# Cell Growth and Differentiation

**Cell Growth**

There are different phases of cell growth in multicellular organisms

- Cell division
- Cell enlargement
- Cell differentiation

**What is growth?**

- Cell growth is the phenomenon by which cells increase their weight/mass and size.
- Animal cells are ≈10 to 20 μm in diameter with a lot of variation.
- red blood cells (≈5 μm in diameter).
- motor neurons can grow 100’s of micrometers in length.
- ≈70% of the weight of a cell is water
- Nucleic acids, proteins, polysaccharides, and lipids (≈25%)
- trace amounts of ions and small molecules
- Animal cellular dry mass is from proteins, which makes up about 18% of the total cell weight
- physical, chemical, and biologic factors can affect cell size.
- In some cells, persistent DNA replication in the absence of cell division (called endoreplication) can increase their cell size.
- Example: Megakaryoblasts, which mature into granular megakaryocytes
- This is found not only in animals but also in plants, and single-celled organisms.
- Adipocytes can grow to ≈85 to 120 μm by accumulating intracellular lipids.
- However, neurons and cardiac muscle cells, cease dividing and grow without increasing their DNA content.
- These cells proportionately increase their macromolecule content.

**Cell Size**

- Cell size is a fundamental feature that contributes to function in multicellular organisms and to fitness in the context of unicellular organisms.
- Size imposes constraints on cellular design
- When cells grow larger, passive diffusion may limit intracellular transport and the decreased surface area to volume ratio may make nutrient uptake limiting for cell growth
- Cell size homeostasis in proliferating cells requires a coordination of growth with division, such that on average each cell division is accompanied by a doubling in cell mass
- In post-mitotic cells, such as neurons, the maintenance of cell size requires that no net cell growth occurs

**Cell volume**

- Cell volume increases with ploidy as observed in a wide variety of eukaryotic cells from yeast to mice.
- Increased ploidy may be increasing nuclear volume, chromatin content, or the expression of unknown genes
- Ploidy increases are needed to prevent genomic DNA from becoming a limiting factor for cell growth.
- Increased ploidy helps to create specialized cell types and to pattern tissues, such as the larval salivary gland in Drosophila, and muscle fibers, megakaryocytes, and giant trophoblast cells in mammals

**Nucleo-cytoplasmic ratio**

- The nucleo-cytoplasmic ratio plays a critical role in metazoan embryonic development
- In many animals, fertilization is followed by a series of rapid and synchronous cleavage divisions that section the huge zygote into thousands of smaller cells.
- After a certain number of divisions cell cycle times lengthen and become asynchronous

- This mid-blastula transition occurs when cells reach a particular nucleo-cytoplasmic ratio.
- Thus, haploid embryos compensate for their decreased nucleo-cytoplasmic ratio by going through exactly one extra cleavage division
- Similarly, artificially increasing the nucleo-cytoplasmic ratio results in fewer cleavage divisions.

**What is cell division?**

- Cell growth and cell division can be distinguished in dividing cells.
- In mammalian cells, growth occurs in the $G_1$ phase of the cell cycle and is tightly coordinated with S-phase (DNA synthesis) and M phase (mitosis).
- Growth factors, hormones, and nutrients are the external cues for cells to grow.
- It is hypothesized that once a threshold cell size is attained, cells irreversibly commit to at least one round of division, thus achieving adequate size is a prerequisite for DNA synthesis and mitosis.
- Deprivation of nutrients and other growth signals, as might be the case in the nutrient-, and oxygen-, starved regions of an advancing tumor, may encourage normal cells to exit the cell cycle into a resting or $G_0$ state.
- Mutations resulting in deregulation of a cell's ability to sense nutrients or growth factors may thus provide tumor cells with a selective growth advantage.

**Cell growth and the cell cycle**

- The dependency of cell cycle progression on growth
- The dependency of growth on cell cycle progression,
- The coordinate control of growth and cell cycle progression,
- or the complete intertwining of growth and cell cycle progression are important for this regulation
- Blocking cell growth in eukaryotes by nutrient or growth factor deprivation results in a cell cycle arrest, usually in $G_1$ phase
- Nutrient deprivation or treatment with translation inhibitors leads to a lengthening of the cell cycle in $G_1$ phase

- Similarly, abundant nutrients or overactivation of growth regulatory pathways can typically shorten the length of the $G_1$ phase

**Cell Differentiation**

**Some terms first**

- The fate of a cell is a description about what happens to it during normal development.
- Fate map is a diagram of an organism at an early stage of development that indicates the fate of each cell or region at a later stage of development.
- The developmental potential, or potency, of a cell describes the range of different cell types it can become.
- The zygote and its very early descendants are **totipotent** - these cells have the potential to develop into a complete organism.
- Totipotency is common in plants, but is uncommon in animals after the 2-4 cell stage.
- As development proceeds, the developmental potential of individual cells decreases until their fate is determined.

