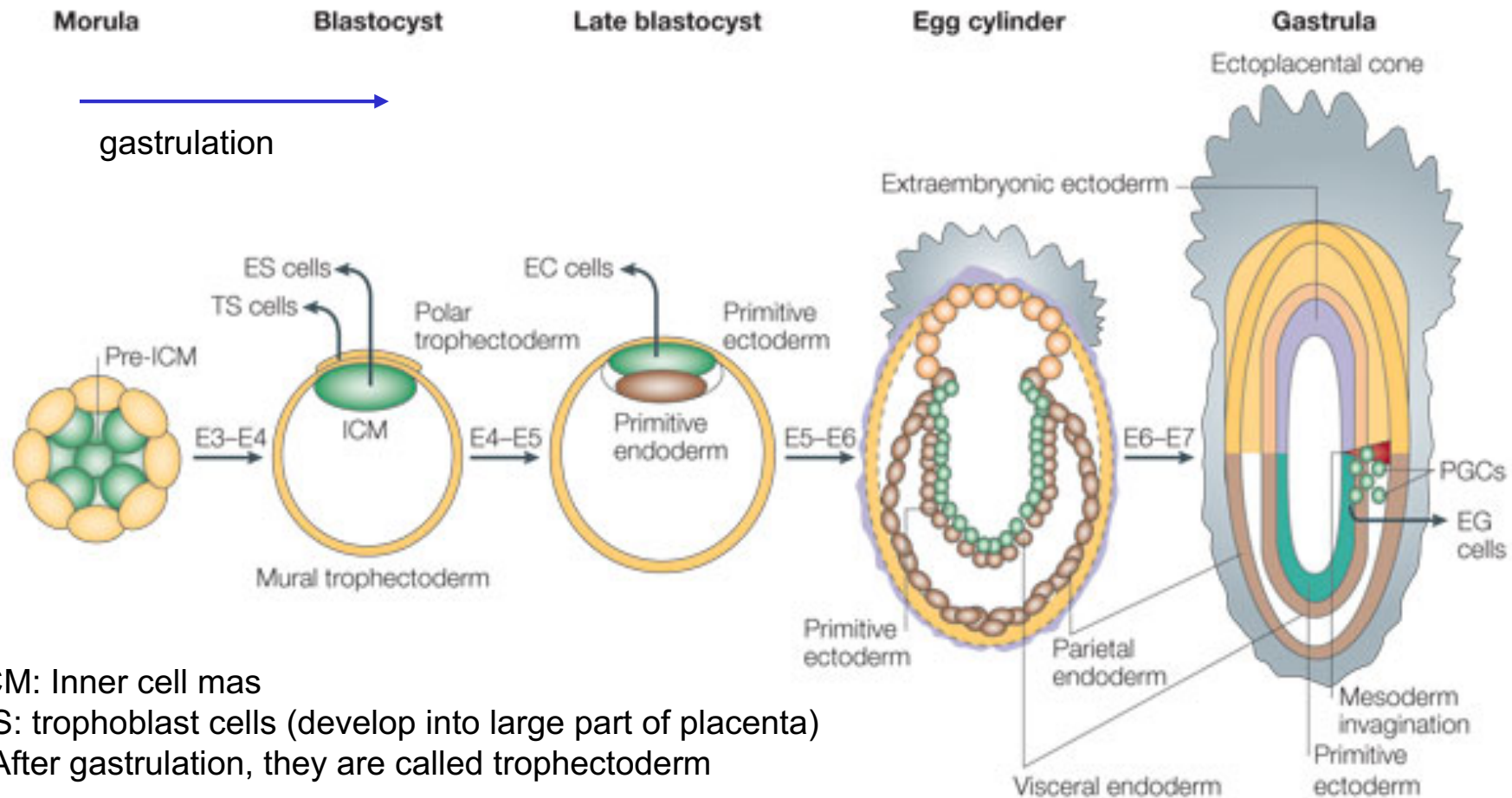
Differentiation continues in **adulthood** as adult stem cells divide and create fully differentiated daughter cells during tissue repair and during normal cell turnover.

Differentiation dramatically changes a cell's size, shape, membrane potential, metabolic activity, and responsiveness to signals.

These changes are largely due to highly controlled modifications in gene expression that are often controlled by **epigenetic** effects.

