# 3.,4. MORPHOGENESIS AND CELL DIFFERENTIATION

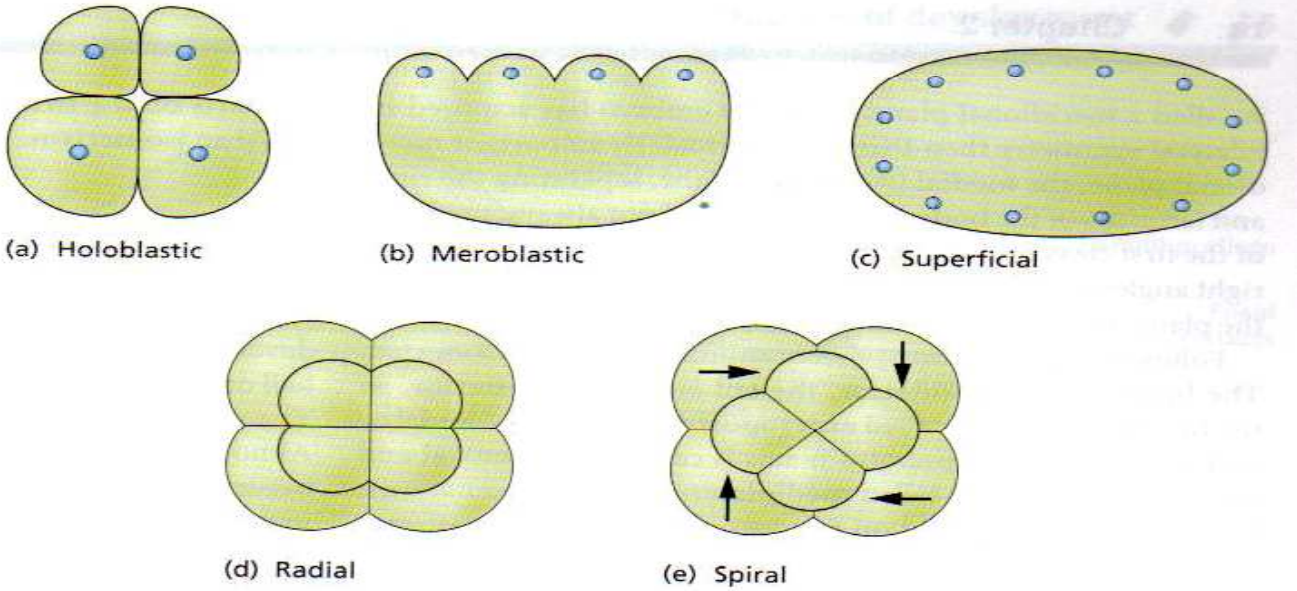
# EARLY DEVELOPMENT

-Sperm to egg fusion creates changes in egg structure that exclude the fusion of any further sperm (a block to **polyspermy**). Fusion leads to rapid increase of intracellular calcium. Calcium triggers metabolic activation of egg, increase of protein synthesis, initiation of second meiotic division in vertebrates, and cytoplasmic rearrangements that are important for future regional specifications of the embryo

- The sperm and egg pronuclei fuse to form a single diploid nucleus, at this stage the fertilized egg is called **zygote.** Zygote is small, sperical and polarized along the vertical axis.The upper hemisphere is called **animal,** the lower, rich on yolk is referred as **vegetal** hemisphere.

- Early cell divisions are called cleavages since there is no cell growth between successive divisions.

- Cleavage patterns differ among the animal groups, the products of cleavage are called **blastomeres**.

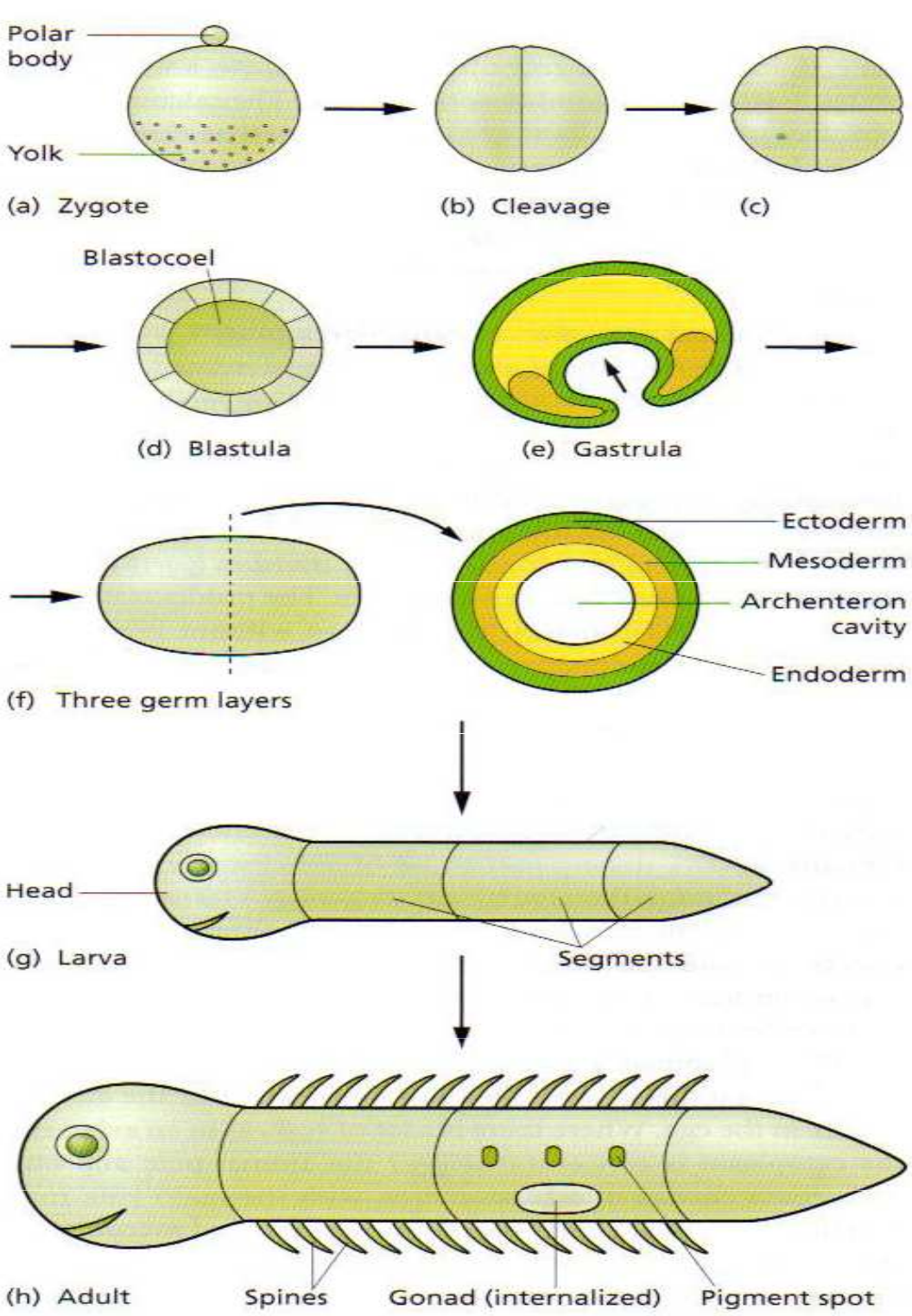


During cleavage a cavity forms in the middle of the ball of cells – **blastocoel** - that expands due to the water uptake. Such embryo is called **blastula**.

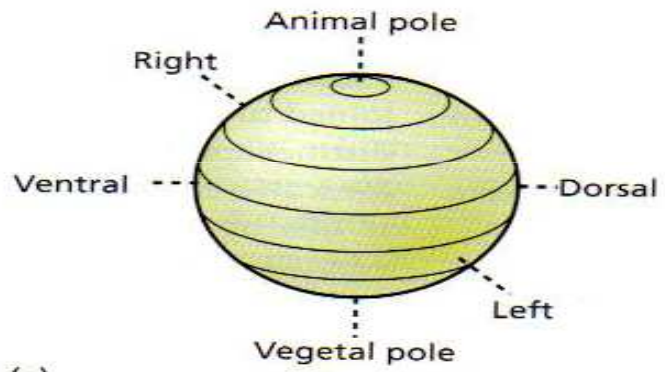
- A complex of gastrulation movements transforms embryo in the **gastrula** characteristic by three tissue layers – **germ layers**.

-The outer layer <u>ECTODERM</u> forms skin and nervous system
-The middle layer <u>MESODERM</u> forms muscle, connective tissue, excretory organs and gonads.
-The inner layer <u>ENDODERM</u> forms gut epithelia.

