

BME 1532-CELL BIOLOGY

Stem Cells and Cancer

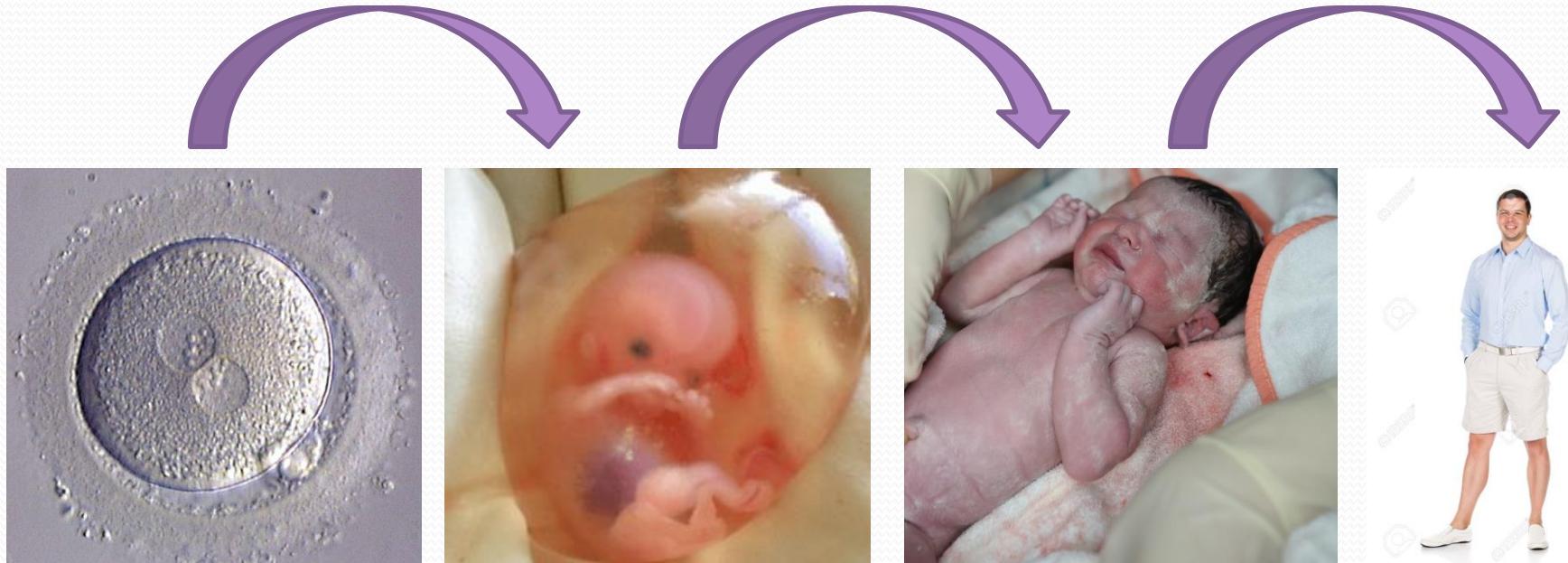
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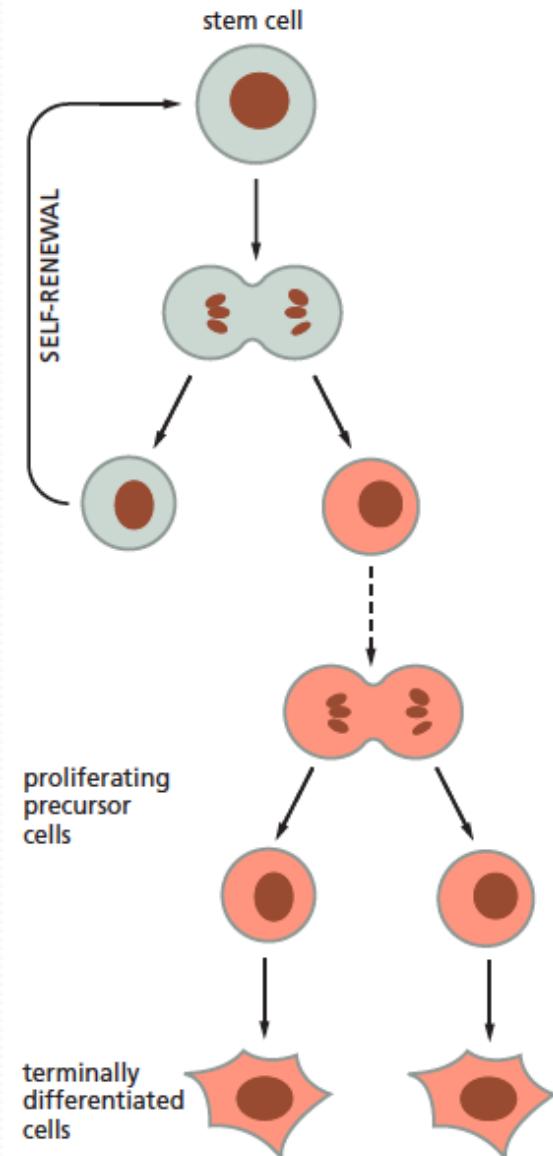
Previously on BME 1532

- Sexual Reproduction
 - Gametes (Sperm and Egg)
 - Zygote
- Advantages of Sexual Reproduction
 - Different homolog chromosome combinations
 - Genetic recombination
- Meiosis
 - Homologous recombination through crossing-over
 - Segregation of homologous chromosomes
- Fertilization
- Mendelian Genetics
 - Genotype, phenotype, allele, dominant, recessive, pedigree, linked genes
 - Mendel's First Law → The Law of Segregation
 - Mendel's Second Law → The Law of Independent Assortment

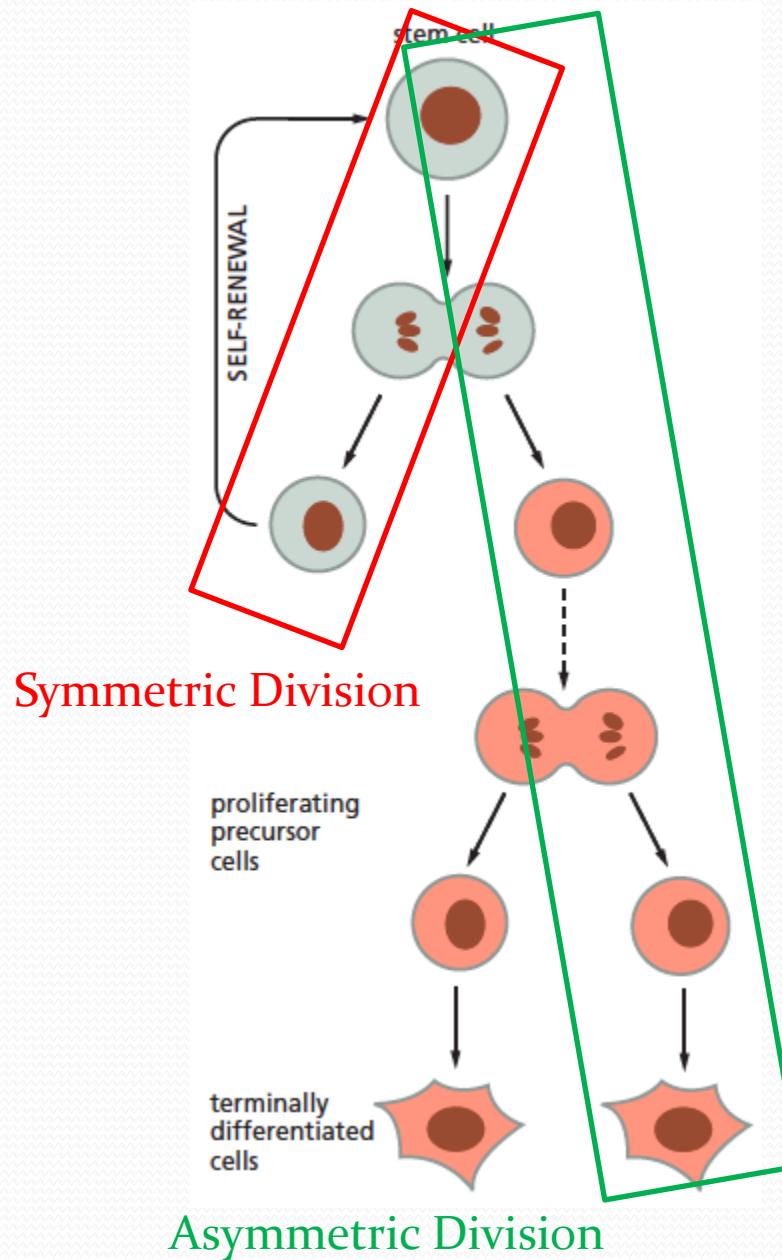
- In almost all adult tissues, cells are continually dying and cells should somehow be replaced.
- Thus the cells and tissues in the body are in a constant turnover with different rates.
- However, most of the differentiated cells in the body are not able to divide and called terminally differentiated.