[www.wikipedia.org](http://www.wikipedia.org)

# Embryonic development of mouse



ICM: Inner cell mas

TS: trophoblast cells (develop into large part of placenta)

- After gastrulation, they are called trophoctoderm

PGCs: primordial germ cells (progenitors of germ cells)

E3: embryonic day 3

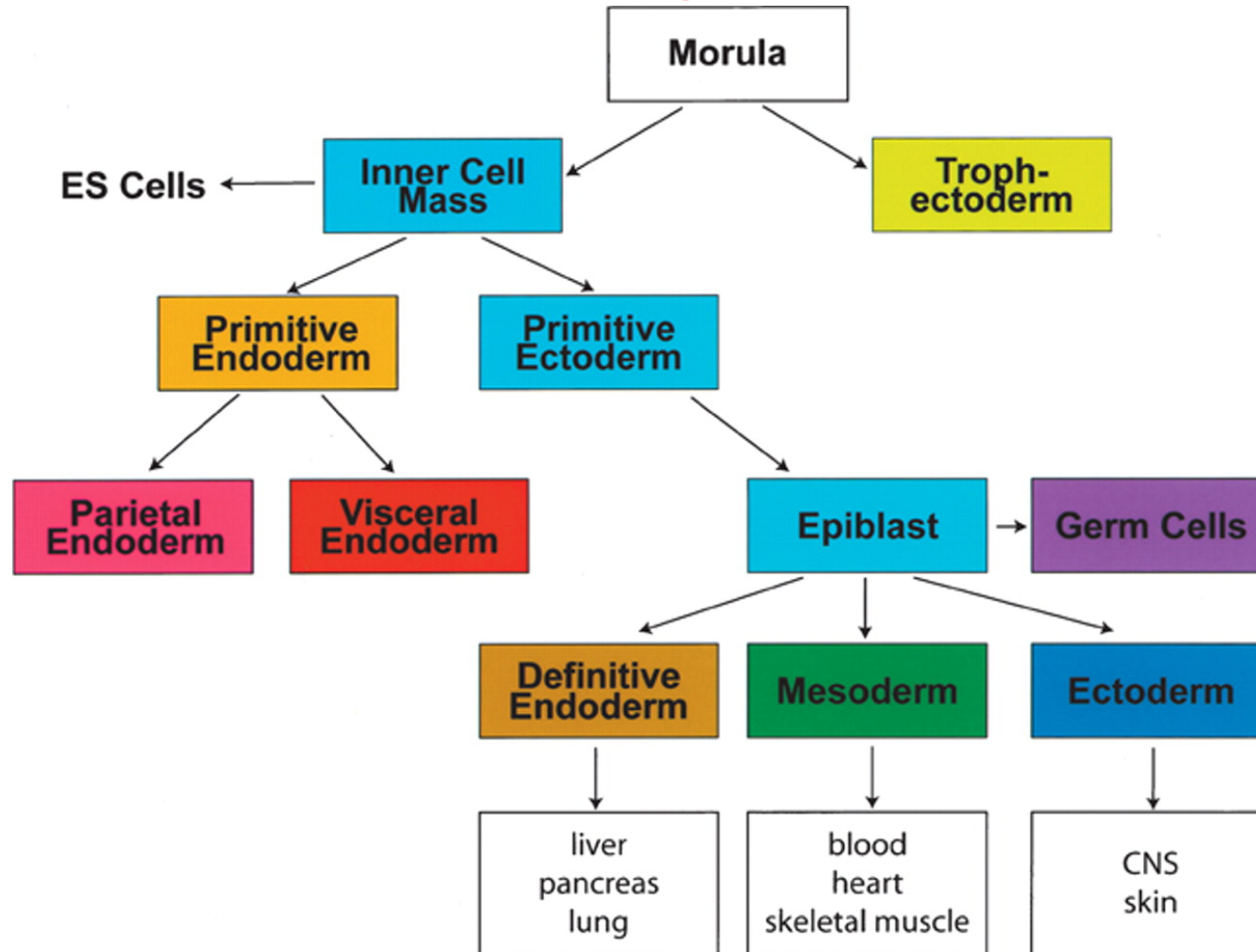
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Nature Reviews | Molecular Cell Biology

Boiani & Schöler, Nat Rev Mol Cell Biol 6, 872 (2005)

SS 2019 – lecture 9

Cellular Programs

# Cell populations in early mouse development



Scheme of **early mouse development** depicting the relationship of early cell populations to the primary germ layers

Keller, Genes & Dev.  
(2005) 19: 1129-1155

# Types of body cells

3 basic categories of cells make up the mammalian body:

**germ cells** (oocytes and sperm cells)

**somatic cells**, and

**stem cells.**

Each of the approximately 100 trillion ( $10^{14}$ ) cells in an adult human has its own copy or copies of the genome except certain cell types, such as red blood cells, that lack nuclei in their fully differentiated state.

Most cells are **diploid**; they have two copies of each chromosome.

Cells differentiate to specialize for different functions.

Somatic cells make up most of the human body, such as skin and muscle cells.