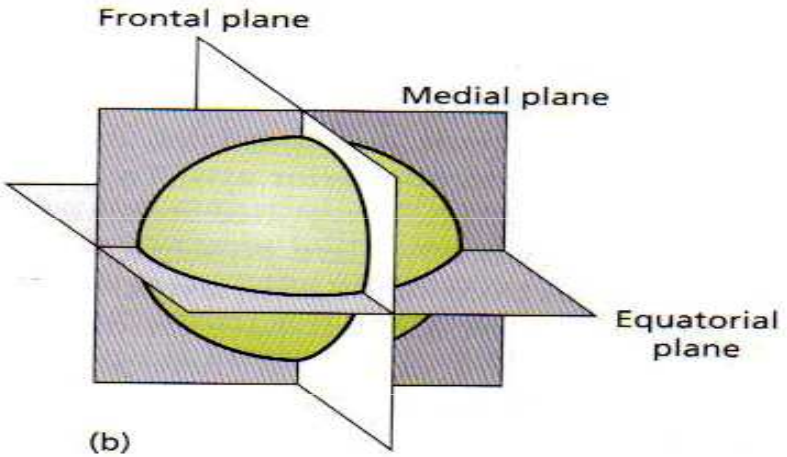
The germ cells appear usually by the stage of gastrulation and are not regarded as belonging to any of the three germ layers.



# AXES AND SYMMETRY




(a)

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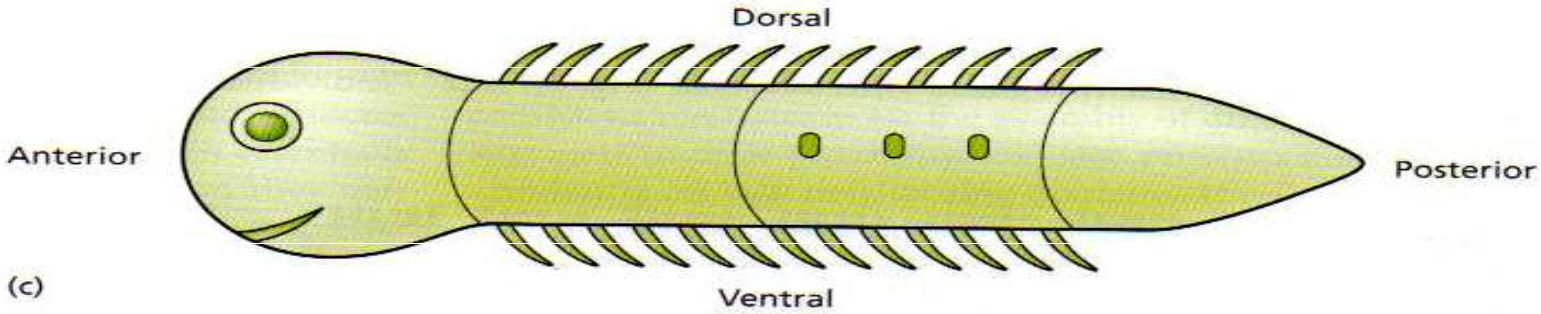
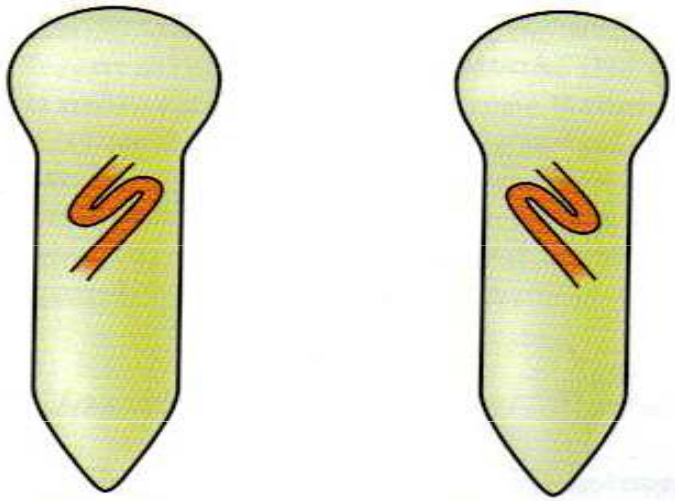



(c)



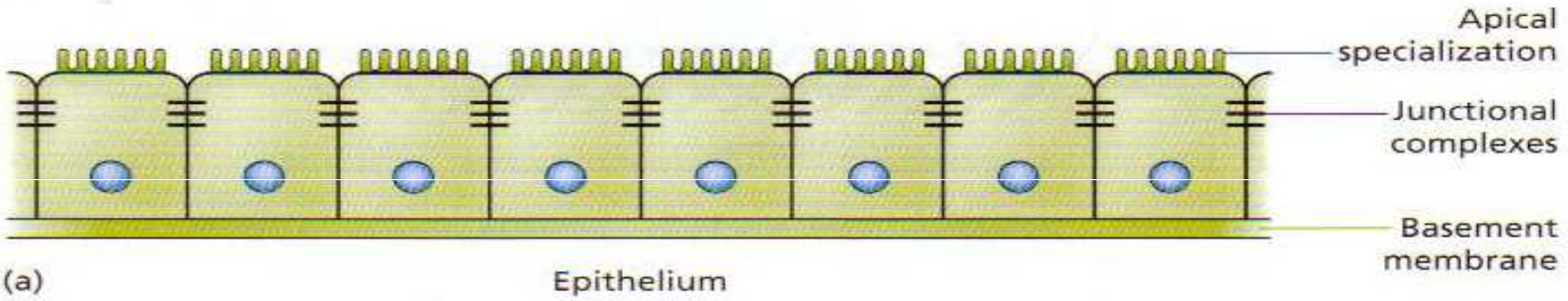
(d)

