Mathematical Modeling of Cancer

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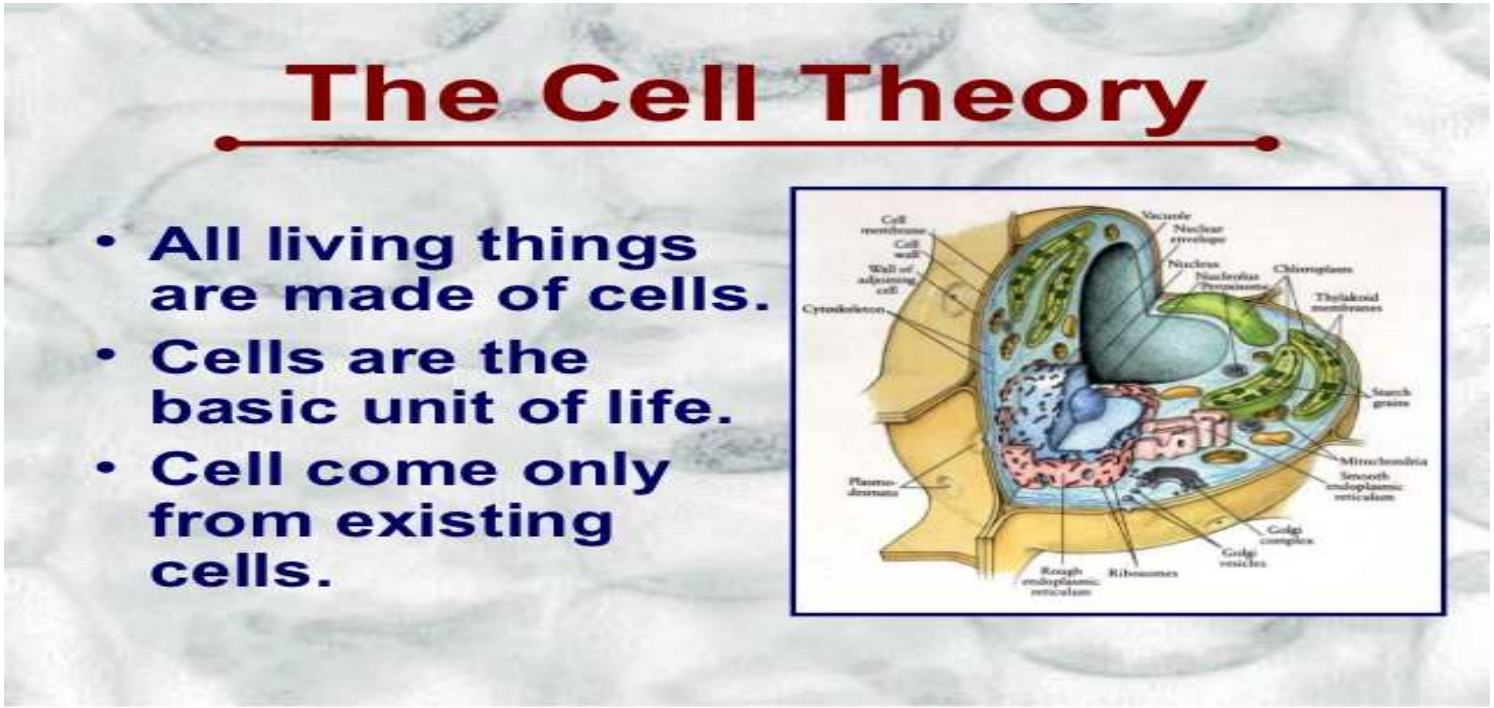
Overview