[www.wikipedia.org](http://www.wikipedia.org)

## Development controlled by transcriptional programs

Embryonic development is a complex process that remains to be understood despite knowledge of the complete genome sequences of many species and rapid advances in genomic technologies.

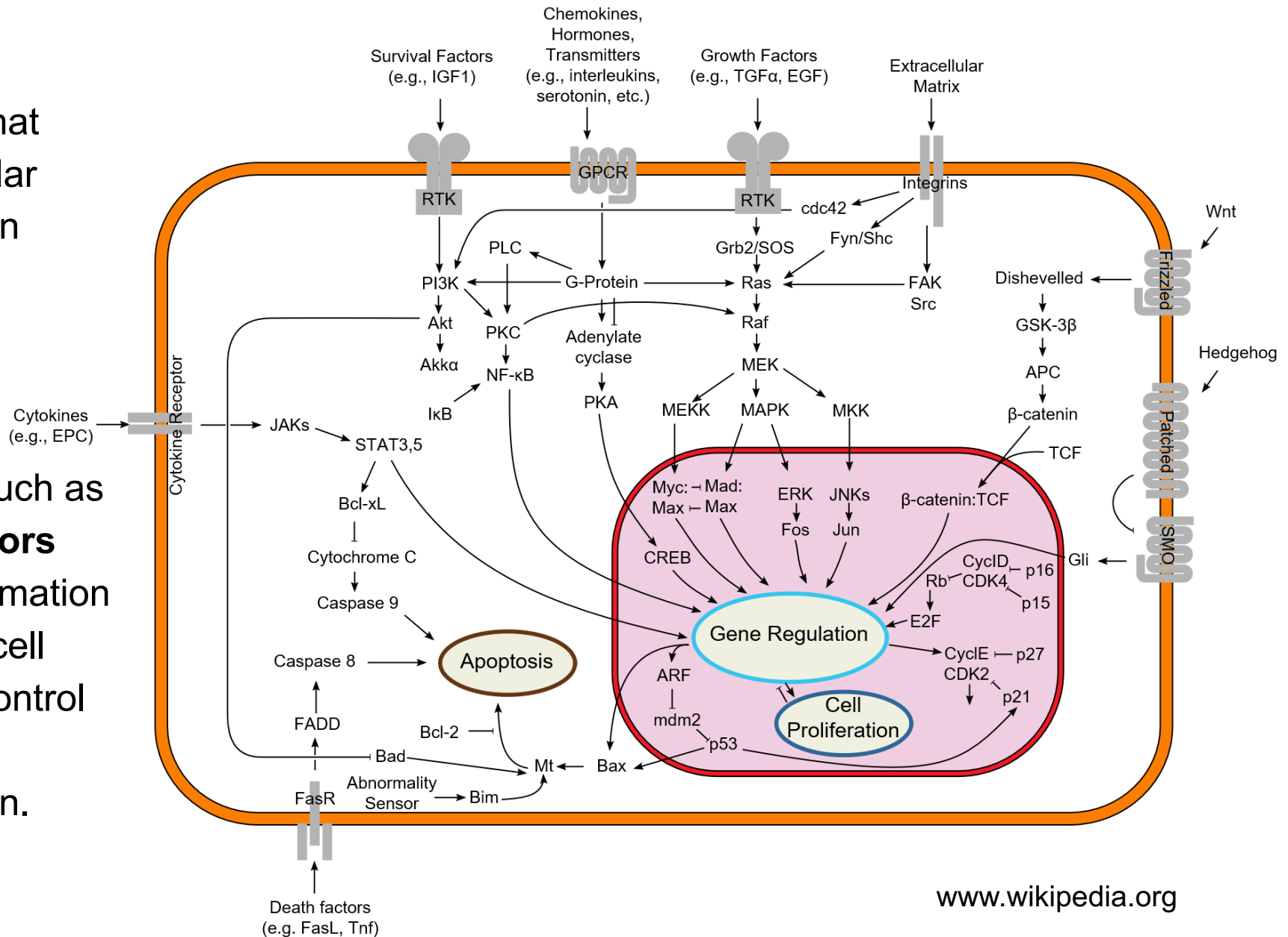
A fundamental question is how the unique gene expression pattern in each cell type is established and maintained during embryogenesis.

It is well accepted that the gene expression program encoded in the genome is executed by **transcription factors** that bind to cis-regulatory sequences and modulate gene expression in response to **environmental cues**.

# Growth factors induce cell differentiation

The major molecular processes that control cellular differentiation involve **cell signaling**.

Signalling molecules such as **growth factors** convey information from cell to cell during the control of cellular differentiation.