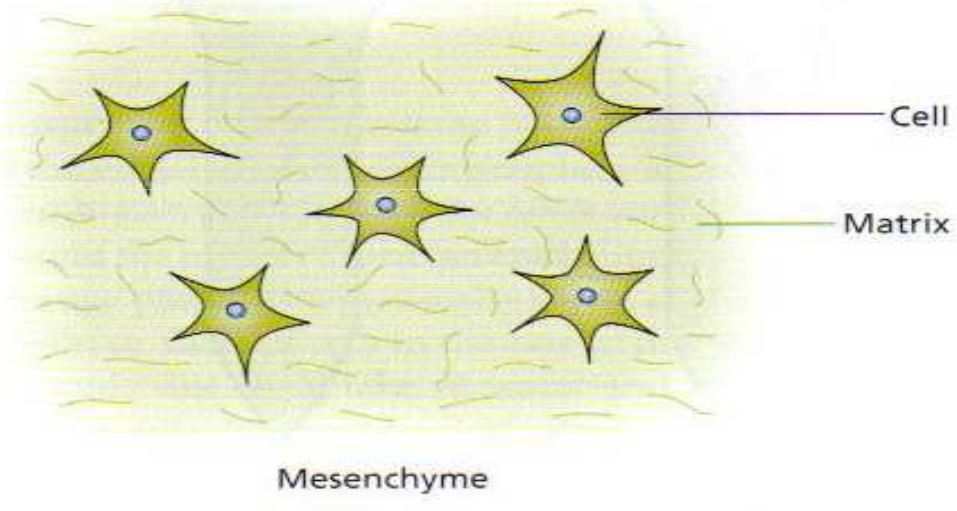
*Situs solitus*

*Situs inversus*

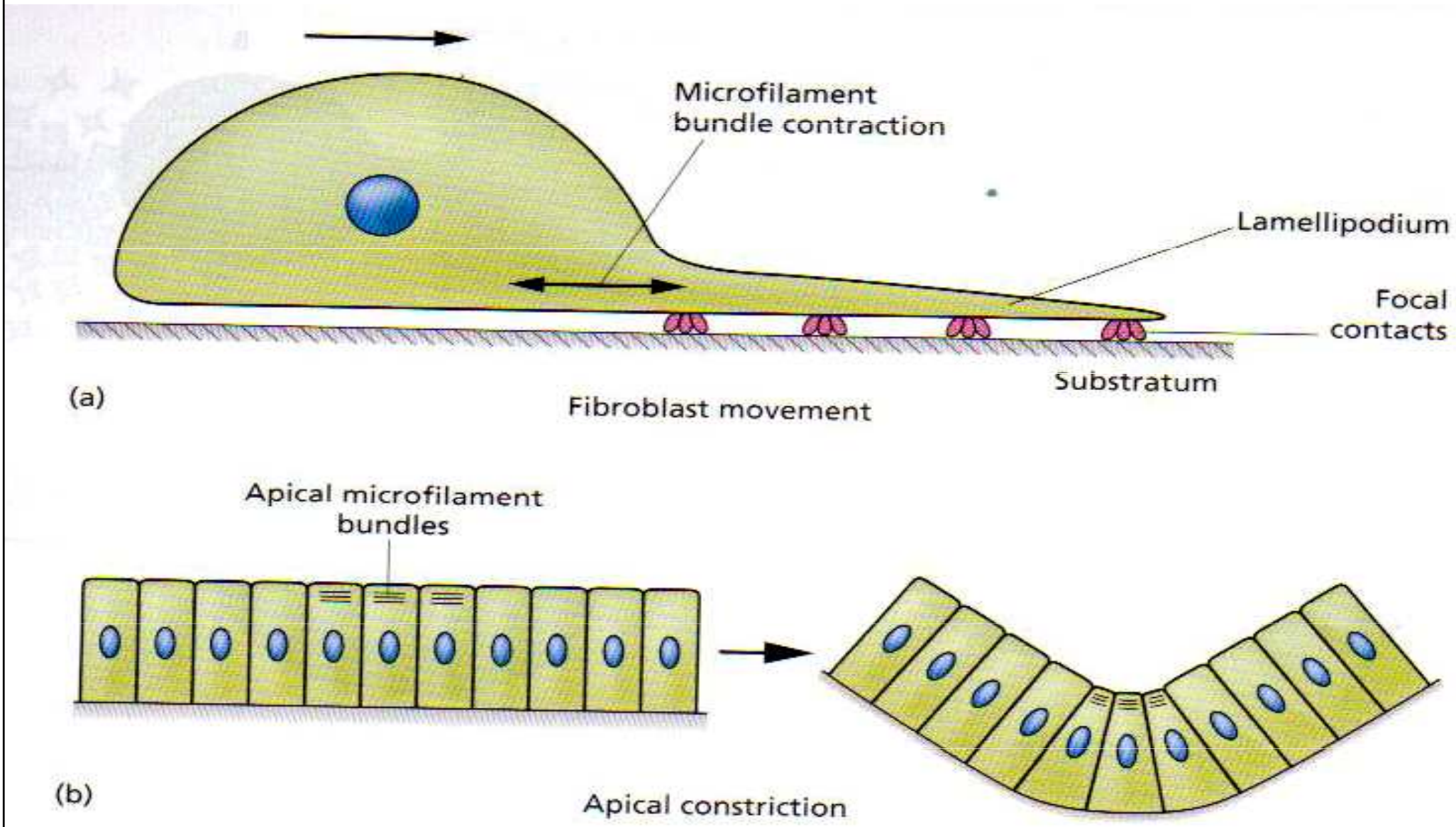
# MORPHOGENETIC PROCESSES

Cell shape changes and movements are fundamental to early development when embryo needs to convert itself from a ball of cells into a multilayered and elongated structure. This is achieved through a process called **gastrulation**. The basic cellular processes operating in gastrulation are common to all animals. In the later stages of developement, the same reperitoire of processes is re-used repeatedly in the morphogenesis of individual tissues and organs. Most embryonal cells are either **epithelial** or **mesenchymal.**



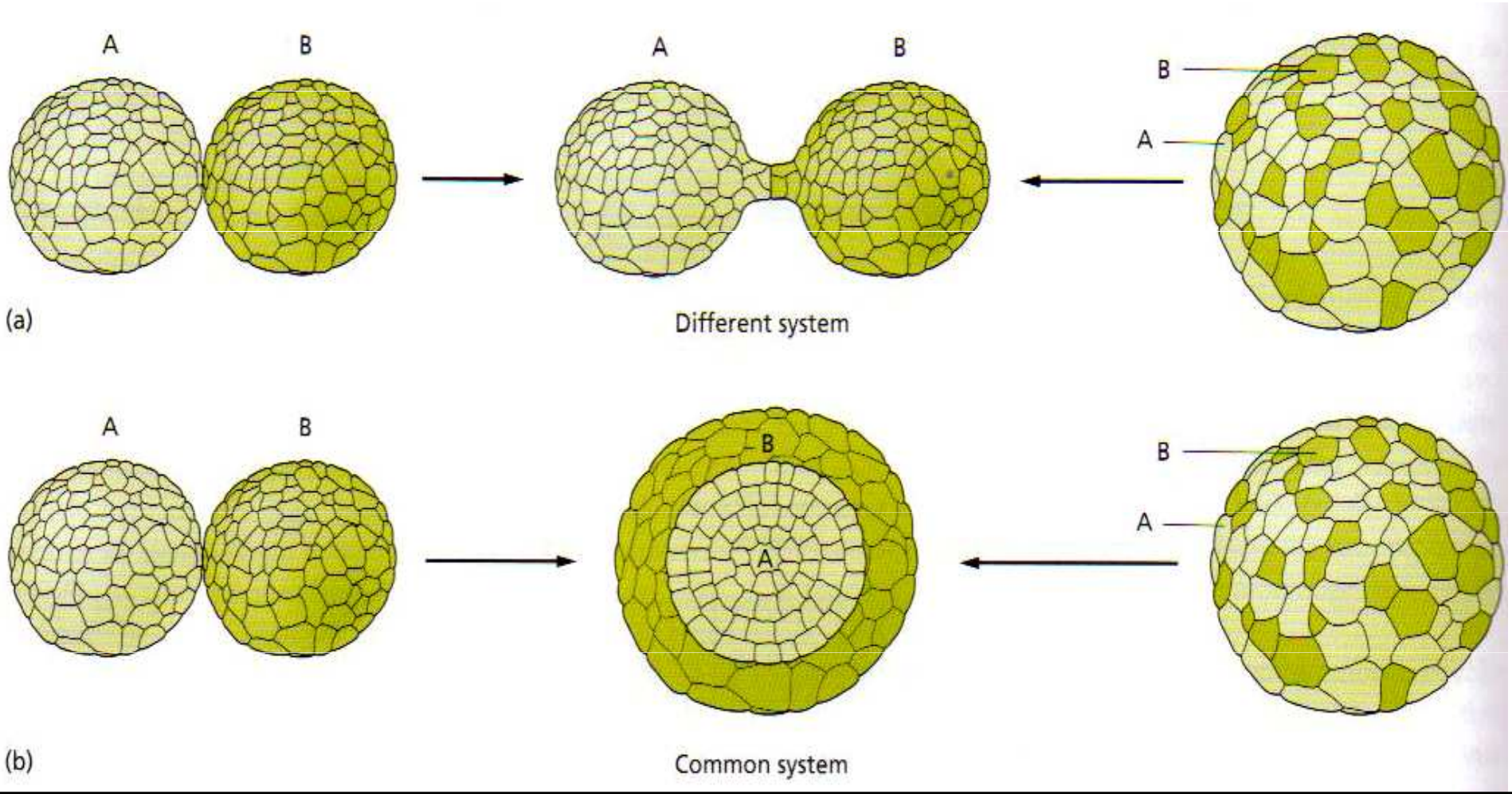



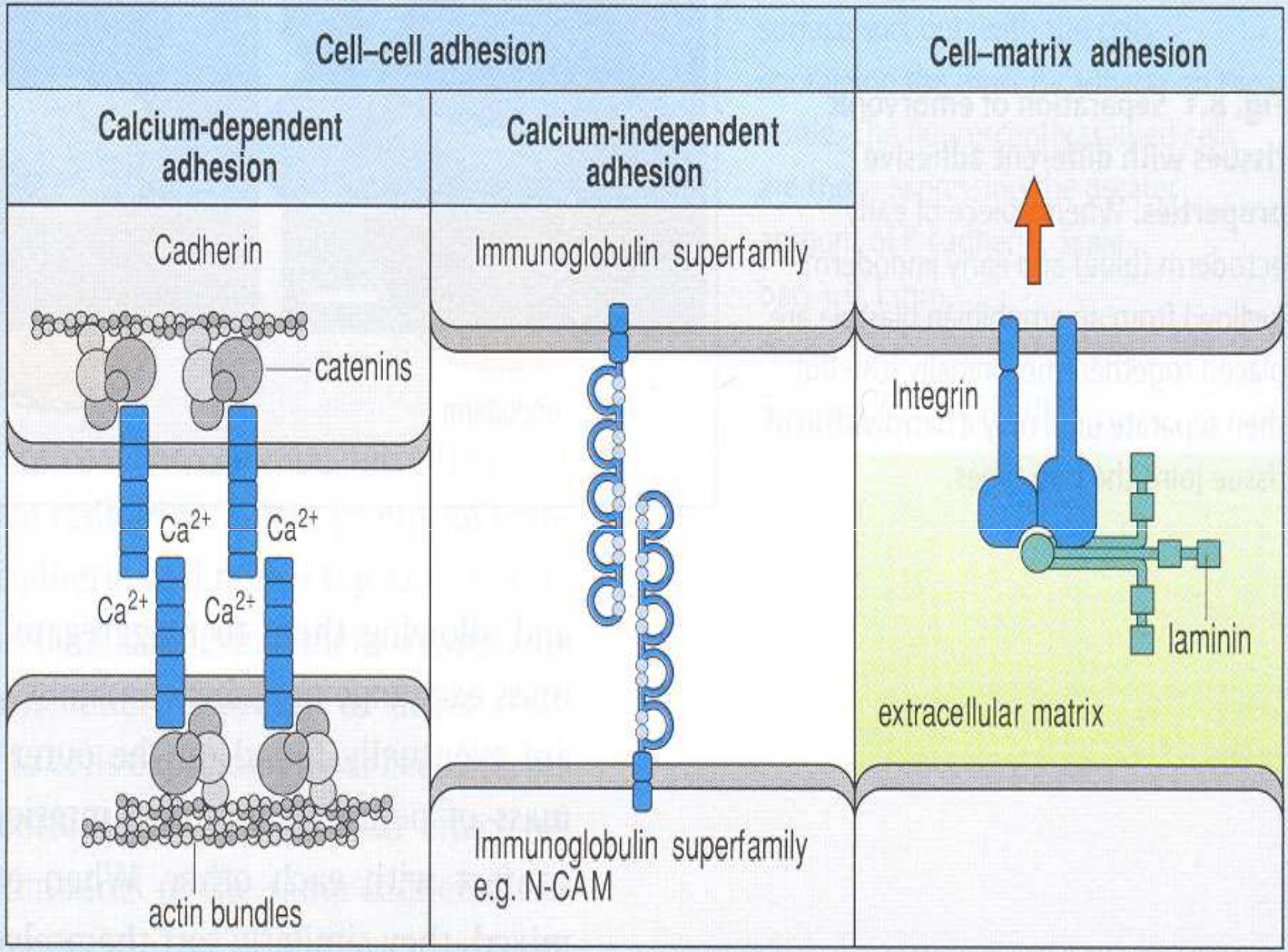
CELL MOVEMENT: Many morphogenetic processes depend on movement of individual cells, such as migrantion of neural crest cells or germ cells that individually move **long distances**. **Short-range** movement are equally important in shape changes in cell sheets.