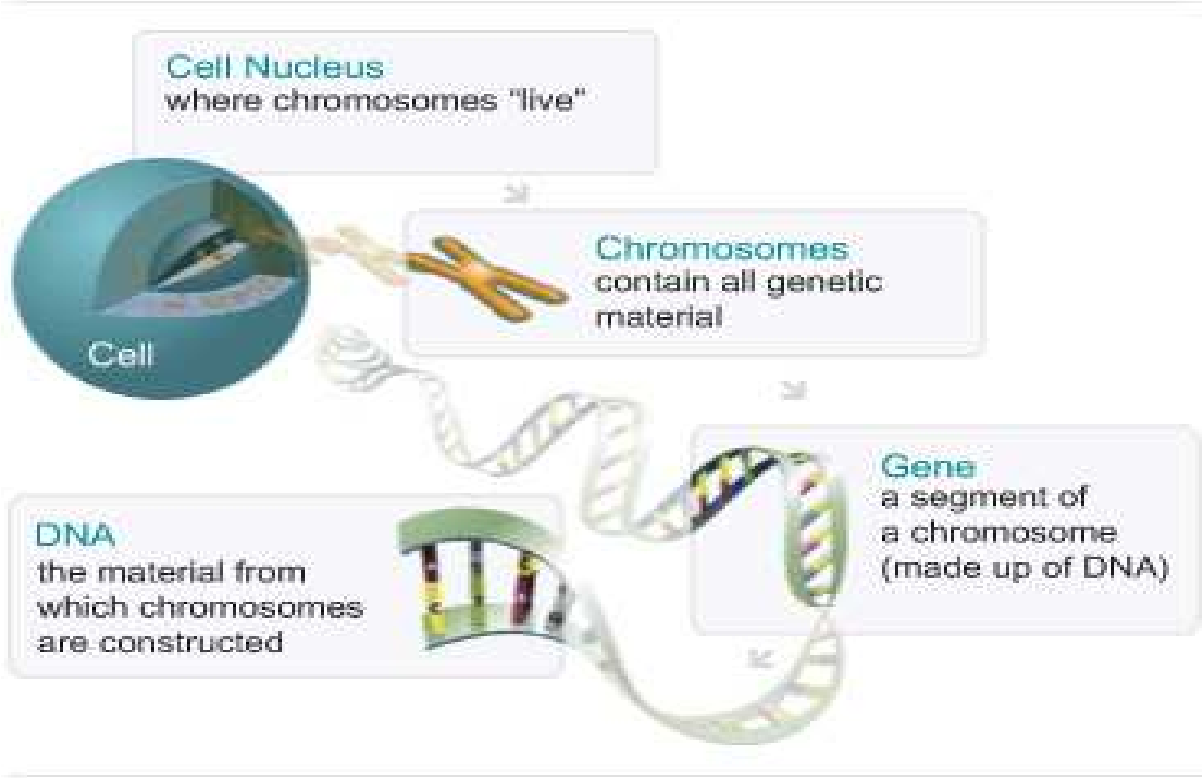
Cells and Healthy Life



They development and healthy life of human

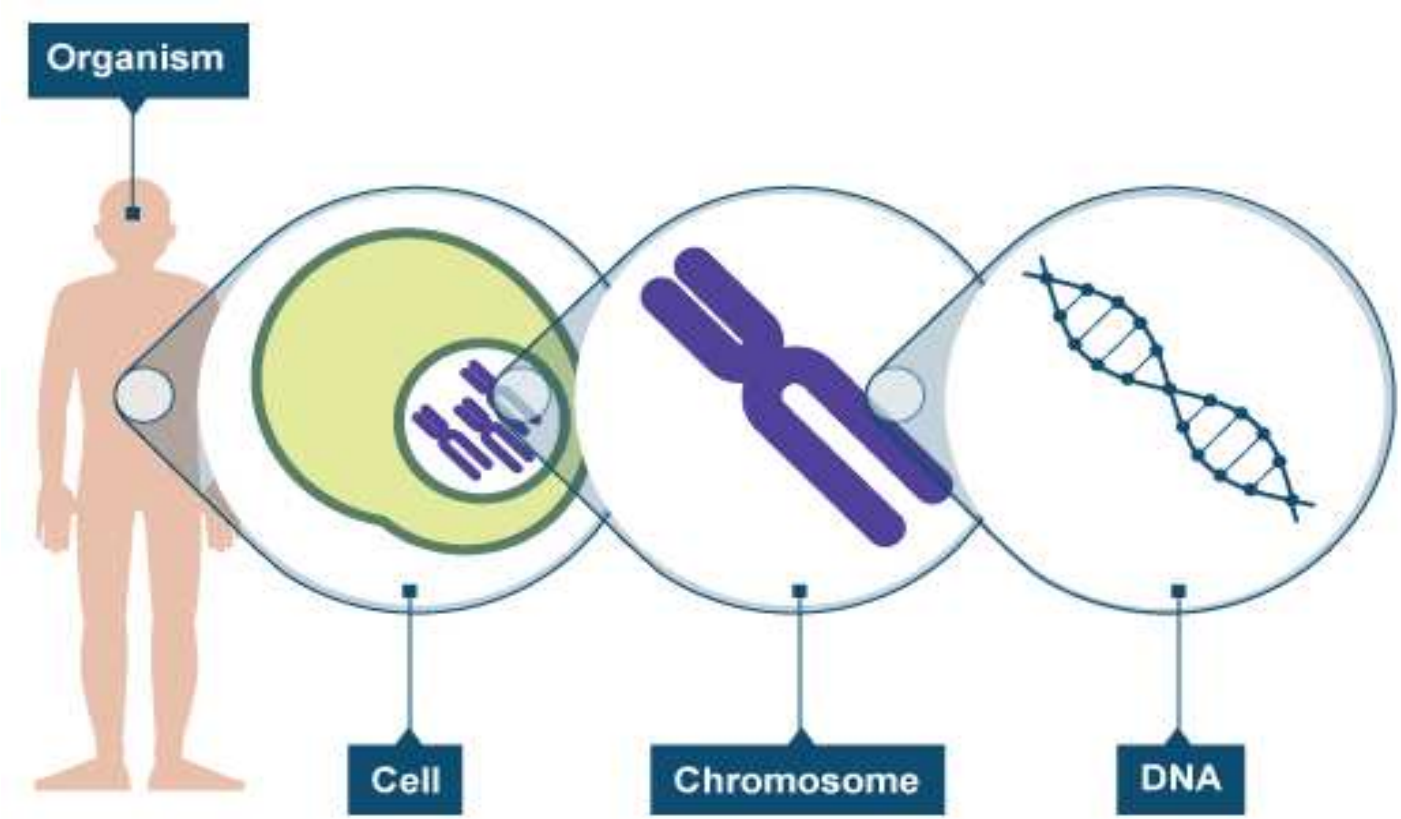
Requires cooperation of more than ten million cells