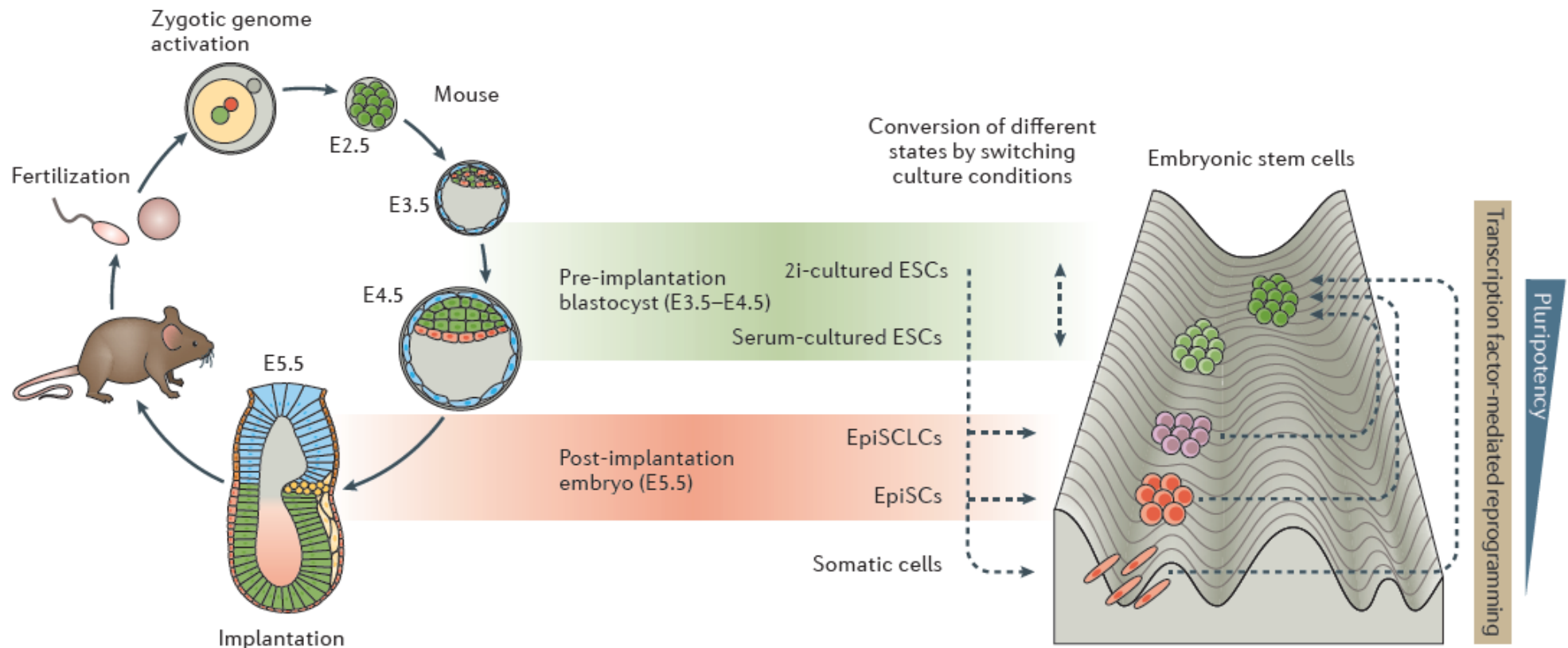
www.wikipedia.org

# Different states of pluripotency

E4.5 epiblast cells: represent ground-state pluripotency

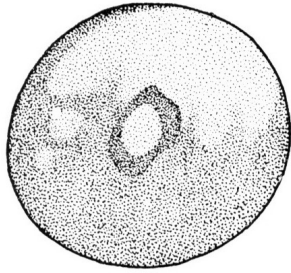
**Implantation:** stage of pregnancy at which the blastocyst adheres to the wall of the **uterus**.

After implantation (E5.5): **epiblast cells** undergo a strong wave of epigenetic reprogramming. They are now „primed“.