CELL ADHESION: Epithelial cells are bound together by **tight junctions**, **adherent junctions**, and **desmosomes**, the latter two involving **cadherins** as major components. Mesenchymal cells may also adhere by means of cadherins but usually more loosely.

The adhesion of early embryo cells is dominated by cadherins – removal of calcium from media disaggregates embryo to single cell. In cadherin adhesion there is **qualitative specificity** – cells carrying E-cadherin stick more strongly to each other than to those bearing N-cadherin (**homophilic adhesion**).




Cell–cell adhesion
Cell–matrix adhesion
Calcium-dependent adhesion
Calcium-independent adhesion
Cadherin
Immunoglobulin superfamily
catenins
Integrin
$Ca^{2+}$
$Ca^{2+}$
$Ca^{2+}$
$Ca^{2+}$
laminin
extracellular matrix
actin bundles
Immunoglobulin superfamily
e.g. N-CAM

# MORPHOGENETIC PROCESSES

**CONDENSATION**: Cells form an aggregate, preludes formation of structure, like skeletal element. Triggered by increase of local cell proliferation, reduction of matrix production and increased adhesion.

**INVAGINATION AND INVOLUTION**: Ways to generate multilayered structures from a simple epithelium. Found in gastrulation, neurulation and formation of glands, sense organs, and insect appendages. Induced by localized apical constriction that proceeds into the into the invagination or involution by different adhesion between invaginating/involuting cells and the surroundings.

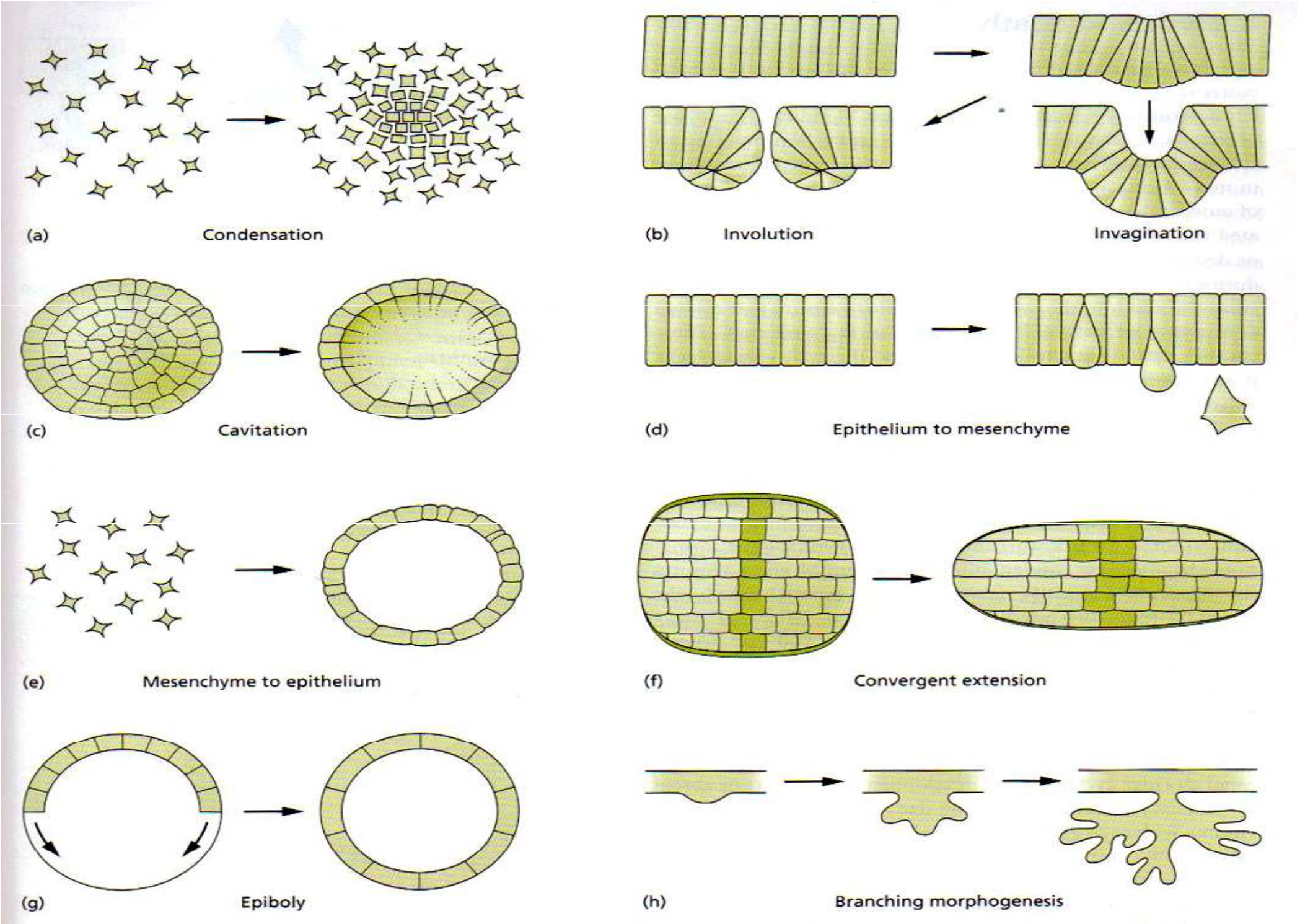
**CAVITATION**: Generation of a fluid-filled space in a mass of cells. Occurs through cell rearrangement ( as in secondary neurulation) or by apoptosis in the interior (as in formation of the mouse egg cylinder).

**EPITHELIAL-TO-MESENCHYMAL TRANSITION**: Occurs whenever cells leave epithelium and move off as a mesenchymal mass. Happens for example in the neural crest from the dorsal neural tube. Caused by local reduction in cell-cell adhesion. The reserve process to the latter is **mesenchyme-to-epithelium** transition, found for instance in the formation of kidney tubules.

**CONVERGENT EXTENSION**: Shaping of the cell sheets when individual cells intercalate in between each other causing a constriction and elongation of the sheet. Caused by contractive activity at the termini of the cells that exerts traction on the extracellular matrix and force the cells in between each other.

**EPIBOLY**: Sheet of cells expands and surrounds and encloses another population.

**BRANCHING MORPHOGENESIS**: When epithelial bud grows into the mesenchymal cell mass. Caused by cell movements or differential growth at the tip. Used in formation of lung and kidney.


(a) Condensation
(b) Involution
Invagination
(c) Cavitation
(d) Epithelium to mesenchyme
(e) Mesenchyme to epithelium
(f) Convergent extension
(g) Epiboly
(h) Branching morphogenesis

