Ontogenesis and its genetic control

In **embryonic development**, the whole body, containing hundreds of different cell types and quadrillions (1015) individual cell types in specific positions, is formed from a single cell (zygote). Therefore the cells need to proliferate, recognize their position or migrate to their correct position and differentiate in the correct cell type. It is useful to treat the processes of proliferation patterning and differentiation separately, but they happen together, as should become clear from the following.

Proliferation

According to proliferation capacity, we have **stem cells**, **progenitor cells** and terminally **differentiated cells**. Stem cells are capable of self-renewal (one daughter stem, second progenitor). They divide slowly, with tight control of DNA integrity. Stem cells are during development gradually limiting their potential, zygote is totipotent (capable of making all cell types), inner cell mass of blastocyst is pluripotent (every cell except trophoblast), stem cells in adult renewing tissues are unipotent (stem cells in intestinal crypts only make enterocytes). Progenitor cells are dividing faster with less control of replication errors, but they are already predestined after several divisions to differentiate and stop division, so they can trade some part of replication fidelity for division time without increasing cancer risk. Differentiated cells are doing their work for the body and cannot divide at all.

Cell proliferation is normally controlled by communication with other cells, i.e. by **cellular signaling**. Signaling pathways for proliferation operate by secreted growth factors – their membrane receptors – intracellular G-proteins – protein kinases – transcription factors – which switch on genes necessary for DNA replication, i.e. cells transit from G1 to S phase. Many of the proliferation signaling molecules are proto-oncogenes. Not all growth factors are always stimulating proliferation, the names are often historical, given before fully understanding the effects of these molecules. For example FGF17? produced by periosteum inhibits chondrocyte proliferation, and activates their hypertrophic differentiation in growth plate of bones.

Patterning

Positional information gathering and resulting patterning of undifferentiated tissue is also controlled by signaling, e.g. sonic hedgehog (Shh) protein is produced in notochord and diffuses to adjacent neural tube and somites. Ventral neural tube then differentiates motoneurons, ventromedial somite is differentiated into sclerotome. This is because Shh forms a gradient of concentration decreasing in direction out of the production place, target cells respond only to higher concentration. Patterning molecules like Shh are called “morphogens”. Very important patterning mechanism is the Turing or reaction-diffusion mechanism, where a slowly diffusing morphogen (activator) activates itself and activates a fast diffusing inhibitor. This leads to creation of activator peaks surrounded by inhibited zones. For example, interplay of Wingless (Wnt) activator and Dickkopf (Dkk) inhibitor is responsible for uniform distribution of hair follicles on skin surface.

Differentiation

Each cell type requires different set of proteins, difrent size, shape etc. Genome is identical in all cells (with few exceptions, like immunoglobulin genes in B-lymphocytes). Therefore, differences among cell types arise from differential regulation of gene expression. Proteins called transcription factors that bind to specific DNA sequences in promoters, enhancers and silencers and activate or inhibit expression of specific sets of genes are playing a major role there. Most often, transcription factors are activated by signaling from other cells (e.g. by morphogens in patterning phase of development). AUtospecification also exists – the transcription factor is switched on without external influence. This is e.g. the case of SRY during male sex determination. Once the trigger signaling wanes, the cell is still remembering its fate, very often due to a positive feedback of the responsible transcription factor to its own expression. Such cell is but reversibly committed to a fate, and this can be changed very easily by different signaling and different transcription factors. However, with sustained activity of the transcription factor and its downstream gene expression program, the genes that are not used (and switched off) are pushed to heterochromatin, by modification of the epigenetic code of histone modifications and DNA methylation. Then the differentiation path is locked in (irreversible), cannot be changed by external signaling, can be reverted only by extensive “nuclear reprogramming” (e.g. by transfer of the cell nucleus to different cell type, as it is in cloning). This irreversible phase can happen without obvious morphologic changes of the cell. Morphological and functional specialization crowns the whole differentiation process. The cells are also stuck in G0 phase of the cell cycle.