Normal cells



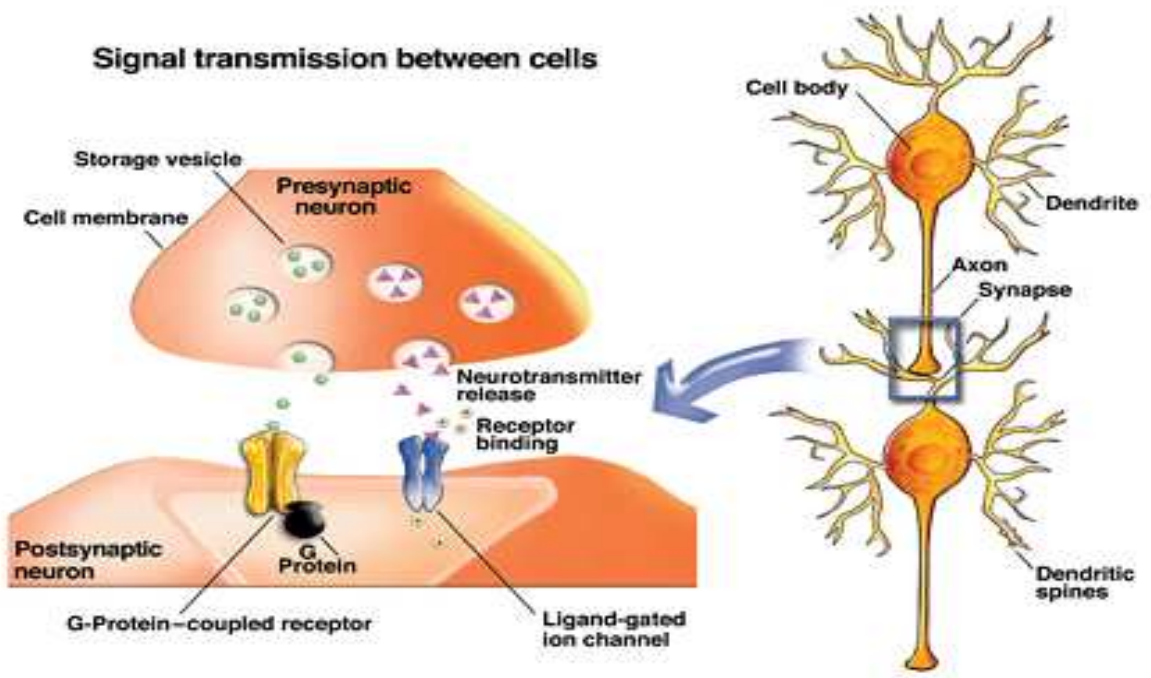
- Two copies of every gene: 1 from mother+1 from father
- Two copies of every chromosome: 1 from mother+1 from father