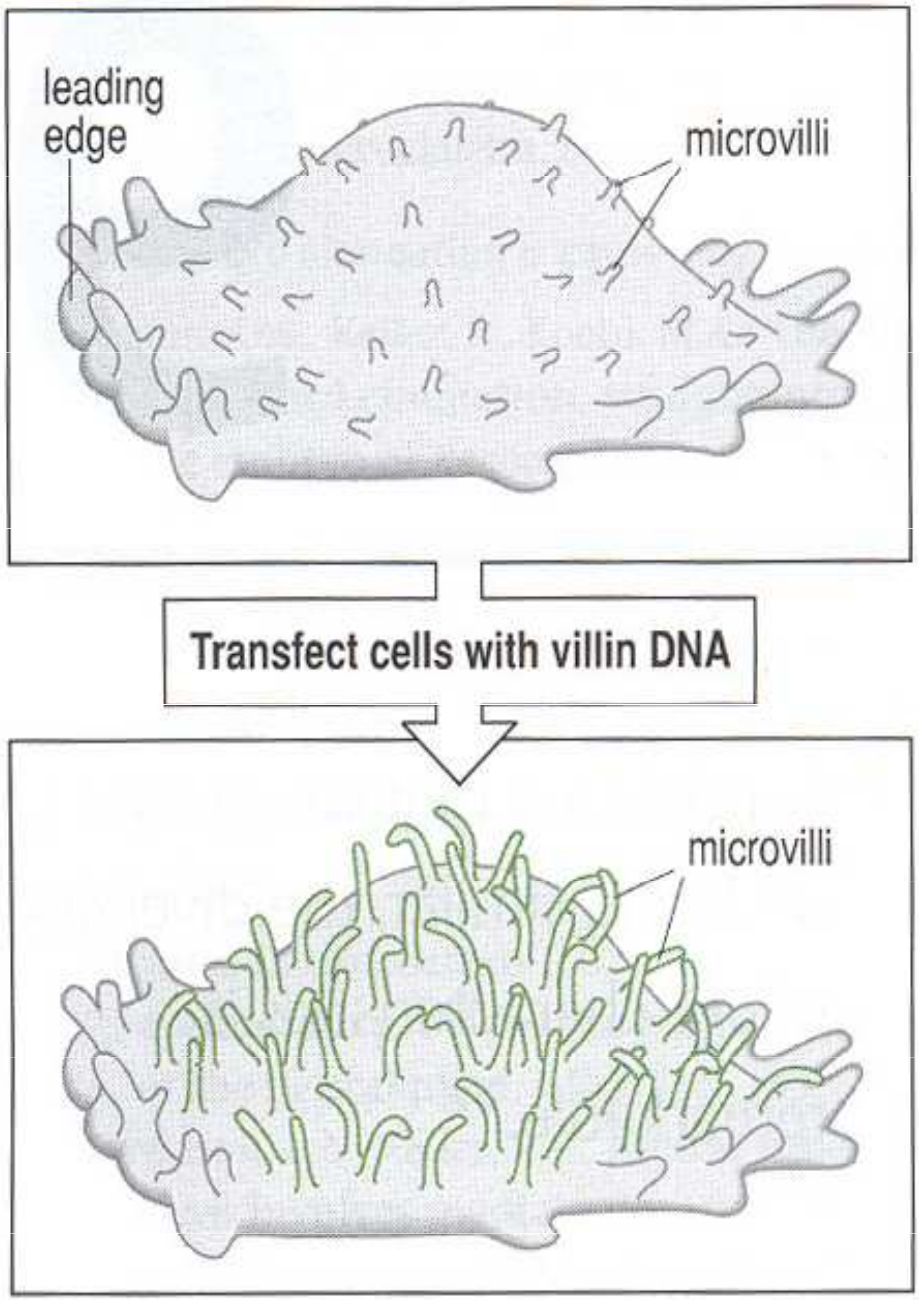
# CELL DIFFERENTIATION

**Cell differentiation** – the emergence of cell types that have clear identity in adult (over 200 types in mammals) vs. transient changes in cell form and gene expression in early development.

Differentiated cell contains proteins specific to its type in addition to common house-keeping proteins.

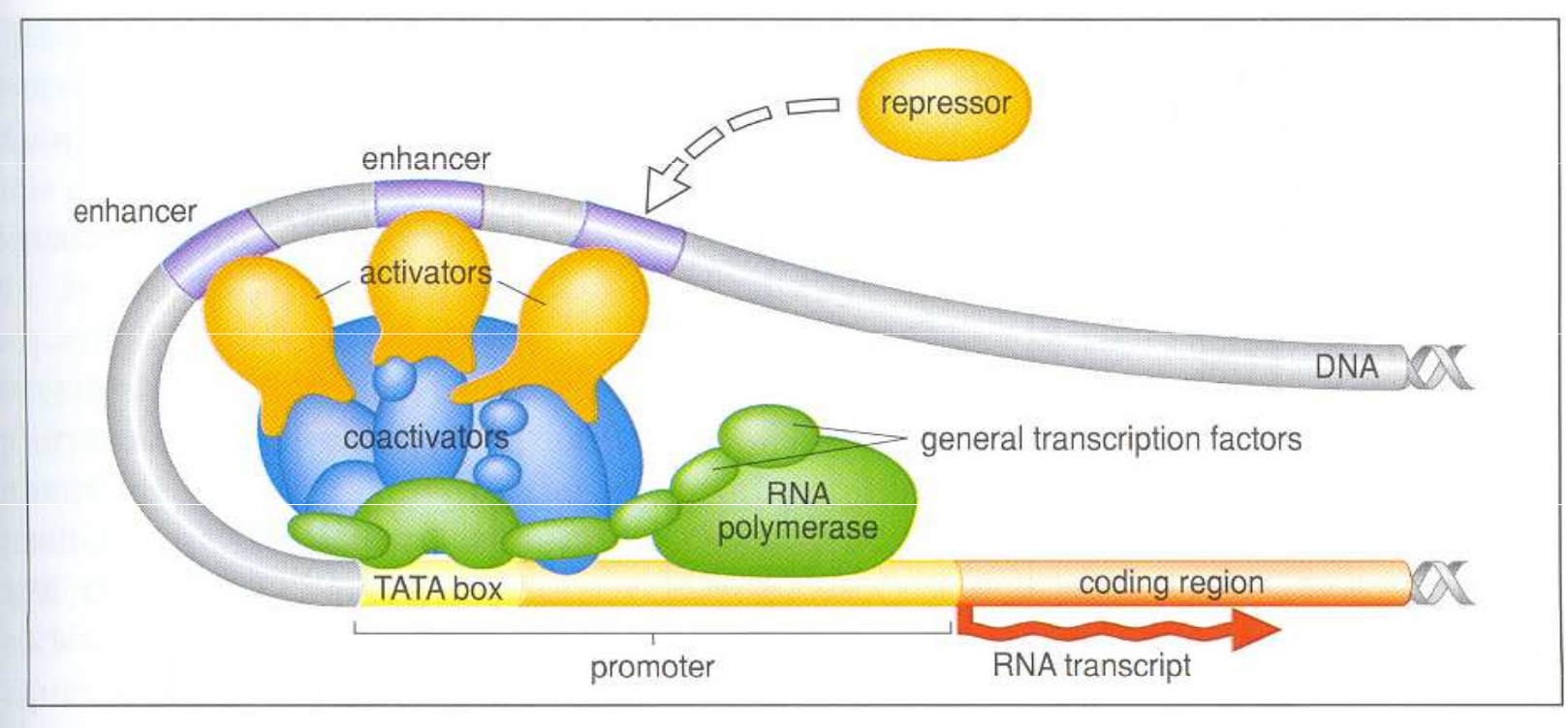
Cell differentiation is often in conflict with proliferation and many terminally differentiated cells can not divide.

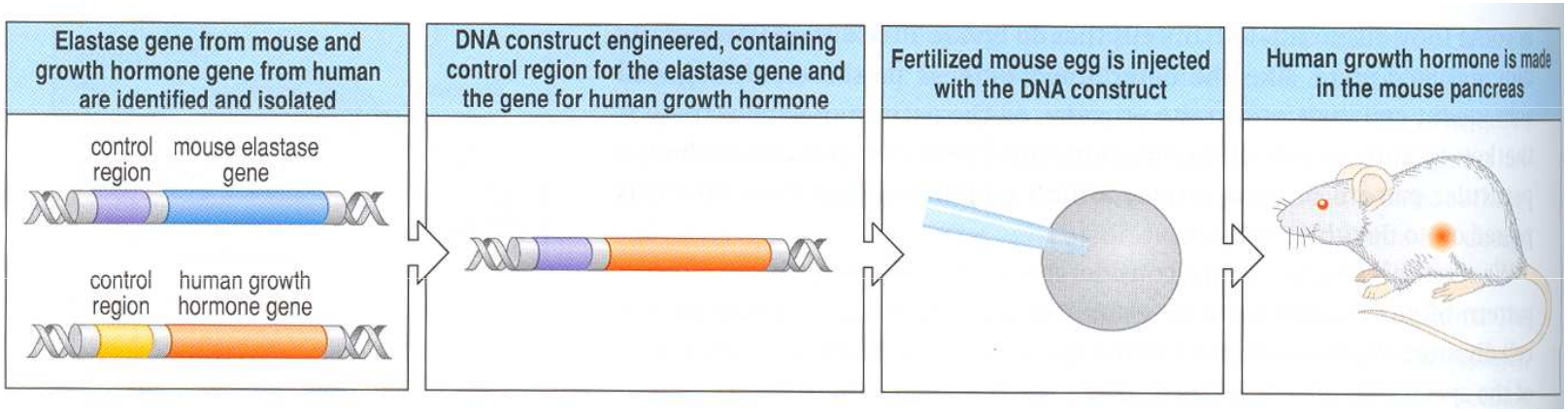
The differentiation is induced by variety of external stimuli including cell-surface proteins, secreted polypeptide cytokines and components of extracellular matrix.