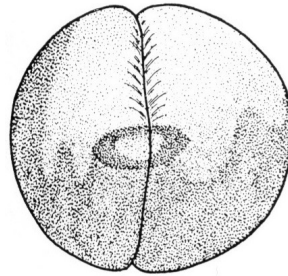




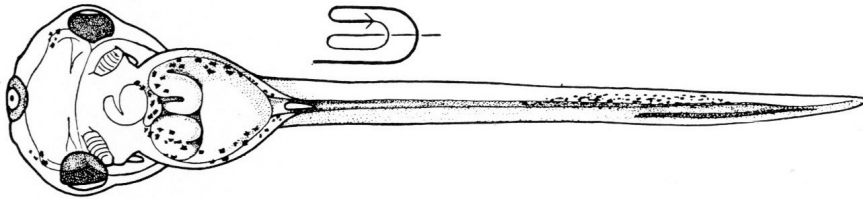
# Xenopus development – xenbase.org



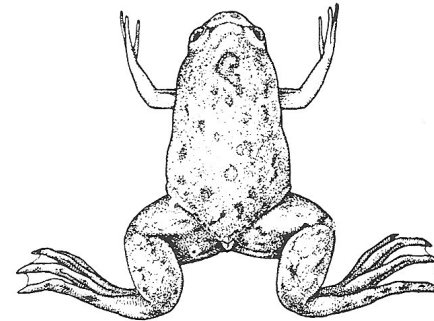
Stage 1 (egg), animal view  
0 min pf @ 23° c



Stage 1 (egg), animal view  
0 min pf @ 23° c



Stage 44, ventral view  
3 days, 20 hr pf @ 23° c



Stage 66, dorsal view  
58 days pf @ 23° c

<http://www.xenbase.org/anatomy/alldev.do>



# Animations illustrating *Xenopus* development

Developmental movies

<http://www.xenbase.org/anatomy/static/movies.jsp>

Cell fate map

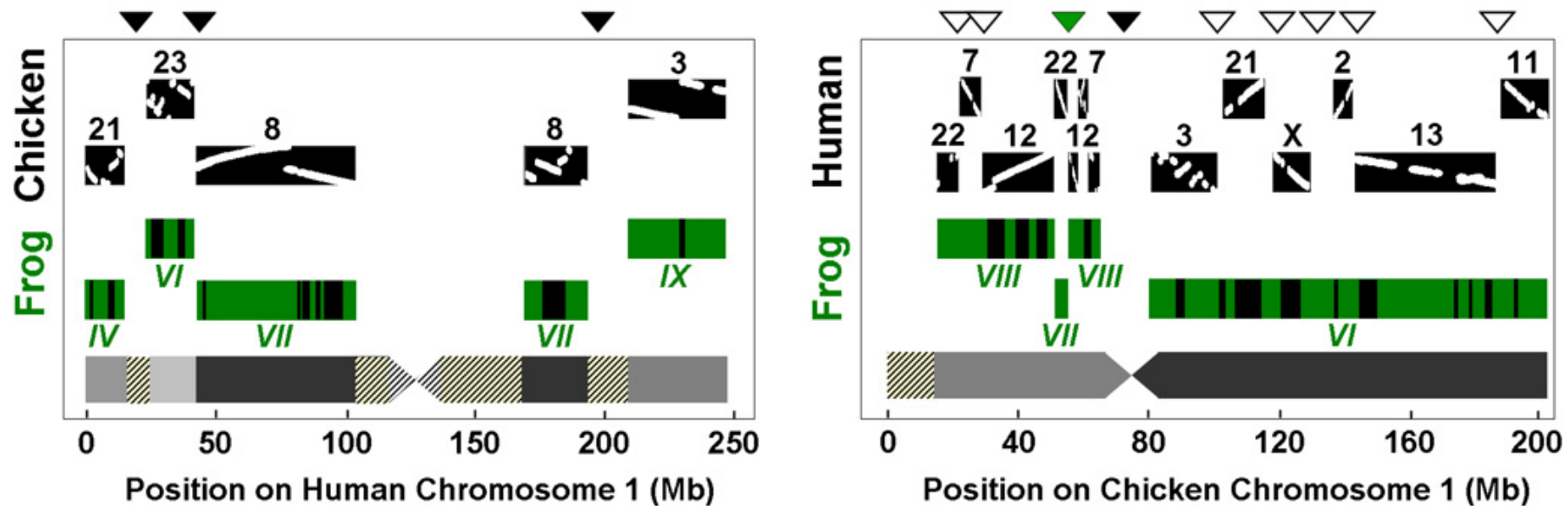
<http://www.xenbase.org/anatomy/static/xenbasefate.jsp>

## *Xenopus tropicalis* genome

The *X. tropicalis* genome encodes over 20,000 protein-coding genes, including orthologs of at least 1,700 human disease genes

It displays long stretches of gene colinearity with human and chicken.  
Of the 272 largest scaffolds (totaling half the assembly) 267 show such colinearity.

60% of all gene models on these scaffolds can be directly associated with a human and/or chicken ortholog by conserved synteny.