Organism to DNA

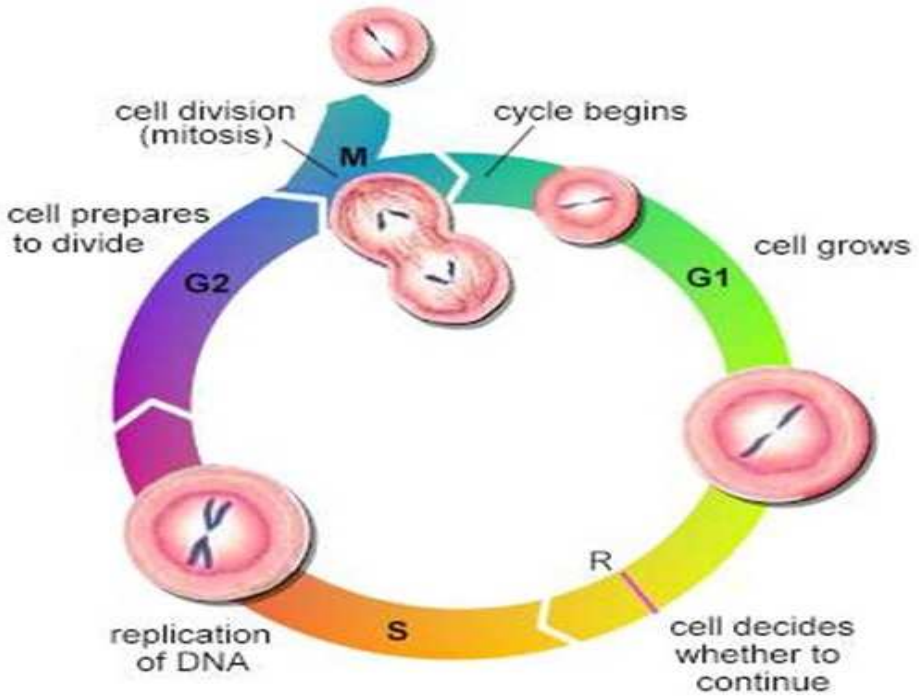


How to maintained cooperation between cells?

- By signals
- Cellular checkpoints: whether cells divide, die or differentiate
  - Checks DNA damage
  - Checks integrity of DNA

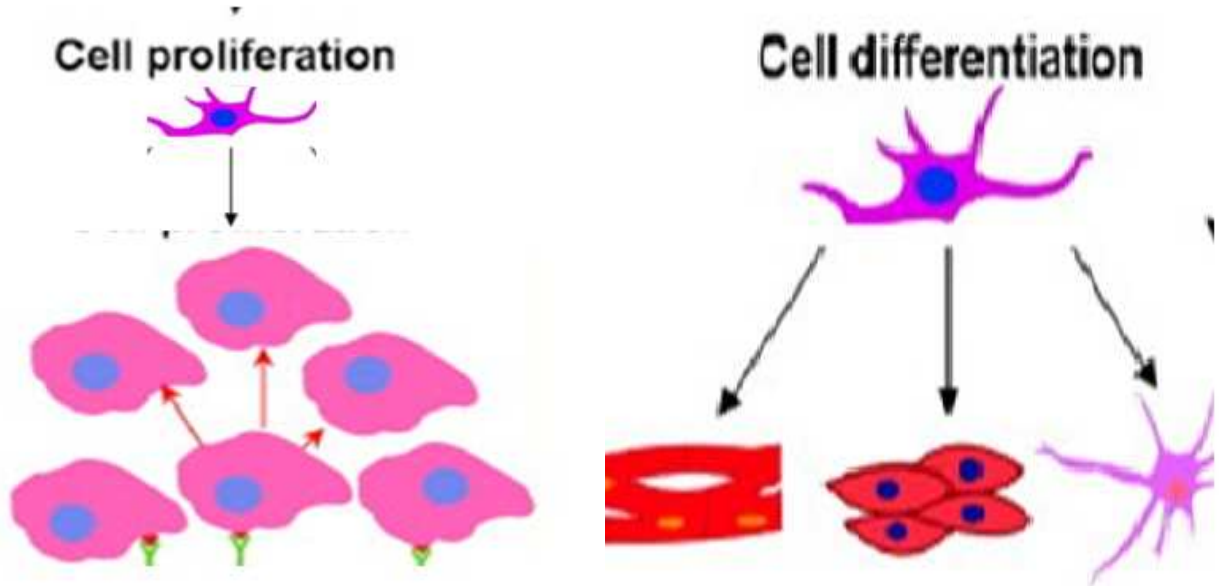


How to maintained cooperation between cells?