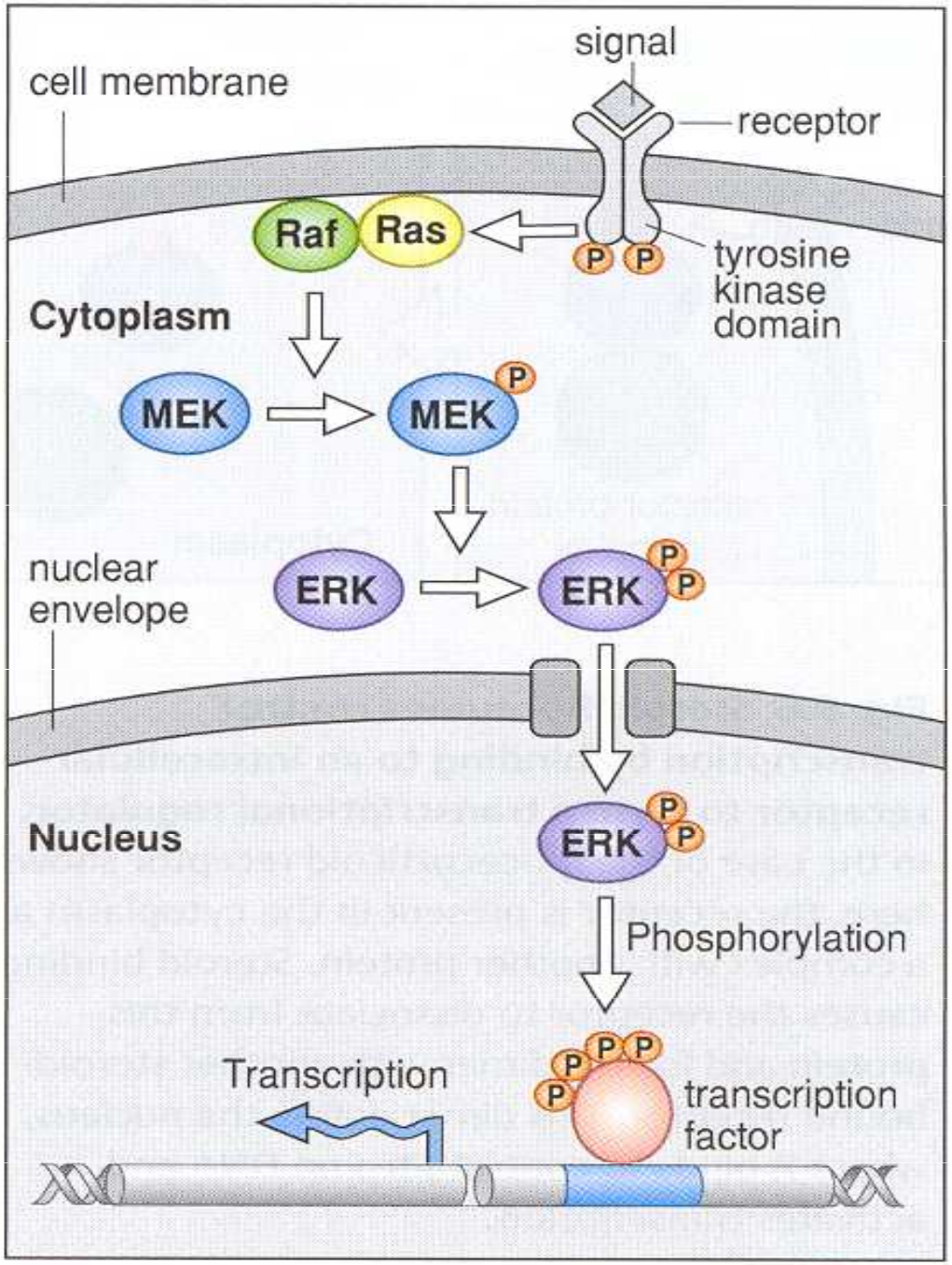
**The control of gene expression** – among differentiated cells, the patterns of gene activity differ enormously, leading to question of what determines the patterns of gene activity and how it is inherited?

- general and tissue-specific transcriptional regulators

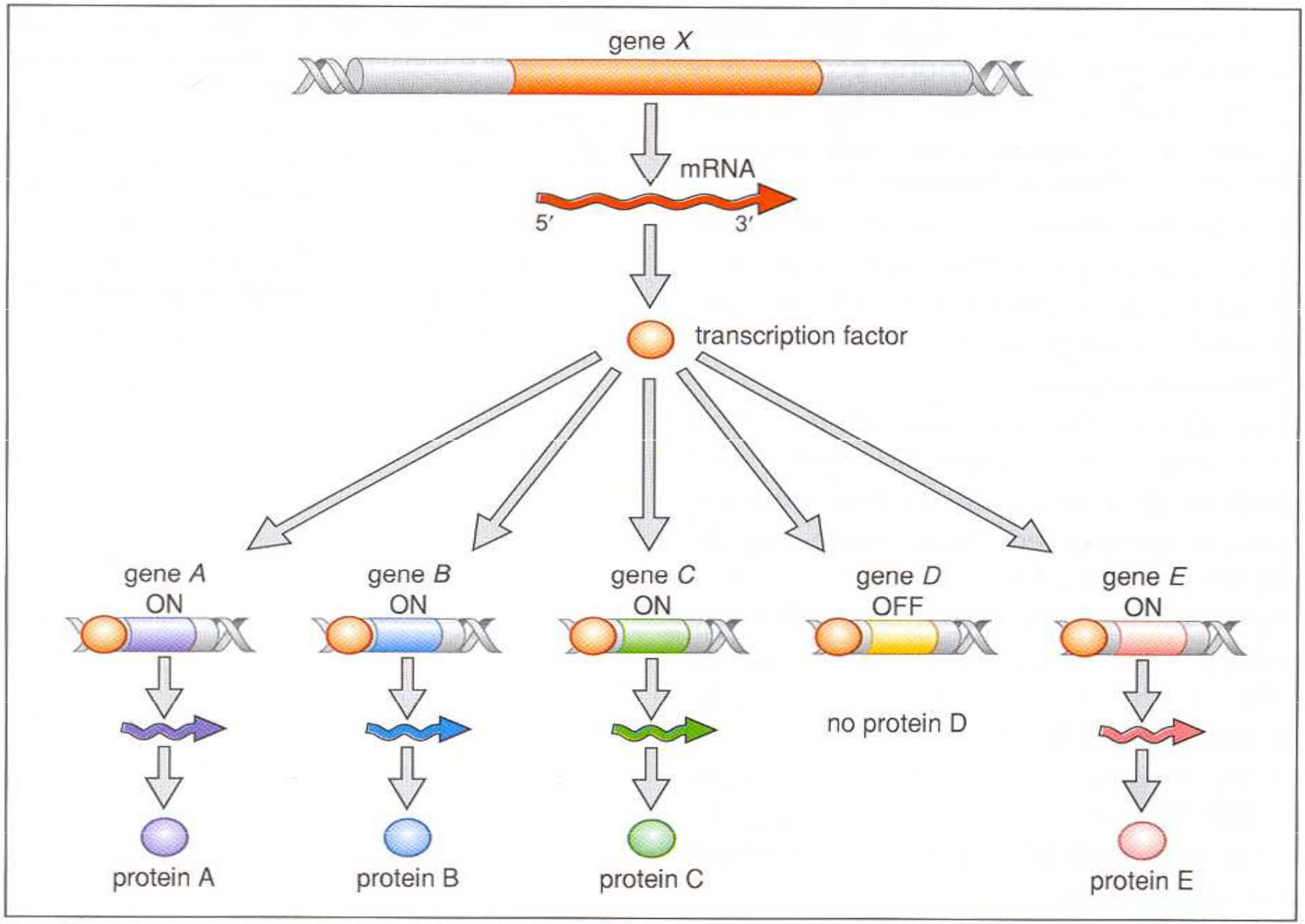


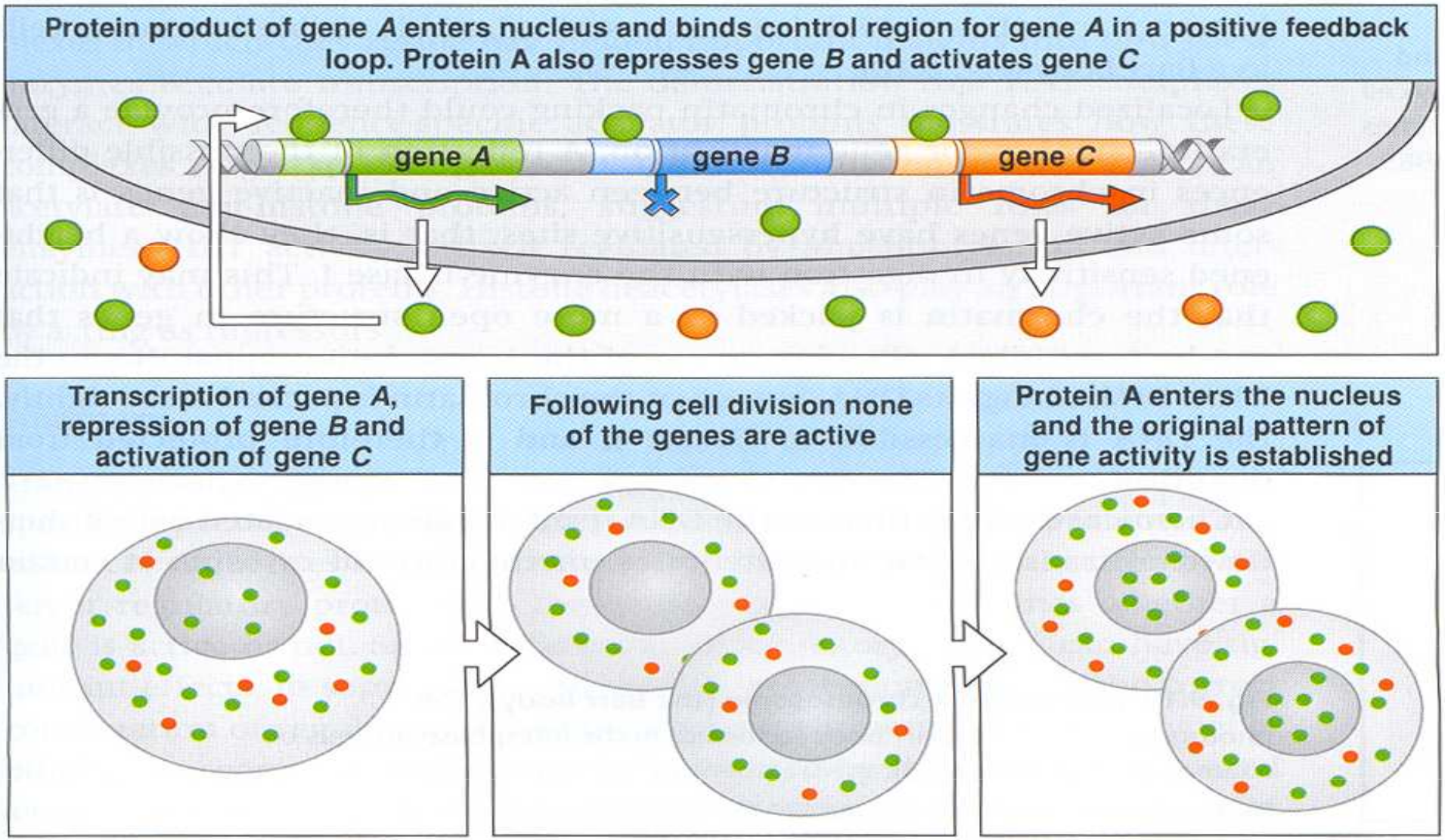
# External signals can activate genes



A central feature of differentiation is that, in a given cell, certain genes are active whereas other are repressed. This is a given by the action of **transcriptional factors** – a gene-regulatory proteins that can switch the genes on or off.