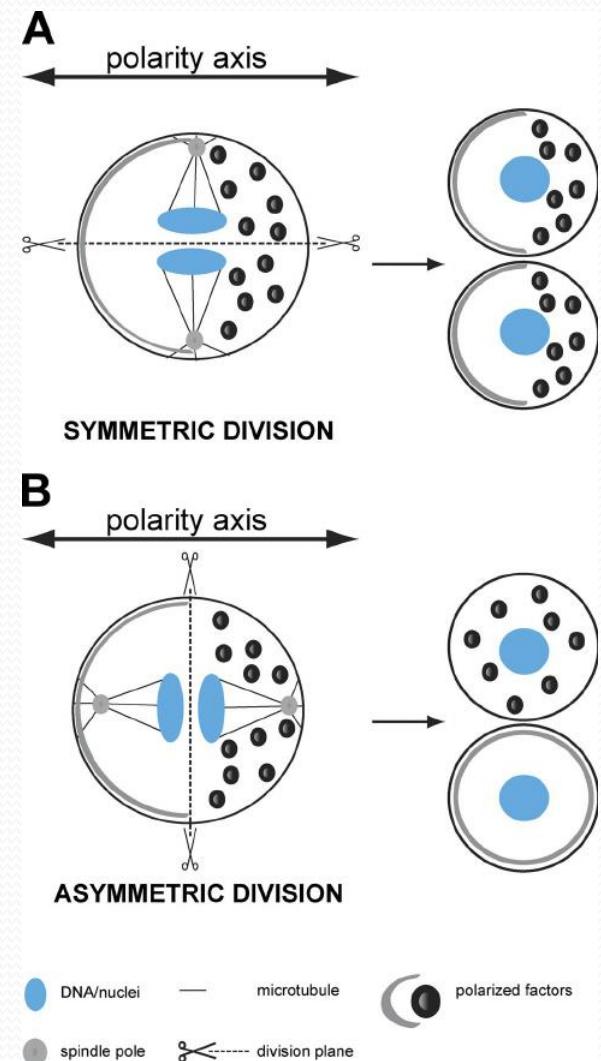
- The cells that replace the terminally differentiated cells that are lost are generated from a stock of proliferating precursor cells, which themselves usually derive from a much smaller number of cells called *stem cells*.
- Both stem cells and proliferating precursor cells are retained in the corresponding tissues along with the differentiated cells.
- Stem cells are undifferentiated cells that can reproduce themselves indefinitely through a process called *self-renewal*.



- When a stem cell divides, though, each daughter has a choice:
- Either it can remain a stem cell through *symmetric division*.
- Or through *asymmetric division* it can give rise to a precursor cell which will differentiate into a terminally differentiated cell.



- Both symmetric and asymmetric division occurs through mitosis.
- However, depending the polarity of the cells and the axis of division cell can produce two different cells through asymmetric division.
- Daughter cells are still genetically identical but transcription factor pool, intracellular signals, gene expression patterns, shape, size, protein and lipid profile of their membrane may differ.

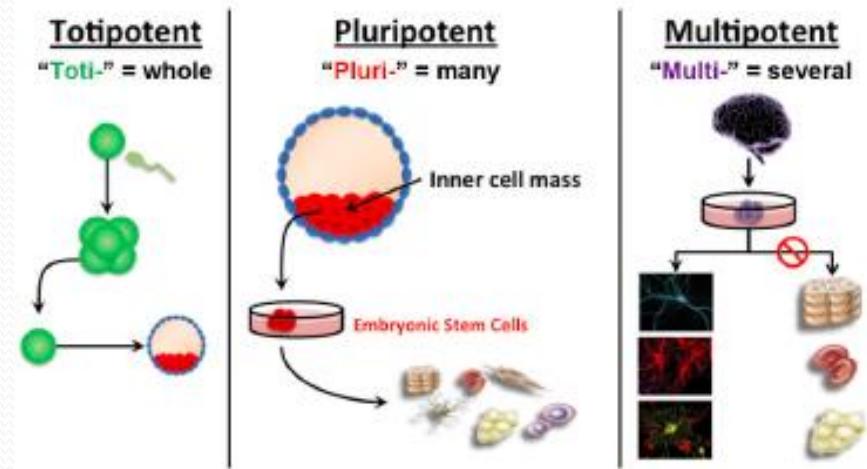


Differentiation

- When stem cells receive a signal to divide asymmetrically it gives rise to precursor cell which can differentiate into another cell type.
- Differentiation occurs through activation of a specific set of genes.
- Thus, cellular differentiation is the process by which a less specialized cell becomes a more specialized cell type.
- What kind of stem cells can give rise to what type of cells depend on the *potency / plasticity* of the stem cell.

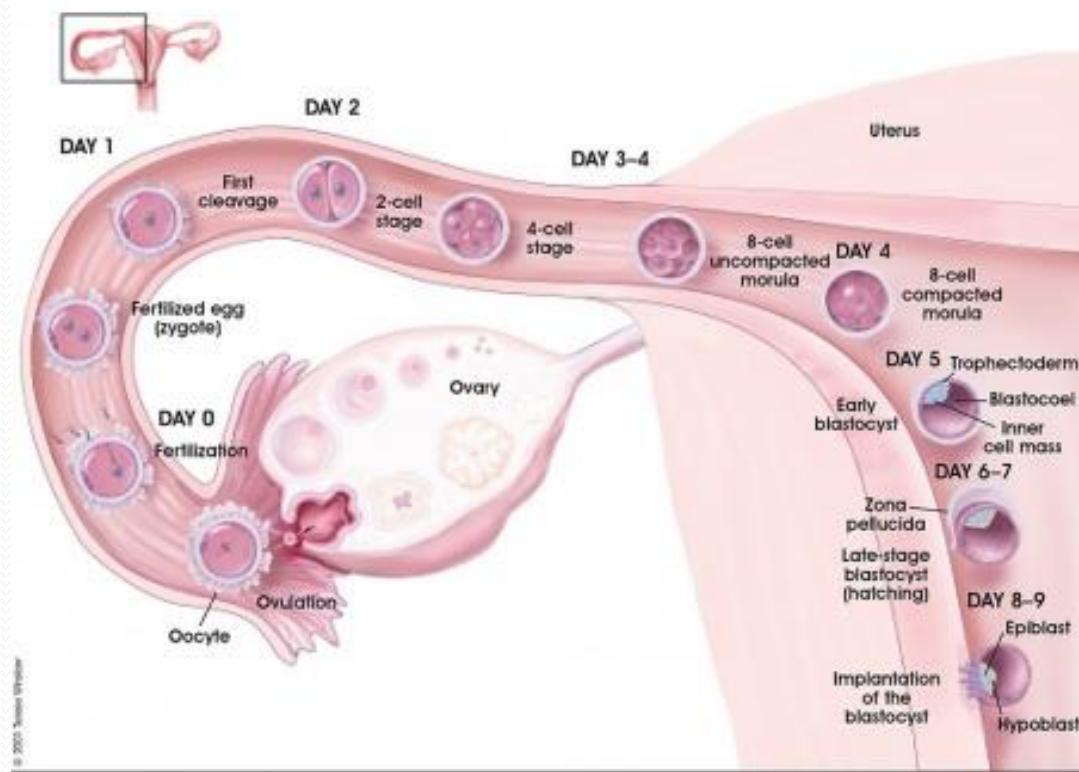
POTENCY

- Potency is the number of possible fates open to a cell.
- It decreases with age and the degree of specialization.
- Stem cells are divided in different groups according to their potency:
 - Totipotent
 - Pluripotent
 - Multipotent
 - Bipotent
 - Unipotent