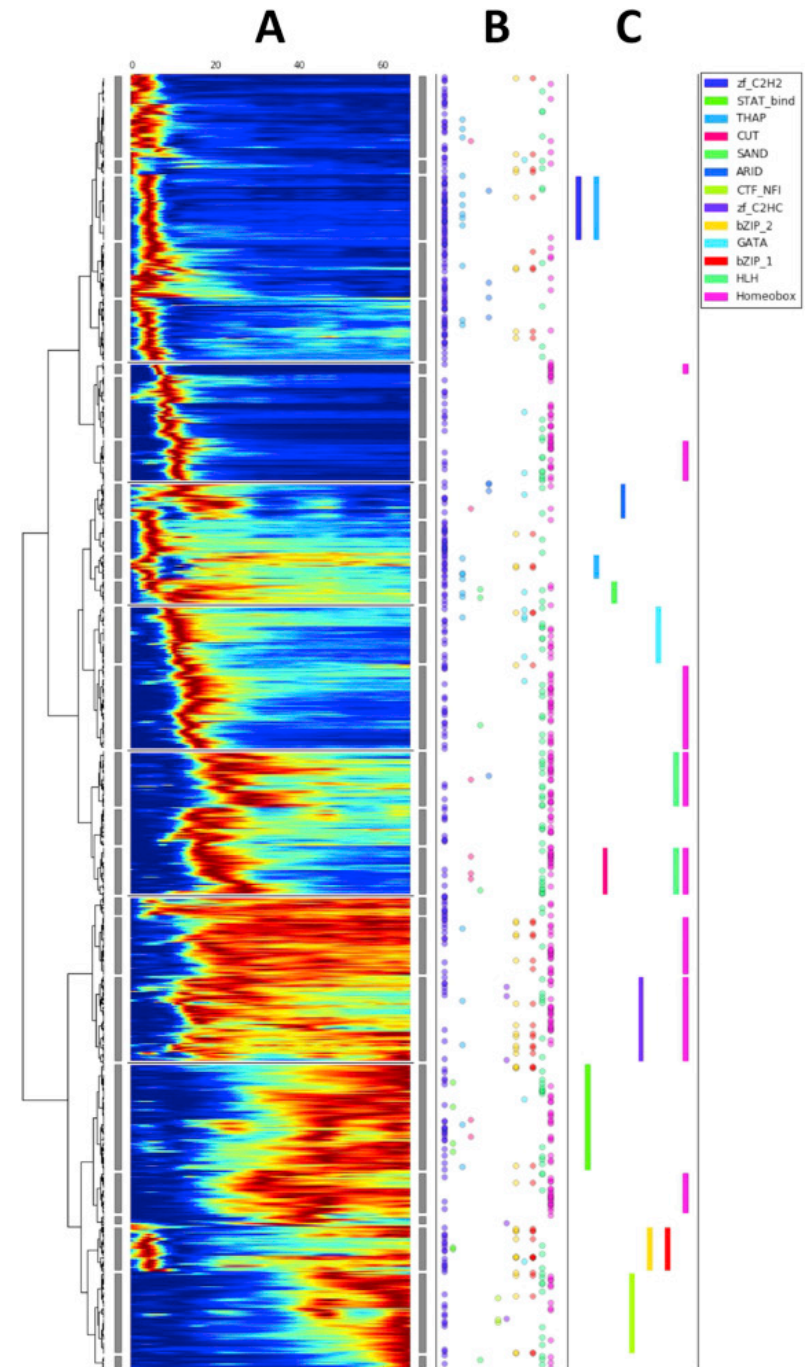
# Xenopus development – TF expression dynamics

Ca. 1250 transcription factors (TFs) are found in *Xenopus tropicalis*

There is a high one-to-one correspondence of TFs between the frog and human despite the ~360 million years since their last common ancestor.

Heat-map of TF expression dynamics during early development (over the first 66 hours post fertilization).