**Determination and Differentiation**

- The **determination** of different cell types (cell fates) involves progressive restrictions in their developmental potentials.
- A cell obviously has many choices while undertaking changes say during development or other cellular processes/programs.
- When a cell “chooses” a particular fate, it is said to be determined, although it may not be very different morphologically from its neighbors.
- Determination implies a stable change - the fate of determined cells does not change.
- Differentiation follows determination, as the cell elaborates a cell-specific developmental program.
- Differentiation results in the presence of cell types that have clear-cut identities and functions, such as muscle cells, nerve cells, and skin cells.

**Differentiation**

- A cell that is able to differentiate into all cell types of the adult organism is known as pluripotent.
- Such cells are called embryonic stem cells in animals and meristematic cells in higher plants.
- A cell that is able to differentiate into a total organism with all cell types, including the placental tissue, is known as totipotent.
- In mammals, only the zygote and subsequent blastomeres are totipotent, while in plants many differentiated cells can become totipotent
- For example cancer cells can be graded differently depending on their level of differentiation as poorly differentiated, moderately differentiated and well differentiated.

**Cellular Differentiation**

- It is the process by which a cell acquires or develops certain properties and functions or capabilities and becomes a more specialized cell type
- Differentiation occurs when a simple zygote turns in to a complex system of tissues and cell types
- Adult stem cells divide and create fully differentiated daughter cells during tissue repair and during normal cell turnover
- Size, shape, membrane potential, metabolic activity, and responsiveness to signals of a cell change drastically during differentiation
- These changes are mostly because of highly controlled gene expression
- With a few exceptions, cellular differentiation almost never involves a change in the DNA sequence itself
- Thus, different cells can have very different physical characteristics despite having the same genome.

**No difference in DNA content between cells**

- In a living organism, each one of its cells contains the same DNA
- However, we all know that we have many different types of cells and tissues

**How to account for this?**

- The answer lies in the way the DNA is expressed in a given type of cell/tissue
- Specific combination of genes turned on (expressed) or turned off (repressed) determines cellular morphology (shape) and function.
- That is why a liver cell is distinct in its shape and function from those of a muscle or brain cell.
- This process of gene expression is regulated by cues/signals from both within and outside cells, and the interplay between these cues and the genome affects essentially all processes that occur during embryonic development and adult life
- How can we say for sure that all of the cells within a multicellular organism contain the same genome?
- As you know a single cell (zygote) with a half-genome from each parent is the starting point for our genesis
- This single cell quickly divides and new cells begin to differentiate, or become different from each other
- This process of differentiation occurs in a wide variety of cell types (e.g., skin, liver, muscle, etc.)

**No difference in DNA content between cells- Evidences**

- This is not accompanied by any permanent loss of genetic material.
- If they get the right environment, fully differentiated cell types are also capable of producing the whole organism/animal.
- This was first shown by transplanting the nucleus of an adult frog skin cell into an enucleated donor embryo, leading to the development of a cloned adult frog
- Later, the intact complete genome of a differentiated cell was used in the cloning of the famous sheep Dolly, showing that in mammals genes are not lost during development, so they must therefore be regulated.

- Hence we now know that the specialized, differentiated cell types of the adult body contain a genome as complete as that of an embryo.
- Thus changes in gene expression, rather than losses of genetic material, play a key role in guiding and maintaining cell differentiation.
- Differential gene expression is not a result of differential loss of the genetic material.
- That is, genetic information is not lost as cells become determined and begin to differentiate.
- In fact, even the nuclei of adult cells contain all of the information needed for the construction of an entire organism, if provided with the proper cytoplasmic components.
- The cloning of Dolly from an adult cell is one of the best convincing evidences available in support of differential gene expression.

**Dedifferentiation and Redifferentiation**

- Dedifferentiation is a cellular process that often occurs in worms and amphibians
- In this process a cell reverts back to its original or some earlier developmental stage from a partially differentiated or terminally differentiated condition.
- Dedifferentiation also occurs in plants.
- The fully differentiated cells sometimes lose some of their properties such as a change in shape or protein expression etc
- Dedifferentiation may be considered as an aberration of the normal development cycle that results in cancer
- It can also be a part of immune response lost during evolution
- Chemicals such as Reversine can induce dedifferentiation in myotubes
- Such dedifferentiated cells are sometimes able to **redifferentiate** into osteoblasts and adipocyte