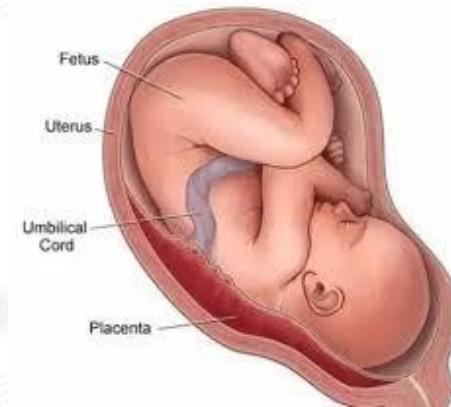
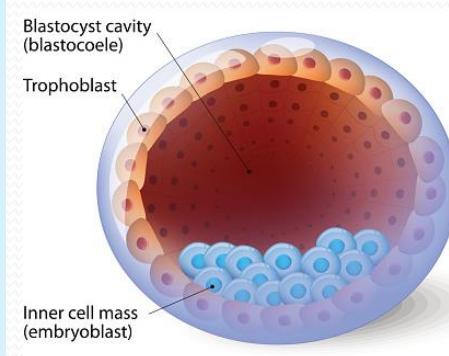
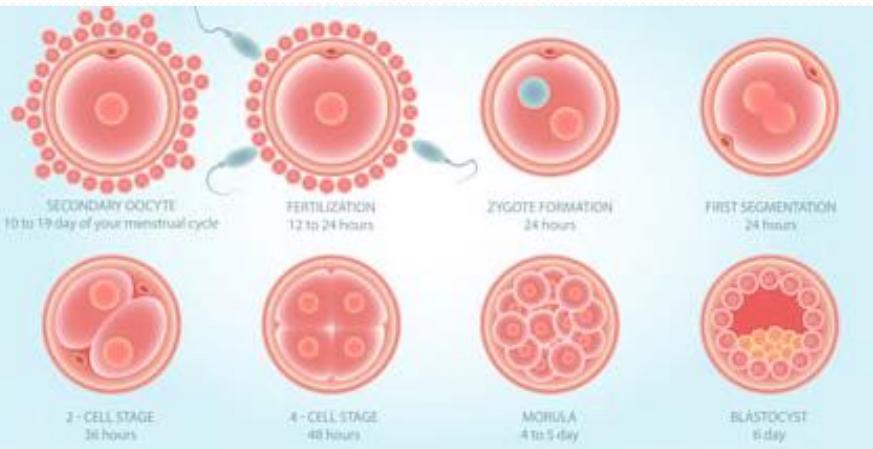


Totipotency

- Zygote is the first and the most potent stem cell of the body.
- It is ***totipotent*** which means it can give rise to a full embryo when it is implanted in the uterus.
- It can differentiate into any cell type of the embryo and the placenta.
- Generally the cells that immediately arise in the first few divisions (up to blastocyst stage) are also totipotent.



- During embryonic development, first major differentiation event occurs at blastocyst stage when embryo develops into a hollow ball of cells: inner cell mass (ICM) inside and trophoectoderm around.
- Trophoectoderm gives rise to *placenta* and the ICM gives rise to embryo.
- Cells of the ICM are pluripotent.

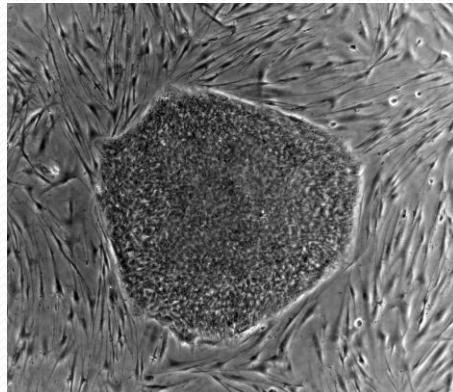


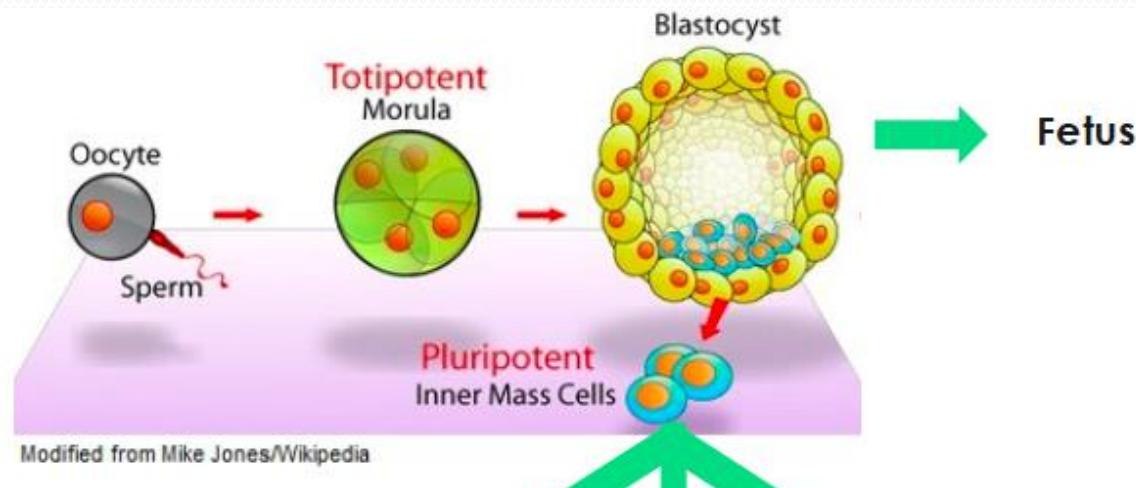
Pluripotency

- Pluripotent cells can give rise to all cells of the embryo.
- However, they can not give rise to an embryo when implanted into uterus without trophoectoderm giving rise to placenta.
- The cells isolated from ICM of the blastocyst stage embryos are called embryonic stem cells (ESCs) which are pluripotent.

Embryonic Stem Cells

- ESCs can be isolated from ICM of blastocyst stage embryos and grown under culture conditions.
- They have the ability to self-renew with an endless capacity under appropriate conditions.
- When appropriate conditions are supplied they can differentiate all cell types from the 3 lineages body: ectoderm, mesoderm, endoderm.
- They form teratomas when implanted in body.
- There are ethical issues involved with their usage.