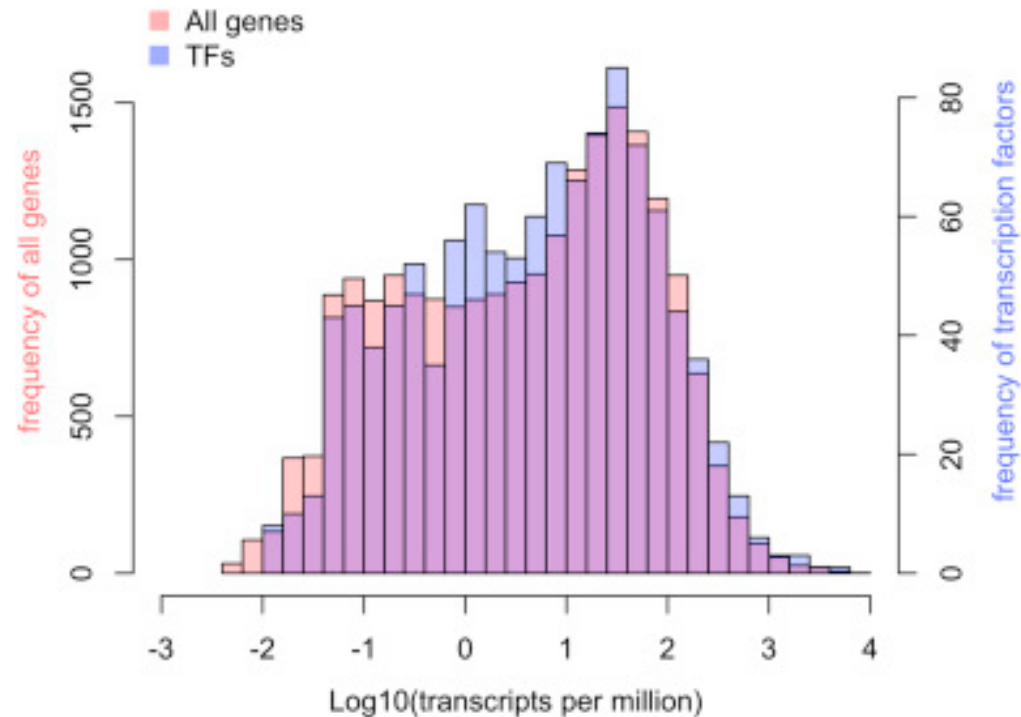
Blitz et al. Develop Biol 426, 409 (2017)



# Xenopus development – TF expression dynamics

Distribution of TF gene expression levels in the early gastrula is indistinguishable from expression of all genes.

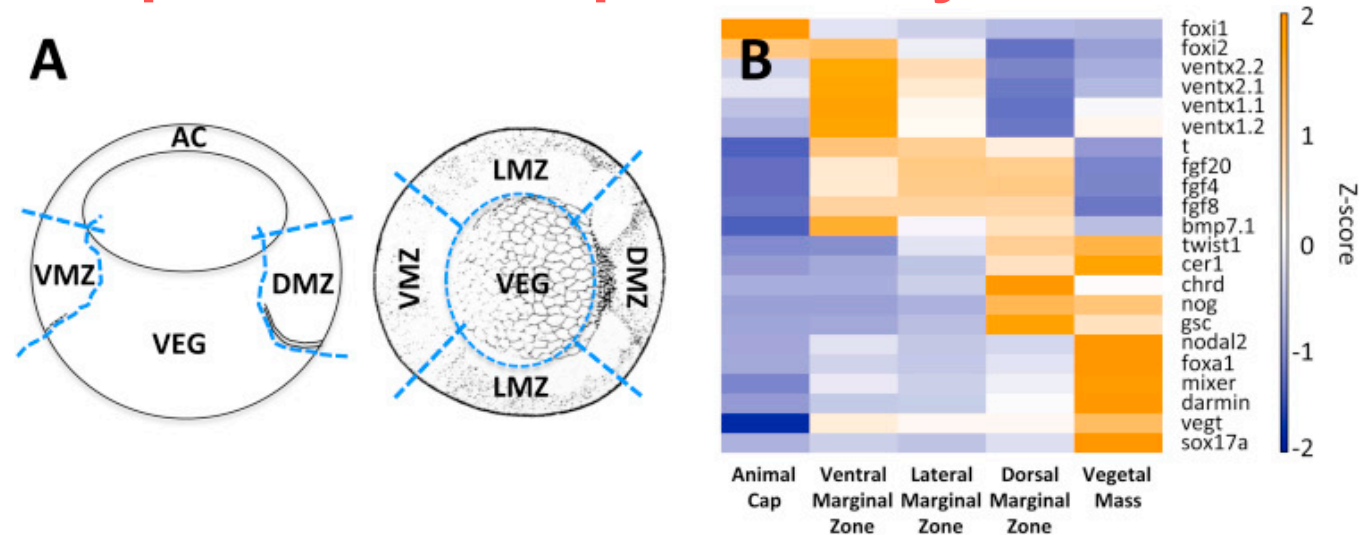
The frequency of appearance of TFs (right vertical axis) and all genes (left vertical axis) is plotted as a function of expression level. The two distributions are nearly identical.



1130 TFs (91% of the catalog) were detectable at *any* expression level in the early gastrula.

Blitz et al. Develop Biol 426, 409 (2017)

# Xenopus development – TF expression dynamics



To perform a screen for TFs with spatially localized mRNA expression we dissected early gastrula embryos into 5 regions:  
animal cap (ectodermally enriched),  
vegetal mass (endodermally enriched), and  
dorsal, lateral and ventral marginal zones (mesodermally enriched).

We performed RNA-seq on mRNAs isolated from these regions, and on whole embryo mRNA collected from stage-matched sibling embryos.

