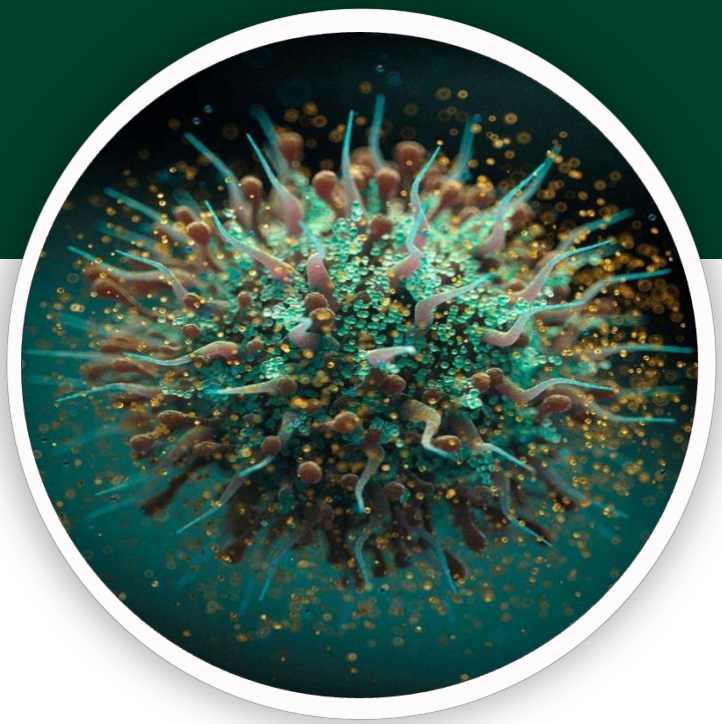


Pathology | Final 8

Neoplasia Pt.3

Written by: NST Members

Reviewed by: NST Members

Normal Cell

- Undergoes **metabolic reactions**
- These reactions **are controlled by genes (DNA)**
- DNA is **transcribed** → **translated** → **proteins**

Cell Division

- Normal cells divide in a **controlled manner**
- Cell division is **controlled by genes:**
- **Proto-oncogenes** → **stimulate growth**
- **Tumor suppressor genes** → **inhibit growth**

Normally, there is a very good **balance** between the expression of both → **everything is under control.**

Assume during the cell cycle, **abnormalities occur such as:**

- **Protein misfolding.**
- **DNA damage.**
- **Changes or abnormalities (as observed in cell injury).**

These abnormalities activate:

- DNA repair **- Apoptosis**

Both are also **controlled by genes** → everything is **controlled.**

So, the whole division process and any problems within **it are controlled by these genes:**

1. **Oncogenes**
2. **Tumor suppressor genes.**
3. **DNA repair genes.**

4. **Genes that regulate apoptosis.**
5. **Genes that regulate the relationship of cells to their surroundings.**

These genes keep the cell controlled.

Transformation to Malignancy

- Transformation to malignancy requires **accumulation of several mutations, One mutation is not enough.**

Cancer **is caused** by **DNA mutations (accumulation of several mutations)**; in these lectures we will discuss the mutations and DNA changes that can cause cancer.