- S phase (non-division phase) and Division phase
- Gap phase
  - G1 devoted for metabolic activity for cell growth and preparation for DNA replication
  - G2 preparation for mitotic cell division takes place

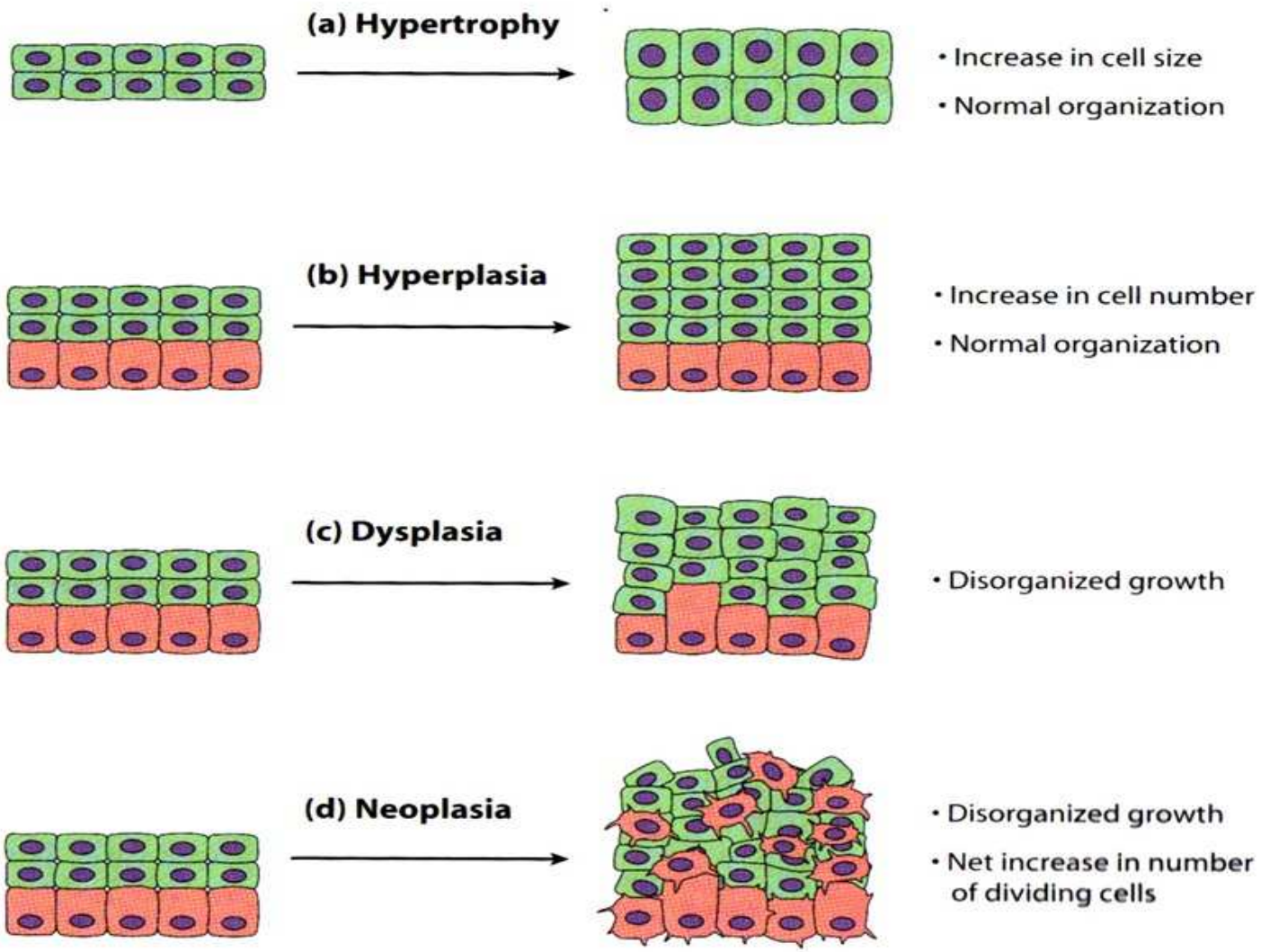
Proliferation and differentiation cells



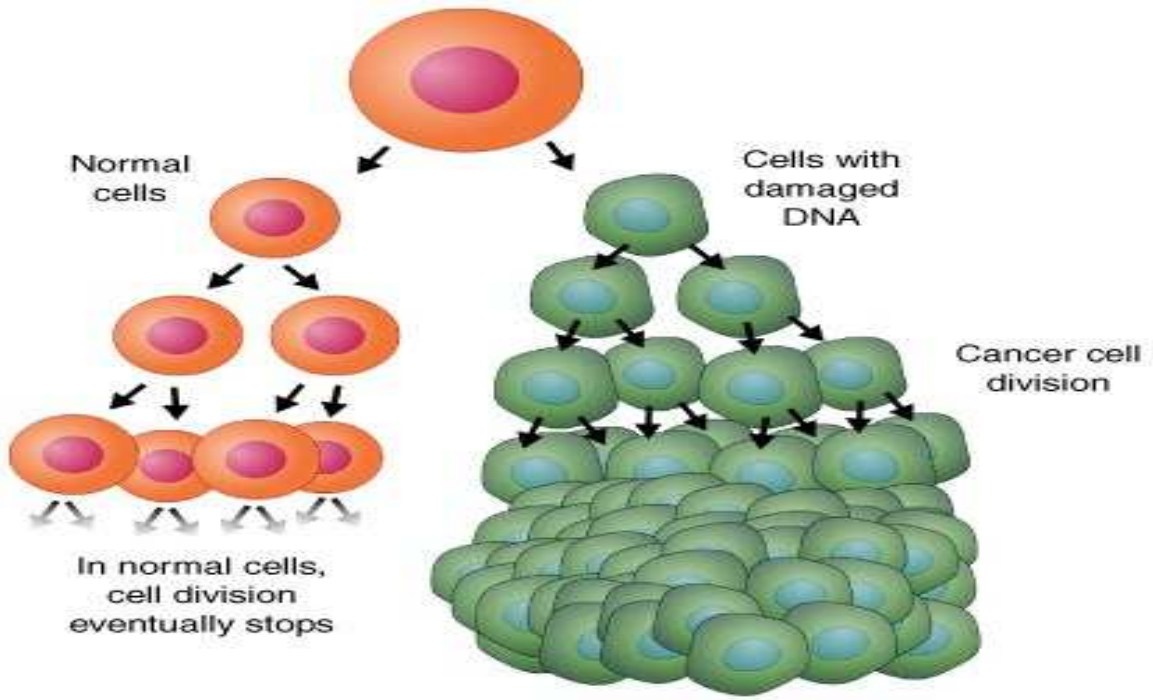
(a) (b)

- (a) Increase in the cell number with exact passage of genetic information to their daughter cells.
- (b) Different kinds of cells with the specialized morphology, metabolism and physiological functions from the cells of the same origin.