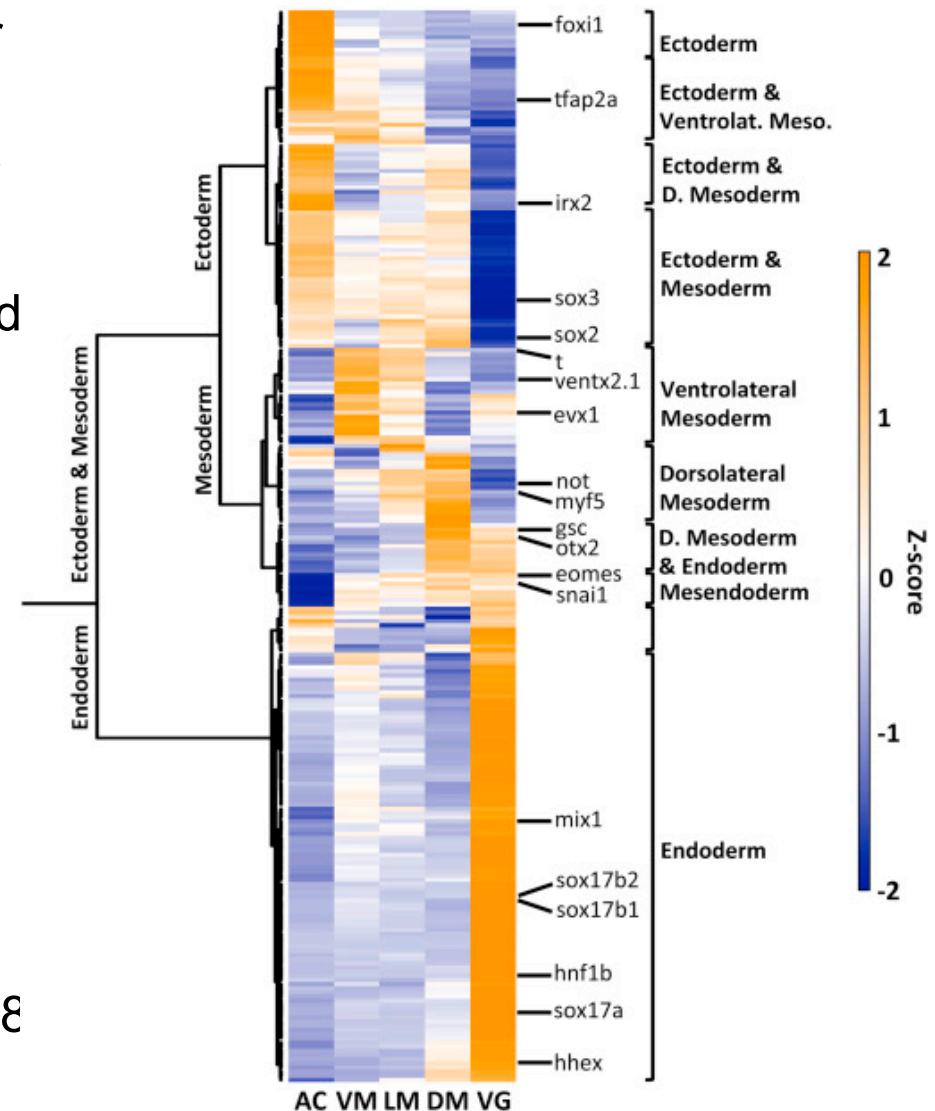
Blitz et al. Develop Biol 426, 409 (2017)

# Xenopus development – TF expression dynamics

We next interrogated the RNA-seq datasets for spatially localized expression of TFs. We performed a pairwise comparison between any two regions of the embryo and found 257 TFs with differential expression, and this was plotted as a clustered heatmap (right). This shows major groupings of genes that we interpret as *predominantly* representing the three germ layers.

We identify 30 TFs enriched dorsally, 26 ventrally, 70 animally, and 130 vegetally.

Using these criteria, the total number showing spatial enrichment along at least one axis is 218 TFs (38 TFs are differentially expressed along more than one axis).



Blitz et al. Develop Biol 426, 409 (2017)



## Paper #7

The dynamics of gene expression in vertebrate embryogenesis  
at single-cell resolution

**James A. Briggs, Caleb Weinreb, Daniel E. Wagner, Sean Megason,  
Leonid Peshkin, Marc W. Kirschner, Allon M. Klein\***

*Science* 01 Jun 2018: Vol. 360, Issue 6392, eaar5780  
DOI: 10.1126/science.aar5780

Paper presentation June 18, 2019

Afrikanischer Krallenfrosch/  
Western lawed frog  
is the only frog with diploid genome  
4-6 cm in size



xenbase.org