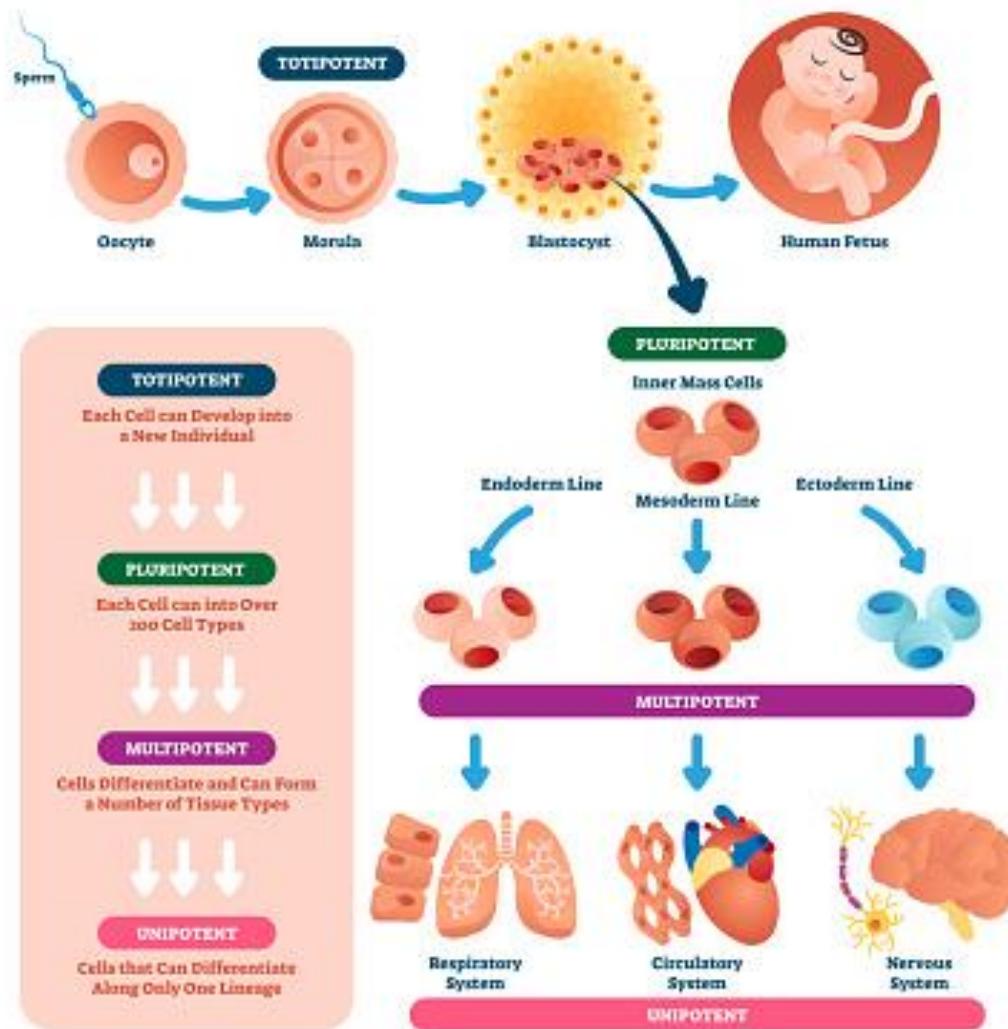
Modified from Mike Jones/Wikipedia



Adult Stem Cells

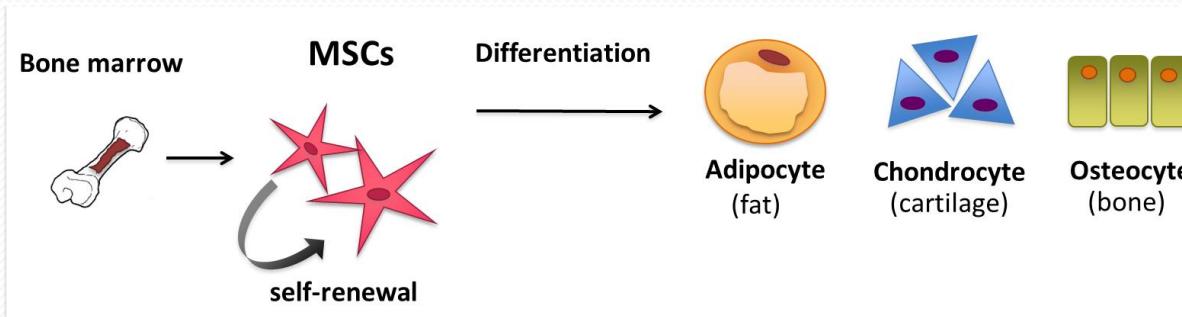
- ASCs are the reserve supply of cells that can multiply and then differentiate when needed for repair of adult organs and tissues.
- They reside in the tissues and organs silently and when they receive the appropriate signals they divide and differentiate to populate in place of the dead cells or repair the damage.
- They are present in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis.
- Adult stem cells can be multipotent, bipotent or unipotent that can renew themselves and with certain limitations differentiate to specialized cell types of the tissue from which they originate.

TOTIPOTENT CELLS



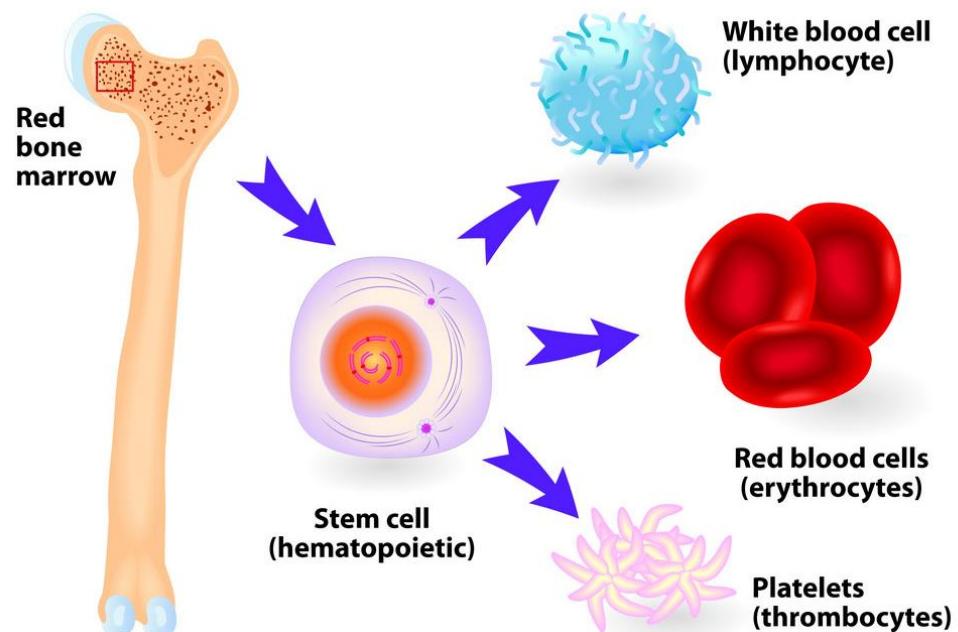
Multipotency

- Mesenchymal stem cells (MSCs) are a type of adult stem cells that are able to self-renew and multipotent.
- They are present in adult tissues like bone marrow, adipose tissue and dental tissues serving as a cell source for regeneration of various mesenchymal tissues.
- MSCs come from mesodermal lineage thus they can differentiate into multiple tissues such as bone, cartilage and adipose under defined culture conditions.



Multipotency

- Hematopoietic stem cells (HSCs) are stem cells that are able to self-renew and multipotent.
- They give rise to blood cells through the process of haematopoiesis.
- They are isolated from bone marrow.

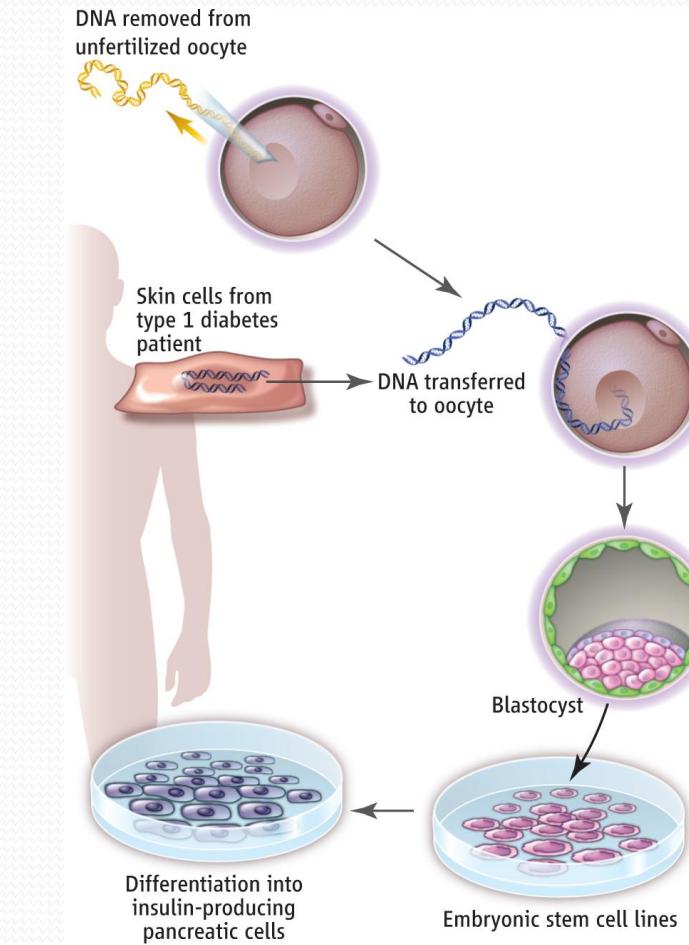


Fetal Stem Cells

- The developing organs and tissues in a fetus contain a relatively large supply of stem cells because they are needed for growth and maturation.
- The difference between embryonic stem cells and fetal stem cells is the fetal stem cells have gone through part of the way to mature cells.
- Stem cells that are isolated from umbilical cord blood as soon as the baby is born are one type of fetal stem cells.
- They are primitive compared to adult stem cells. They are also multipotent but their potency is better.