Different ways of increase in cell size



Cancer



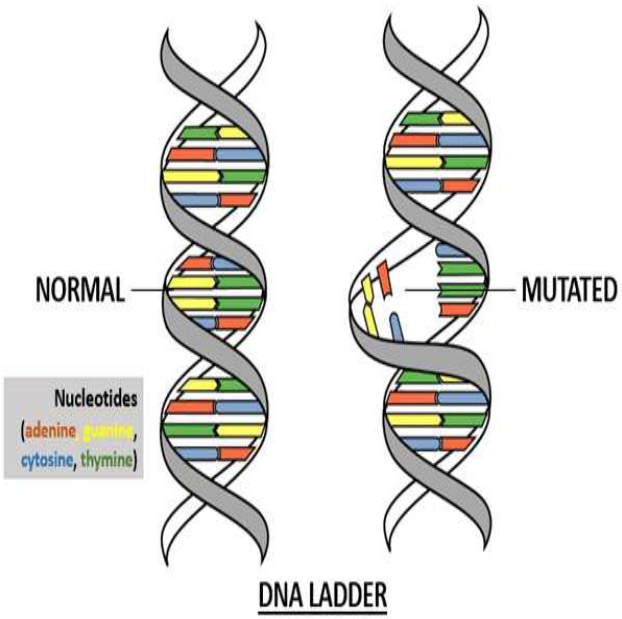
Most basic level, cancer represents

The collapse of the cooperation among the cells $\Rightarrow$ Selfish or uncontrolled growth of cells $\Rightarrow$ Death of organism.

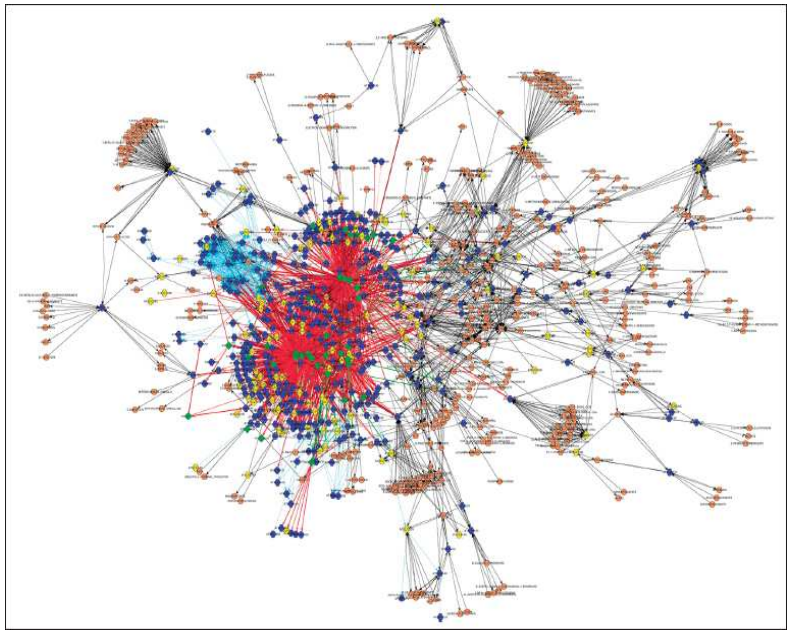
Mutations in genetic material

Cancer is a disease of DNA

uncontrolled growth of cells is the result of alteration or mutations in genetic material⇒breaks out of regulatory networks which ensure cooperation