In many cells the particular pattern of gene activity can be reliably transmitted through many cell divisions via passing on the transcription regulators.

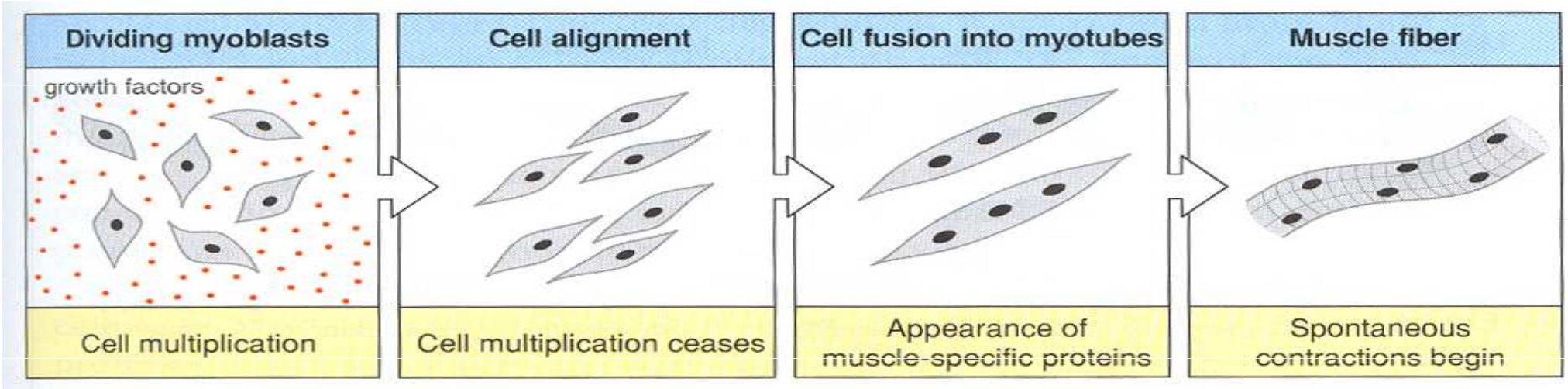


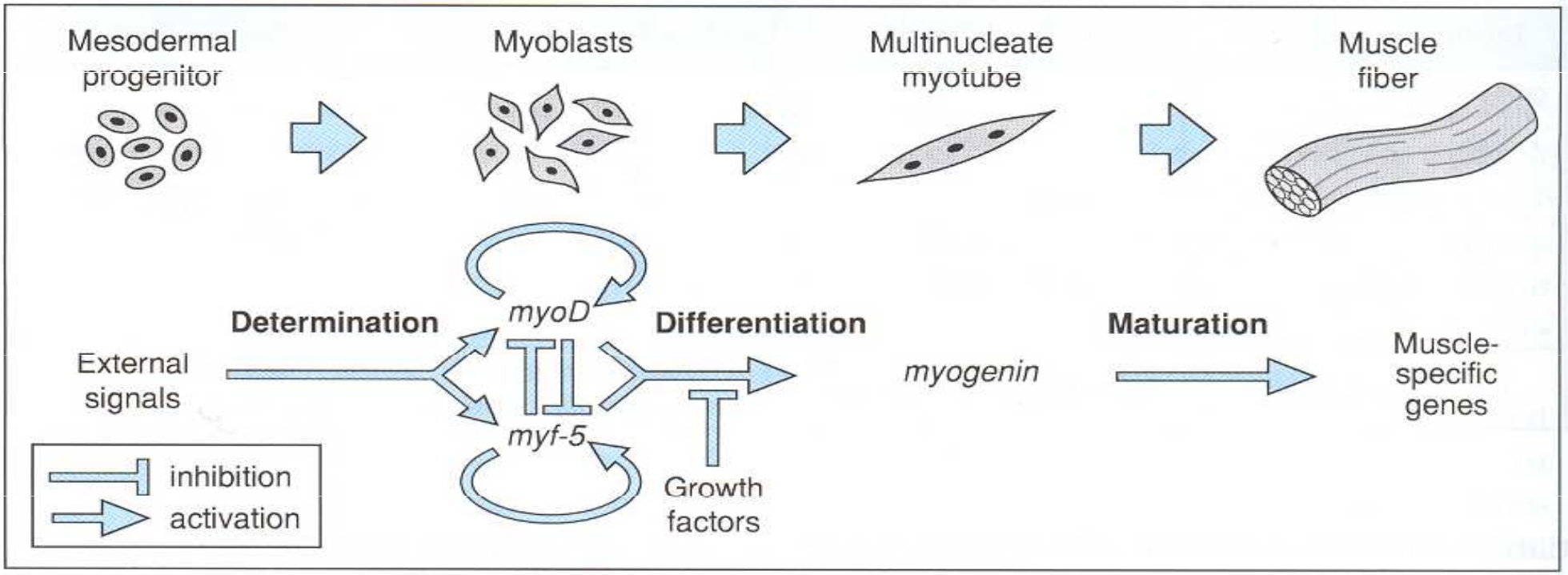

…….or structural alterations of chromosomes - chromatin packing in X-chromosome inactivation.

……..or chemical modification of chromosomes (DNA methylation, histone acetylation).