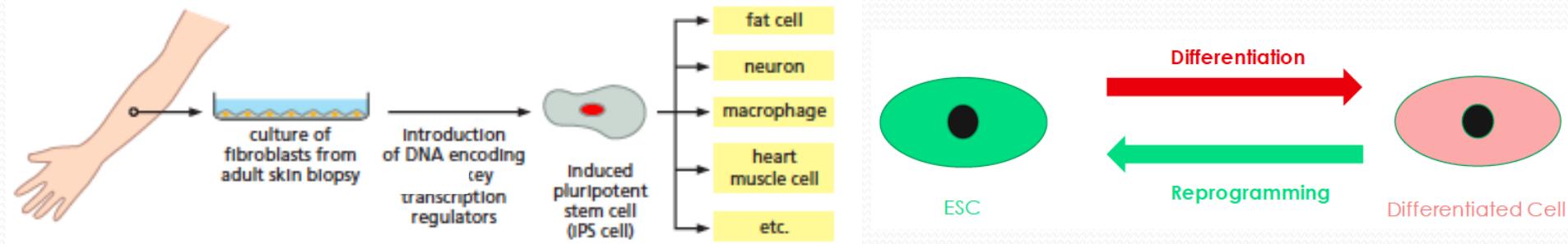
Therapeutic Cloning

- Therapeutic cloning uses the technique of nuclear transplantation to produce cultured ES cells, rather than a cloned animal.
- This approach is an elaborate method for generating personalized ES cells, with the aim of generating various cell types that can be used for tissue repair or to study disease mechanisms.
- It can be done by injecting the DNA of a differentiated cell into an enucleated oocyte.
- At embryonic blastocyst stage ESCs can be isolated from ICM, cultured and differentiated to any tissue of interest.
- Because the cells obtained are genetically almost identical to the original donor cell, they can be grafted back into the adult from whom the donor nucleus was taken, thereby minimizing immunological rejection.



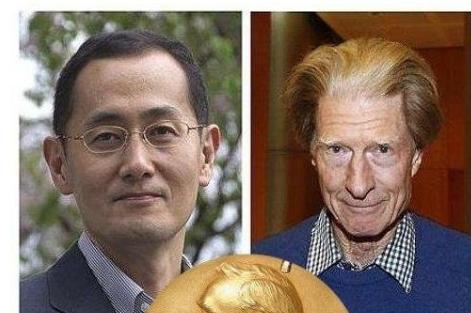
Induced Pluripotent Stem Cells

- The problems associated with making personalized ES cells by nuclear transplantation can now be bypassed by an alternative approach, in which cells are taken from an adult tissue, grown in culture, and reprogrammed into an ESC-like state by artificially driving the expression of a set of transcription factors.
- These ESC-like cells are called induced pluripotent stem cells (iPS cells).



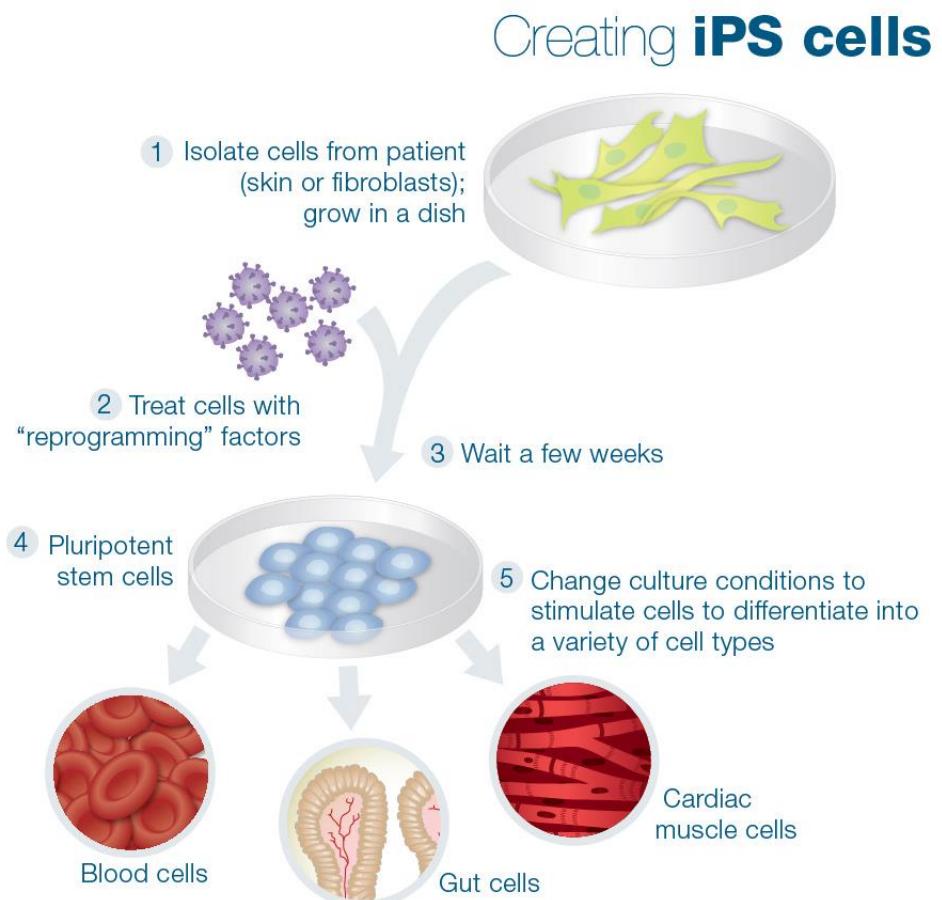
- John B. Gurdon discovered in 1962 that the specialisation of cells is reversible. In a classic experiment, he replaced the immature cell nucleus in an egg cell of a frog with the nucleus from a mature intestinal cell. This modified egg cell developed into a normal tadpole. The DNA of the mature cell still had all the information needed to develop all cells in the frog.
- In 2006, Shinya Yamanaka established for the first time murine ESC-like cell lines from Mouse embryonic fibroblasts (MEFs) and skin fibroblasts by simply expressing four transcription factor genes encoding *Oct4*, *Sox2*, *Klf4*, and *c-Myc* → Yamanaka Factors.

The Nobel Prize in Physiology or Medicine 2012 was awarded jointly to Sir John B. Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent."



Induced Pluripotens Stem Cells

- iPS cell lines exhibit similar morphology, growth and differentiation properties, teratoma formation as ESC and express ESC-specific genes.
- They override ethical concerns about ESCs.

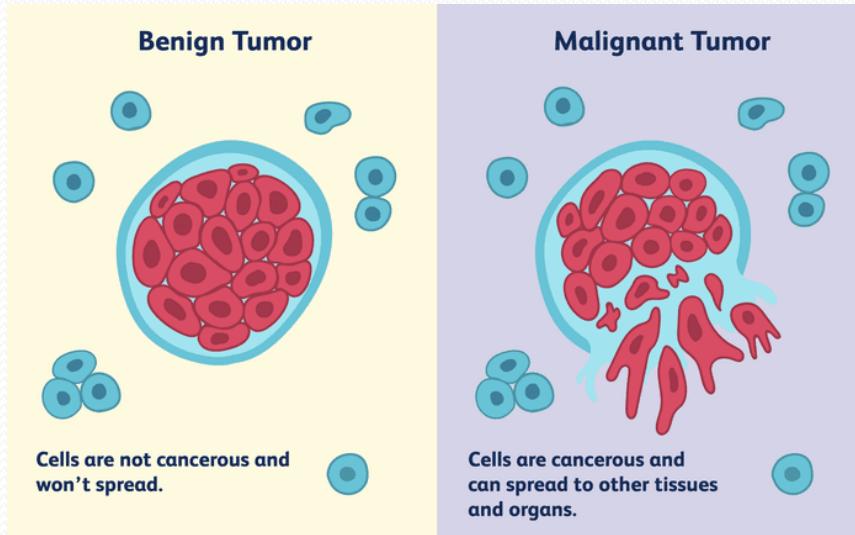


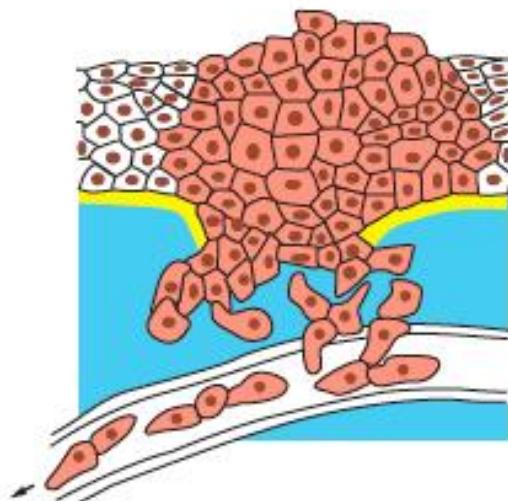
Cancer

- As tissues grow and renew themselves, each individual cell must adjust its behavior according to the needs of the organism as a whole.
- The cell must divide only when new cells of that type are needed, and refrain from dividing when they are not; it must live as long as it is needed, and kill itself when it is not; it must maintain its specialized character; and it must occupy its proper place and not stray into inappropriate territories.
- In a large organism, no significant harm is done if an occasional single
- cell misbehaves. But a potentially devastating breakdown of order occurs when a single cell suffers a genetic alteration that allows it to survive and divide when it should not, producing daughter cells that behave in the same antisocial way.
- Such a relentlessly expanding clone of abnormal cells can disrupt the organization of the tissue, and eventually that of the body as a whole. It is this catastrophe that happens in cancer.