(c)



(d)

Basic cancer genetics

Role of specific genes

- ensure the integrity of cells is maintained
- uncontrolled growth is prevented.

Mutation

the molecular hallmark of cancer growth

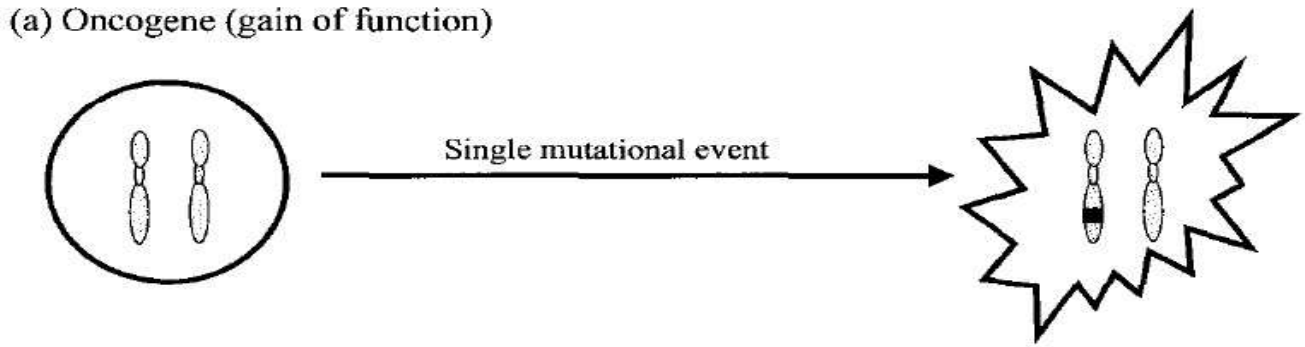
Gene families in cancer development

- Oncogenes
- Tumor suppressors genes
- Repair genes

Oncogene functions and mutation

Oncogenes function

promote the regulated production of cells in the presence of appropriate growth signals.



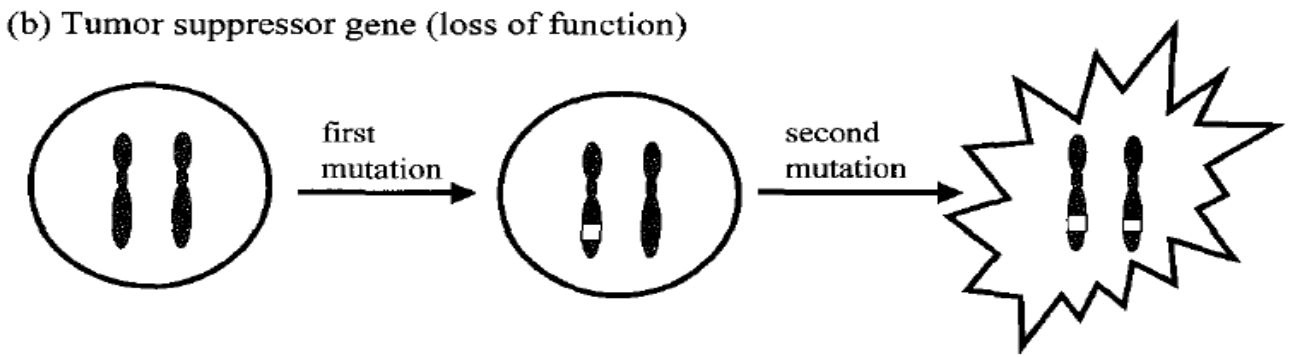
After mutation

- gain of function if one of the two copies receives an activating mutation
- induce cell to divide continuously irrespective of the presence or absence of growth signals

Tumor suppressor gene functions and mutation

Tumor suppressor gene function

- Cells with minor damage that can be repaired: cell activity is halted $\rightarrow$ gene function is suspended $\rightarrow$ gene is repaired $\rightarrow$ cell are repaired
- Cell damaged seriously: cells are killed (apoptosis)