# MODELS OF CELL DIFFERENTIATION

## Muscle cell

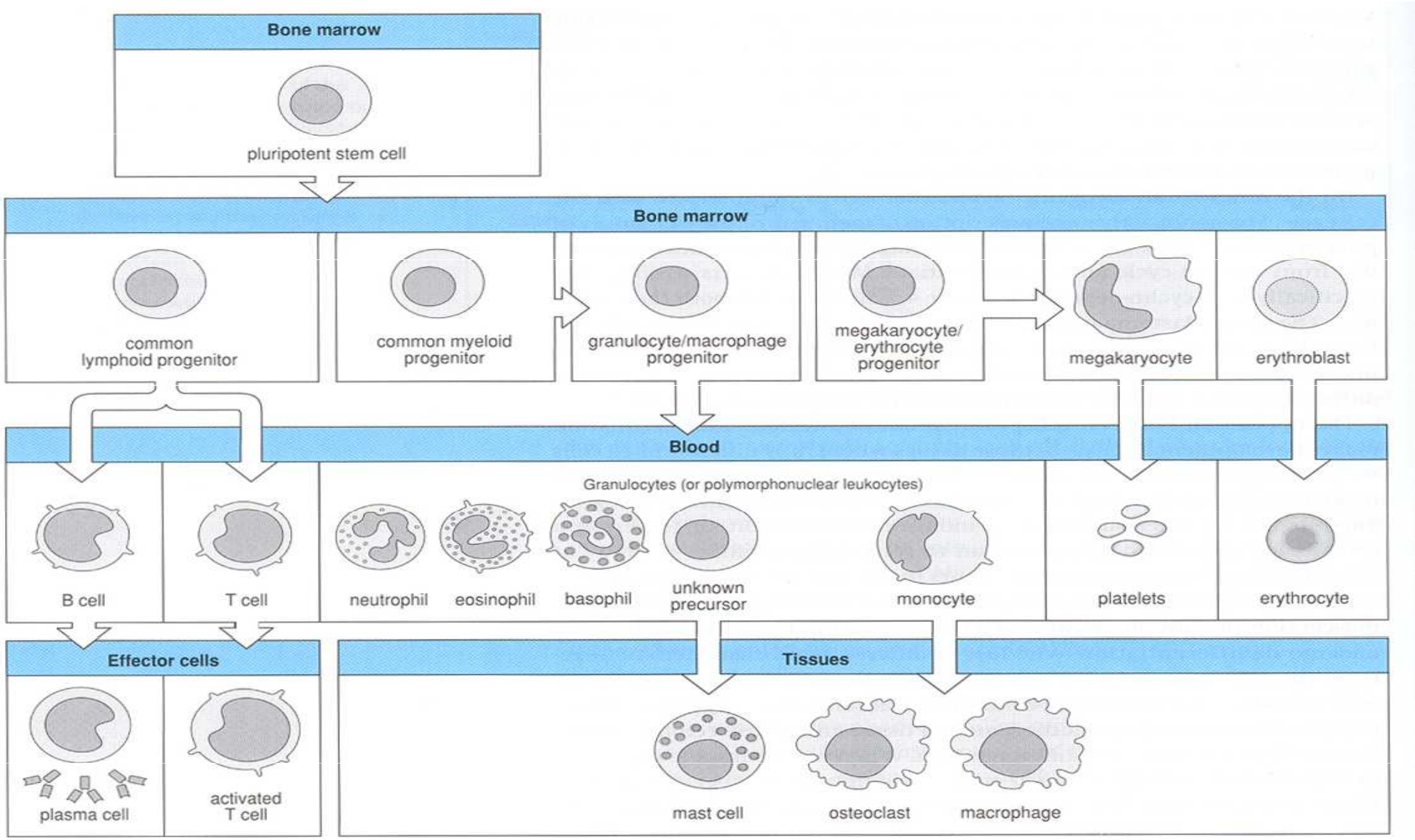


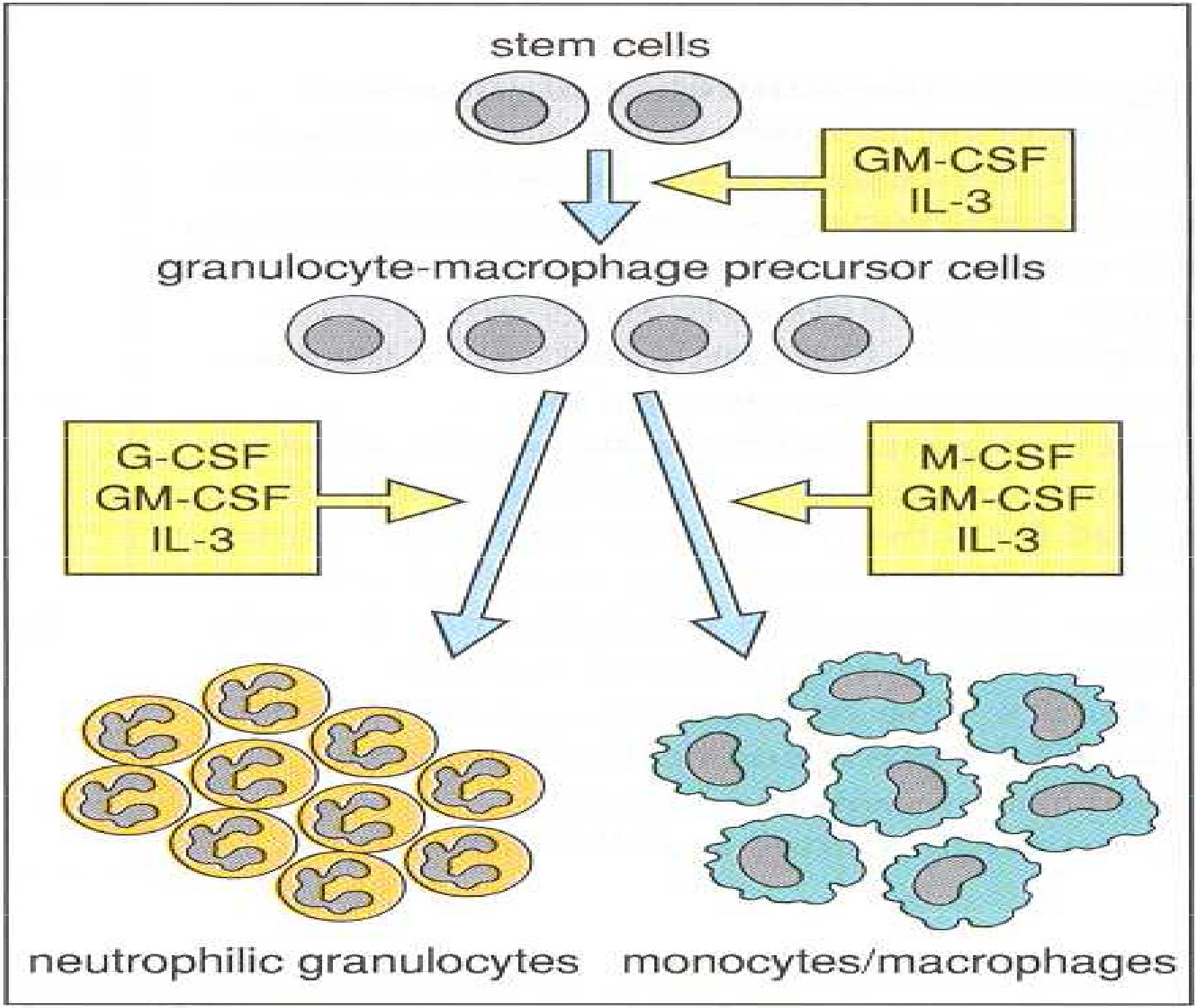



# Blood cells

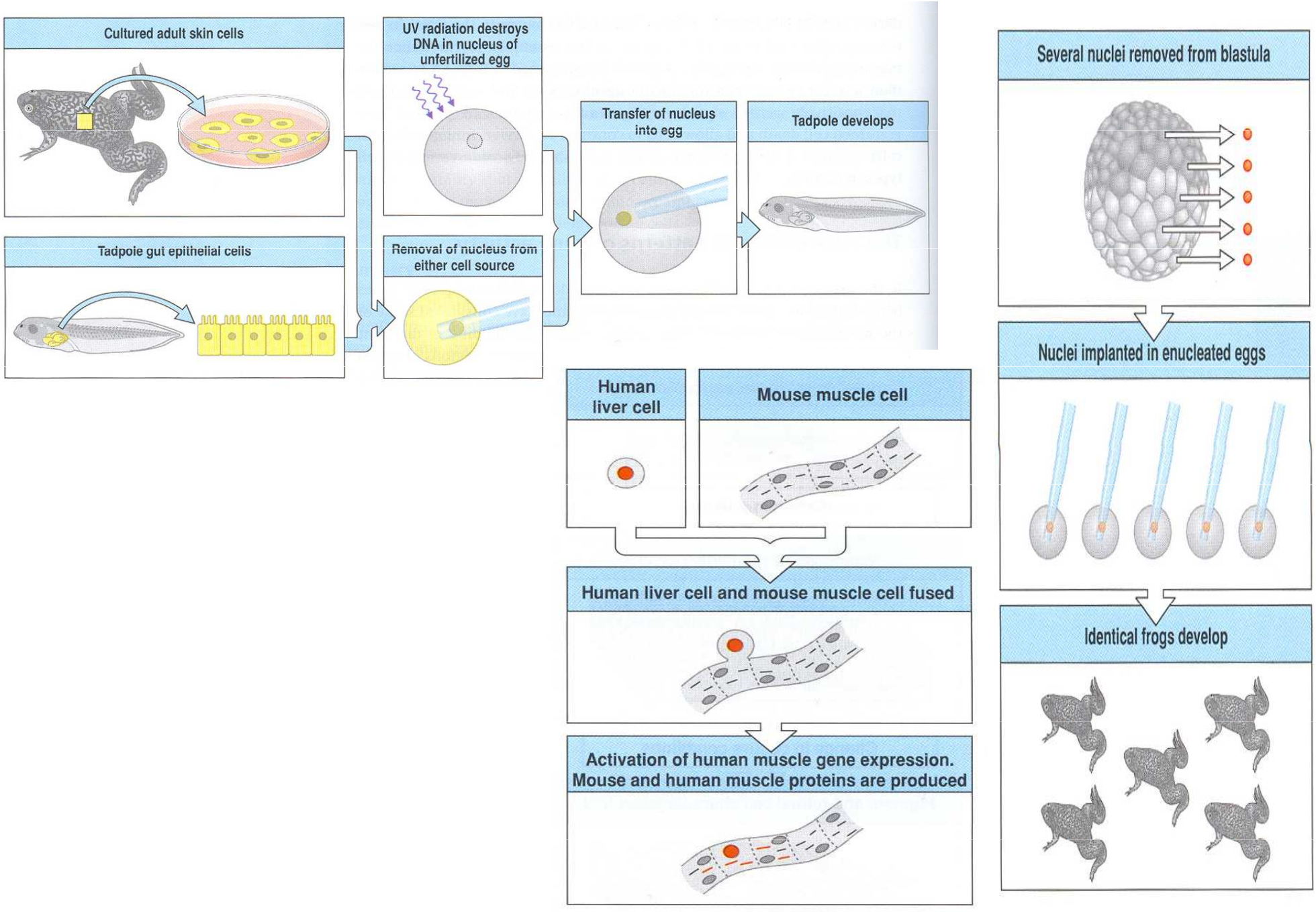
-all blood cells originate from pluripotent stem cells located in bone marrow

- one liver hematopoetic stem cell expresses 200 transcription factors, 174 cell membrane associated proteins, 28 secreted proteins and 147 signaling molecules




stem cells
GM-CSF
IL-3
granulocyte-macrophage precursor cells
G-CSF
GM-CSF
IL-3
M-CSF
GM-CSF
IL-3
neutrophilic granulocytes
monocytes/macrophages

THE REVERSIBILITY OF PATTERNS OF GENE ACTIVITY: How reversible are the patterns of gene activity and thus the cell differentiation?



# The differentiatiated state of a cell can change by transdifferentiation