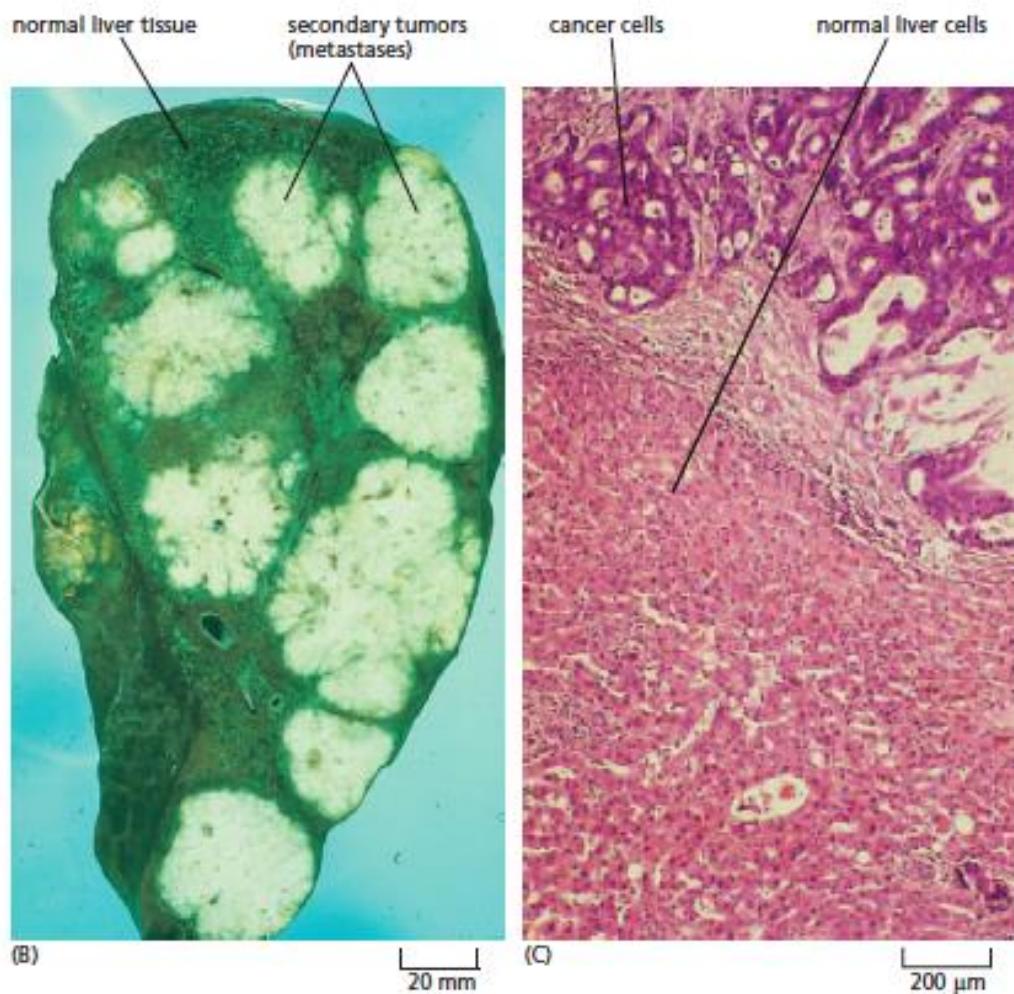
Benign or Malignant Tumor

- Cancer cells are defined by two heritable properties: they and their progeny (1) proliferate in defiance of the normal constraints and (2) invade and colonize territories normally reserved for other cells.
- It is the combination of these socially deviant features that creates the lethal danger.
- Cells that have the first property but not the second proliferate excessively but remain clustered together in a single mass, forming a *tumor*. But the tumor in this case is said to be *benign*, and it can usually be removed cleanly and completely by surgery.
- A tumor is cancerous only if its cells have the ability to invade surrounding tissue, in which case the tumor is said to be *malignant*.
- Malignant tumor cells with this invasive property often break loose from the primary tumor and enter the bloodstream or lymphatic vessels, where they form secondary tumors, or metastases, at other sites in the body .
- The more widely the cancer spreads, the harder it is to eradicate.





(A)



Causes of Cancer

- Although it is still hard to discover which specific factors in the environment or lifestyle are significant, and many remain unknown, some have been precisely identified.
- The most cases of cervical cancer depend on infection of the cervical epithelium with certain subtypes of a common virus, called human papillomavirus.
- This virus is transmitted through sexual intercourse and can sometimes, if one is unlucky, provoke uncontrolled proliferation of the infected cells.
- However, in the great majority of human cancers viruses do not appear to play a part.

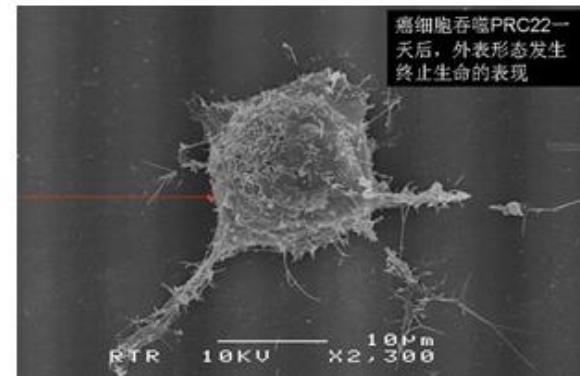
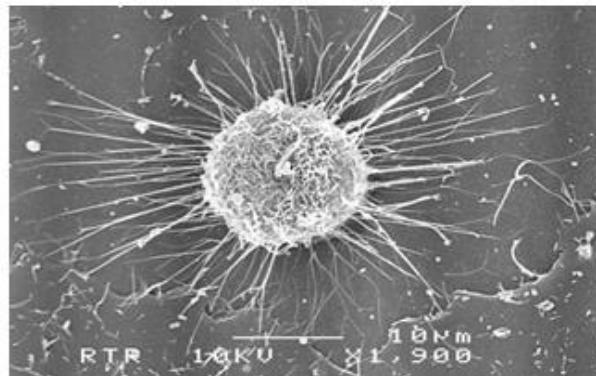
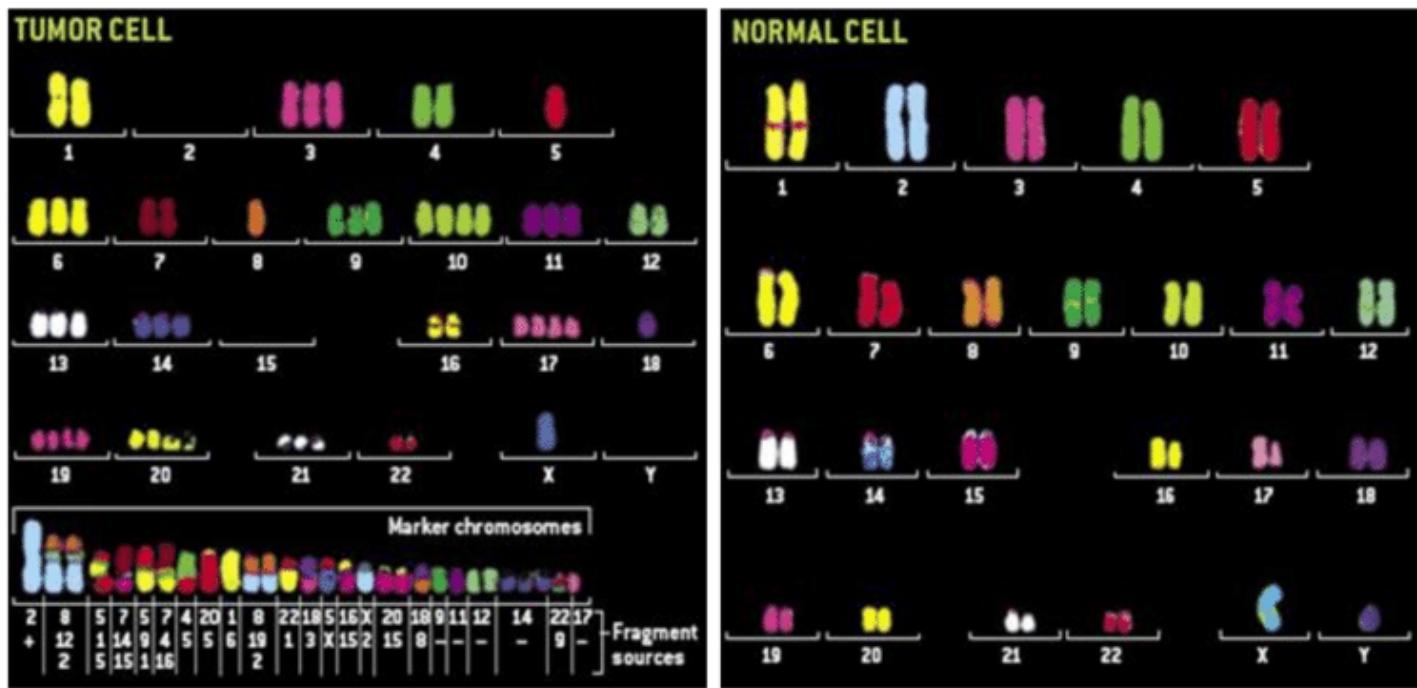
- Being exposed to radiation is the most effective cause of cancers.
- There also chemical carcinogens that can result in cancer.
- Obesity and smoking are other environmental factors that increase the risks of cancer.
- By stopping the use of tobacco, we could prevent about 30% of all cancer deaths.
- No other single policy or treatment is known that would have such a dramatic impact on the cancer death rate.