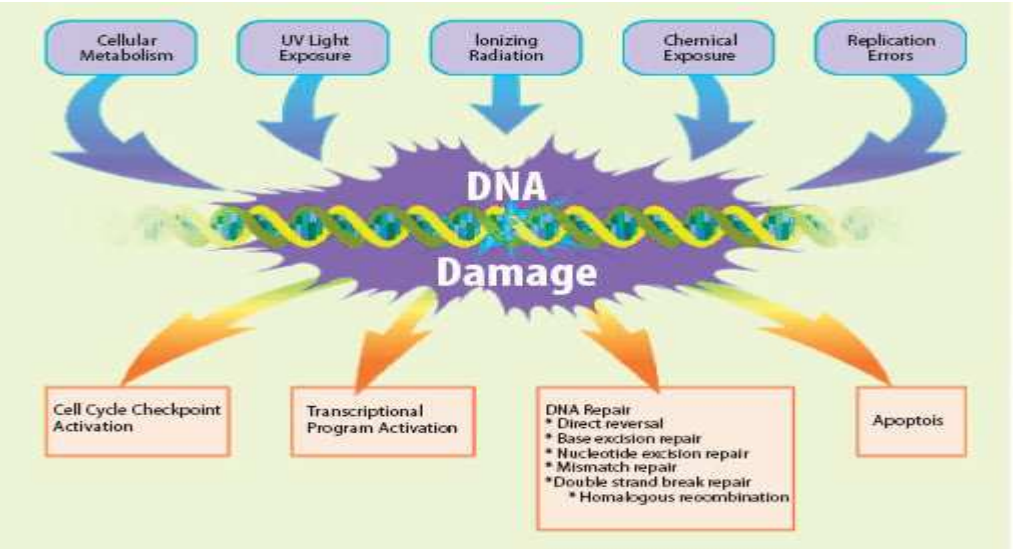
After mutation

- loss of function if both copies are muted
- the growth of altered cells is not prevented anymore and this promote the development of cancer.

Repair gene functions and mutation

Repair gene function

It is responsible for maintaining the integrity of genomes.



After mutation

cells can acquires new genetic alterations at faster rate, which promotes the mutations in oncogenes or tumor suppressor genes at faster rate

Mathematical model

Let us view cancer as a population of cells, which has some potential to grow.

We can model cellular growth by following ODE

$$\dot{x} = rx\left(1 - \frac{x}{k}\right), \quad x(0) = 1$$

- $x = x(t)$ is the number of cancer cells at time t
- r is the growth rate
- k is the carrying capacity

Note: Carrying capacity is the maximal size of the population of cells can reach, defined by the nutrient supply, spatial constraints etc.

Mathematical modeling continued...

Let us suppose that

- the population of cells is heterogeneous
- and all cells compete with each other and with surrounding healthy cells for nutrients, oxygen and space.

Then we can imagine the following systems

$$\dot{x}_i = r_i x_i - \phi x_i, \quad 0 \leq i \leq n, \quad x_i(0) = \hat{x}_i \tag{1}$$

where x_i is the number of cells of type i, with the corresponding growth rate, r_i.

Mathematical modeling continued...

Let us suppose that we have total of n types.

We can model the the competition by the term ϕ in a variety of ways, e.g. by setting

$$\phi = \frac{\sum_{i=0}^{n} r_i x_i}{N} \tag{2}$$

where $N = \sum_{i=0}^{n} \hat{x}_i$ is the total number of cells in the system.

Now we allow mutations in the system.

In other words, each cell division (happening with rate r_i for each type) has chance to result in the production of a different type.

Let us assume for simplicity that the type i can mutate into type $(i+1)$ only, according to the following simple diagram:

$$x_0 \to x_1 \to \cdots \to x_{n-1} \to x_n. \tag{3}$$

Mathematical model continued...

Then the equations become,

$$
\begin{aligned}
\dot{x}_0 &= r_0 (1 - u_0) x_0 - \phi x_0, \\
\dot{x}_i &= u_{i-1} r_{i-1} x_{i-1} + r_i (1 - u_i) x_i - \phi x_i, \quad 1 \leq i \leq n-1, \\
\dot{x}_n &= u_{n-1} r_{n-1} x_{n-1} + r_n x_n - \phi x_n, \\
x_i(0) &= \hat{x}_i, \quad 0 \leq i \leq n,
\end{aligned}
$$

where ϕ is defined as before, and u_i is the probability that a cell of type $(i+1)$ is created as a result of a division of a cell of type i.

The above equations are called the quasi-species equations.

Concluding Remarks

- One of the oldest and most successful methodologies in theoretical cancer research is using the available incident statistics, creating models to explain the observations.

The End