- Cancer is fundamentally a genetic disease: it arises as a consequence of pathological changes in the information carried by DNA.
- It differs from other genetic diseases in that the mutations underlying cancer are mainly somatic mutations—those that occur in individual somatic cells of the body—as opposed to germ-line mutations, which are handed down via the germ cells from which the entire multicellular organism develops.
- It develops by accumulation of mutations.
- Most of the identified agents known to contribute to the causation of cancer, including ionizing radiationmost chemical carcinogens and tobacco are mutagens: they cause changes in the nucleotide sequence of DNA.
- However, even in an environment free of all mutagens, mutations will occur spontaneously as a result of fundamental limitations on the accuracy of DNA replication and DNA repair.

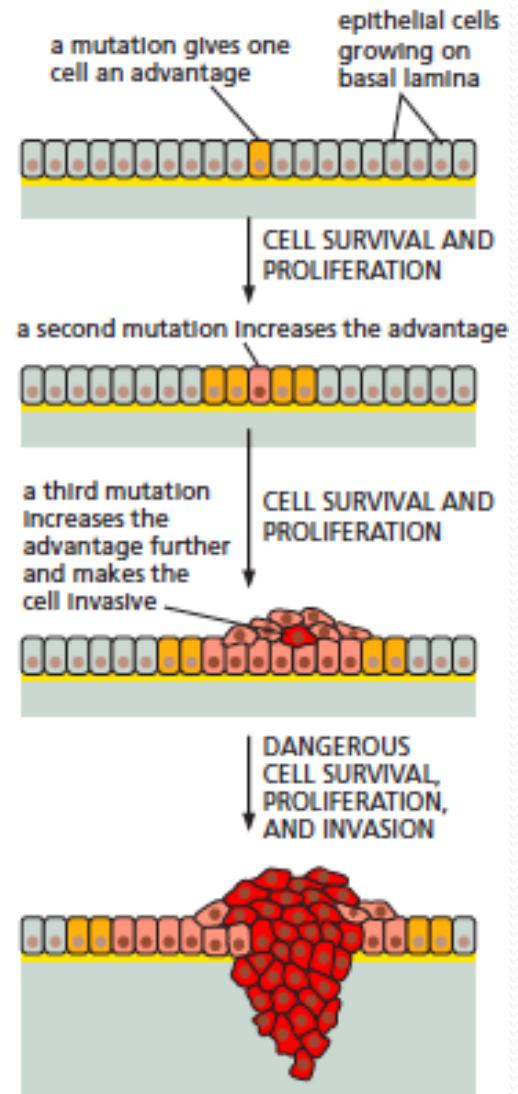
- It takes more than a single mutation to turn a normal cell into a cancer cell.
- Precisely how many are required is still a matter of debate, but for most full blown cancers it could be at least 10—and, they have to affect the right type of gene.
- These mutations do not all occur at once, but sequentially, usually over a period of many years.
- Cancer, therefore, is most often a disease of old age, because it takes a long time for an individual clone of cells—those derived from a common founder—to accumulate a large number of mutations

Genetic Instability

- In fact, most human cancer cells not only contain many mutations, but they are also genetically unstable.
- This genetic instability results from mutations that interfere with the accurate replication and maintenance of the genome and thereby increase the mutation rate itself.
- Sometimes, the increased mutation rate may result from a defect in one of the many proteins needed to repair damaged DNA or to correct errors in DNA replication.
- Sometimes, there may be a defect in the cell-cycle checkpoint mechanisms that normally prevent a cell with damaged DNA from attempting to divide before it has completed the repair
- Sometimes, there may be a fault in the machinery of mitosis, which can lead to chromosomal damage, loss, or gain.
- Genetic instability can generate extra chromosomes, as well as chromosome breaks and rearrangements—gross abnormalities that can be seen in a karyotype.



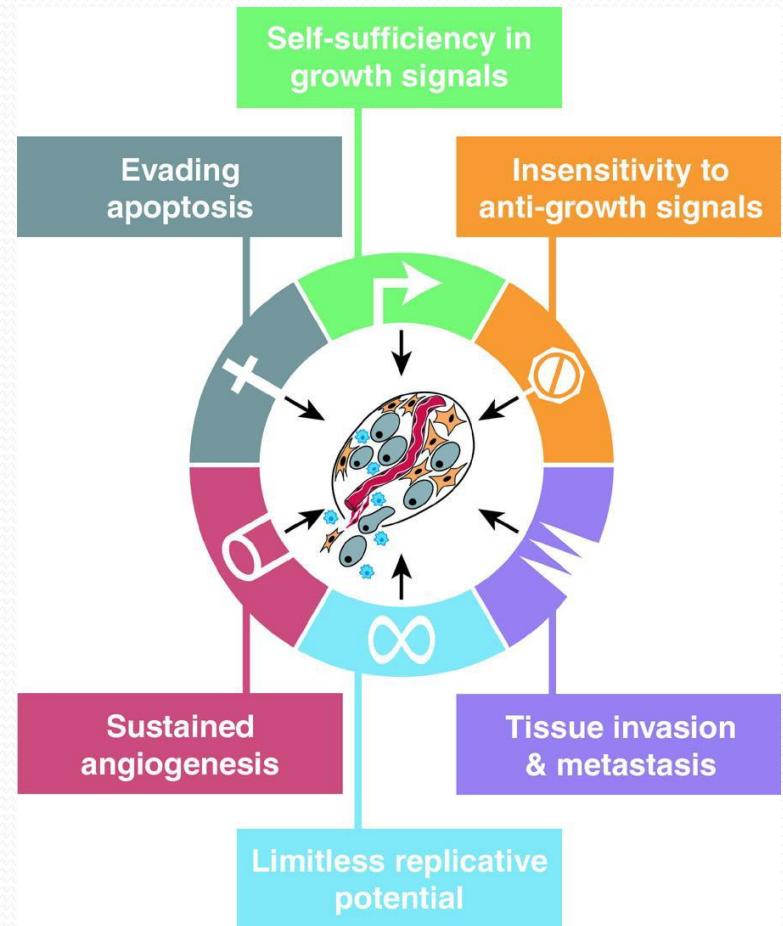
- The mutations that lead to cancer do not cripple the mutant cells. On the contrary, they give these cells a competitive advantage over their neighbors.
- It is this advantage enjoyed by the mutant cells that leads to disaster for the organism as a whole.
- As an initial population of mutant cells grows, it slowly evolves: new chance mutations occur, some of which are favored by natural selection because they enhance cell proliferation and cell survival.



- To be successful, a cancer cell must acquire a whole range of abnormal properties—a collection of subversive behaviors.
- A proliferating precursor cell in the epithelial lining of the gut, for example, must undergo changes that permit it to carry on dividing when it would normally stop.
- That cell and its progeny must also be able to avoid cell death, displace their normal neighbors, and attract a blood supply to nourish continued tumor growth.
- For the tumor cells to then become invasive, they must be able to detach from the epithelial sheet and digest their way through the basal lamina into the underlying connective tissue.
- To spread to other organs and form metastases, they must be able to get in, and then out, of blood or lymph vessels and settle, survive, and proliferate in new sites.

Hallmarks of Cancer

- Different cancers require different combinations of properties.
- Nevertheless, we can draw up a general list of characteristics that distinguish cancer cells from normal cells.
- Those characteristics are called hallmarks of cancer.



Self-sufficiency in growth signals

- Cancer cells have a reduced dependence on signals from other cells for their survival, growth, and division. Often, this is because they contain mutations in components of the cell signaling pathways that normally respond to such stimuli.
- An activating mutation in a Ras gene, for example, can cause an intracellular signal for proliferation even in the absence of the extracellular cue that would normally be needed to turn Ras on, like a faulty doorbell that rings even when nobody is pressing the button.

Insensitivity to anti-growth signals & Resisting Apoptosis

- Cancer cells can survive levels of stress and internal derangement that would cause normal cells to kill themselves by apoptosis.
- This avoidance of cell suicide is often the result of mutations in genes that regulate the intracellular death program responsible for apoptosis.
- For example, about 50% of all human cancers have an inactivating mutation in the p53 gene. The p53 protein normally acts as part of a DNA damage response that causes cells with DNA damage to either cease dividing or die by apoptosis.
- Chromosome breakage, for example, if not repaired, will generally cause a cell to commit suicide; but if the cell is defective in p53, it may survive and divide, creating highly abnormal daughter cells that have the potential for further mischief.

Limitless replicative potential

- Unlike most normal human cells, cancer cells can often proliferate indefinitely.
- Most normal human somatic cells will only divide a limited number of times in culture, after which they permanently stop; this is at least partly because they have lost the ability to produce the enzyme telomerase, so the telomeres at the ends of their chromosomes become progressively shorter with each cell division.
- Cancer cells typically break through this proliferation barrier by reactivating production of telomerase, enabling them to maintain telomere length indefinitely.

Tissue Invasion and Metastasis

- Cancer cells are abnormally invasive, at least partly because they often lack certain cell adhesion molecules, such as integrins and cadherins, that help hold normal cells in their proper place.

Sustained Angiogenesis

- Like normal tissues, tumors require sustenance in the form of nutrients and oxygen as well as an ability to evacuate metabolic wastes and carbon dioxide.
- The tumor-associated neovasculature, generated by the process of angiogenesis, addresses these needs.

- Two main classes of genes are critical for cancer:
 - Proto-oncogenes
 - Tumor suppressor genes
- Proto-oncogenes are genes that normally help cells grow and divide.
- Acquiring gain-of-function mutations a proto-oncogene can turn into an oncogene resulting in a hyperactive protein that continuously signal the cell to divide.
- Tumor suppressor genes are genes that slow down cell or arrest division, repair DNA mistakes, or direct cells to apoptosis.
- Acquiring loss-of-function mutations , the activity of tumor suppressors are destroyed.

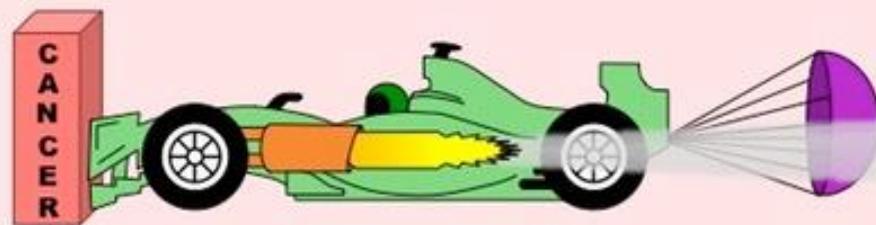


Normal Cell Cycle



Proto-oncogene (gas) Tumor Suppressor Gene (brakes)

Mutations leading to Cancer

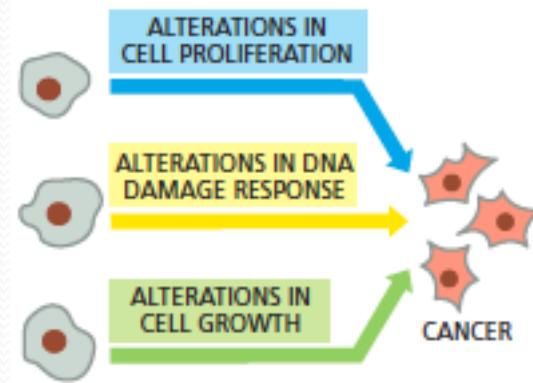


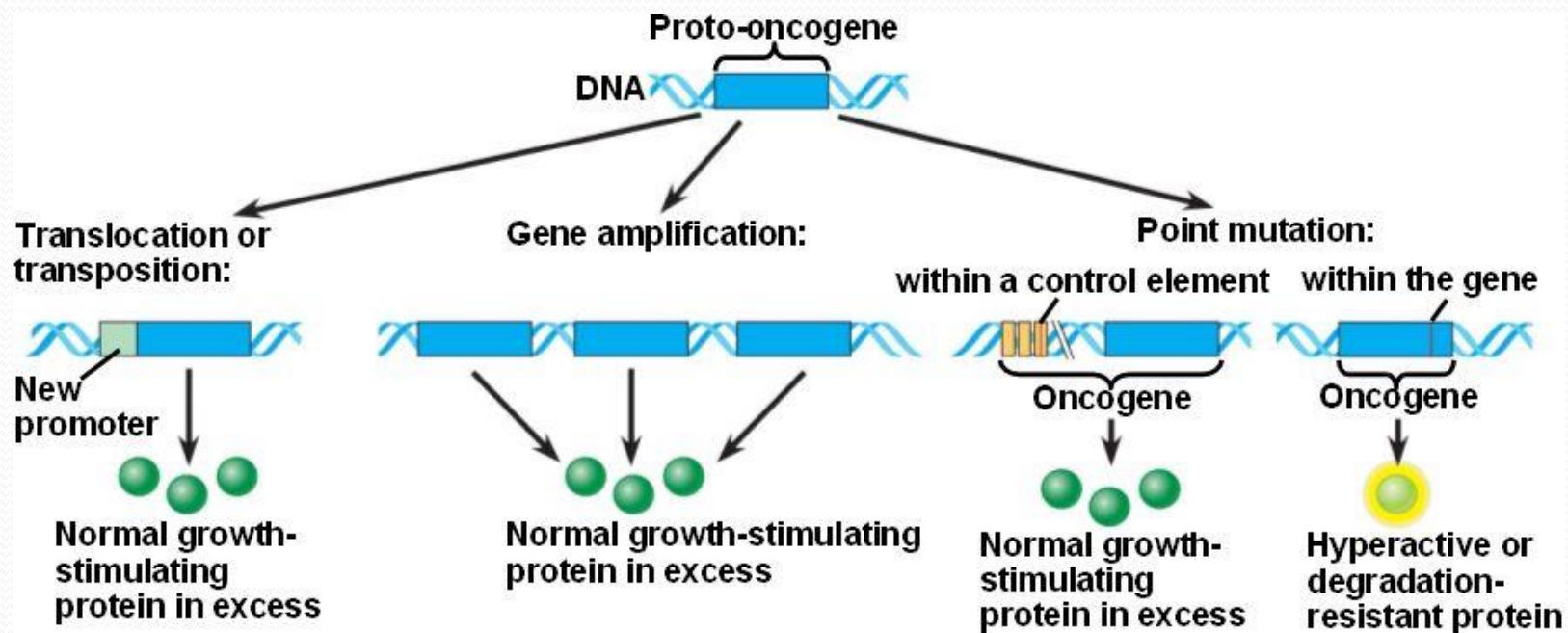
Proto-oncogene → Oncogene = *Too much gas!*



Tumor Suppressor Gene Inactivated = *No brake!*

- Proto-oncogenes and tumor suppressor genes code for proteins of many different types, corresponding to the many kinds of misbehavior that cancer cells display.
- Some of these proteins are involved in signaling pathways that regulate cell survival, cell growth, or cell division.
- Others take part in DNA repair, mediate the DNA damage response, modify chromatin, or help regulate the cell cycle or apoptosis.
- Activation of an oncogene and inactivation of a tumor suppressor gene can both promote the development of cancer.
- And both types of mutations are called into play in most cancers.





(a) RAS Cell cycle-stimulating pathway