Molecular basis of cancer

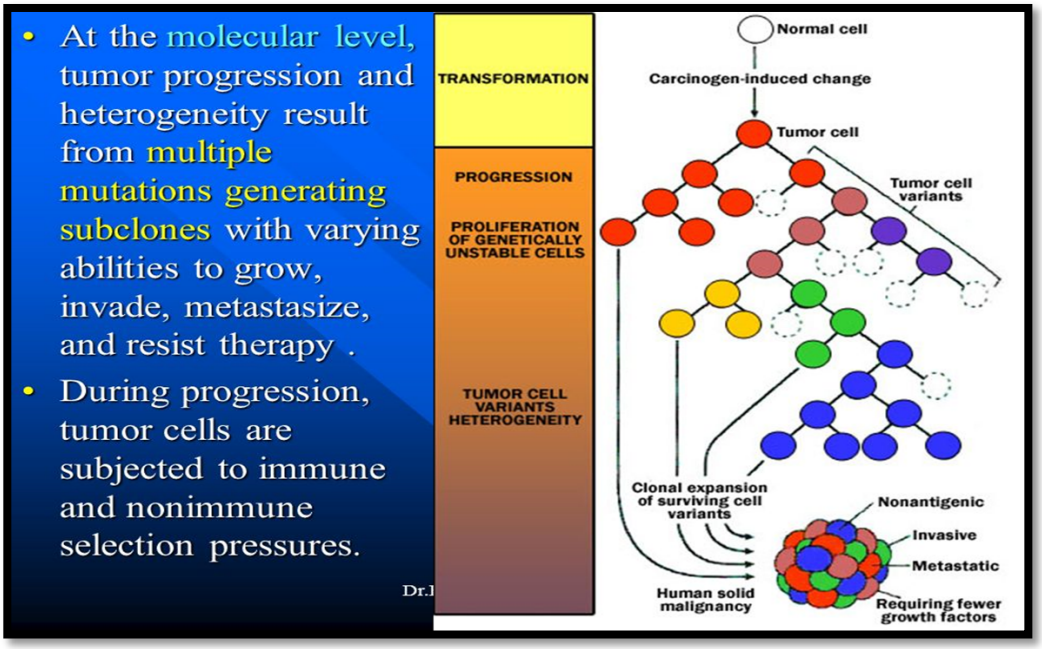
- **Neoplasms are caused by nonlethal, genetic damage,** which causes **uncontrolled cellular proliferation.**
- **Nonlethal:** not kill the cell so cells can still multiply.
- **Genetic damage:** mutations or non-mutational damages (details later in this lecture)
- **Uncontrolled proliferation… not all genetic damages produce tumors; they only do so if they result in a crazy cell that can multiply continuously in an uncontrolled, uninhibited fashion!**

Tumor clonality

- **Tumors** are **clonal** when they originate from the **same parent** mutated cell.
- Note: tumors **start as a clone**, but with time they acquire several mutations in some of the cells. They become heterogeneous. This is because some cells develop mutations that make them acquire characteristics like: ability to invade, to metastasize.

- So: malignant cells originate from one single transformed cell that acquires a mutation allowing it to proliferate in an uncontrolled manner.
- This cell keeps proliferating, forming a clone.
- But the proliferating cells acquire additional mutations, that help the tumor mass to grow further or to avoid death, or to metastasize.
- Each cell with a new mutation proliferates, forming a sub-clone.
- The end result is a tumor mass where each cell has the original mutation in the parent cell plus extra mutations that differ between the sub-clones.

Clonality: tumor starts from **one transformed cell → forms a clone.** With **progression**, cells **acquire additional mutations → subclones → heterogeneity (invasion, metastasis, drug resistance).**



Carcinogenesis is a multistep process

Carcinogenesis is a multistep process, at a molecular level tumor progression and heterogenicity arise from multiple mutations generating subclones with various abilities to metastasize, invade, grow and resist therapy.

During progression, tumor cells are subjected to immune and nonimmune selection pressures.

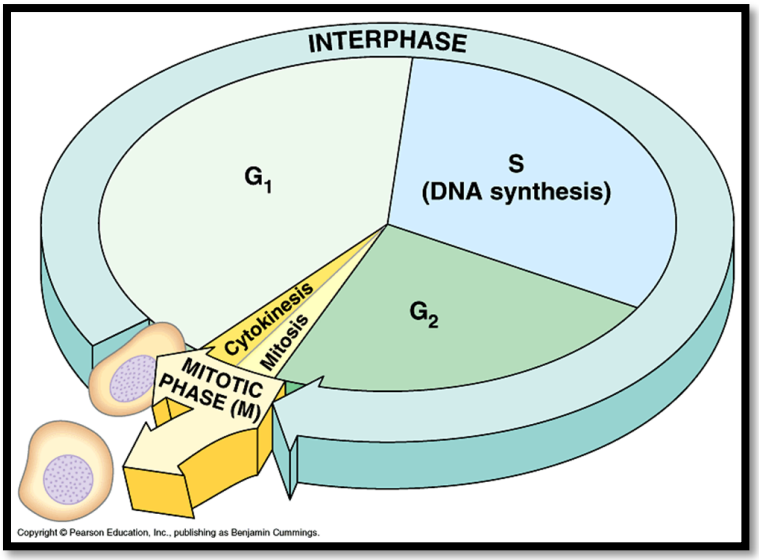
What are the genetic damages that can transform cells?

- For genetic damage to transform a cell, **it has to cause uncontrolled proliferation.**
- So: for cancer to occur there is **stimulation of genes that cause cell proliferation**, or **downregulation of genes that inhibit proliferation.**

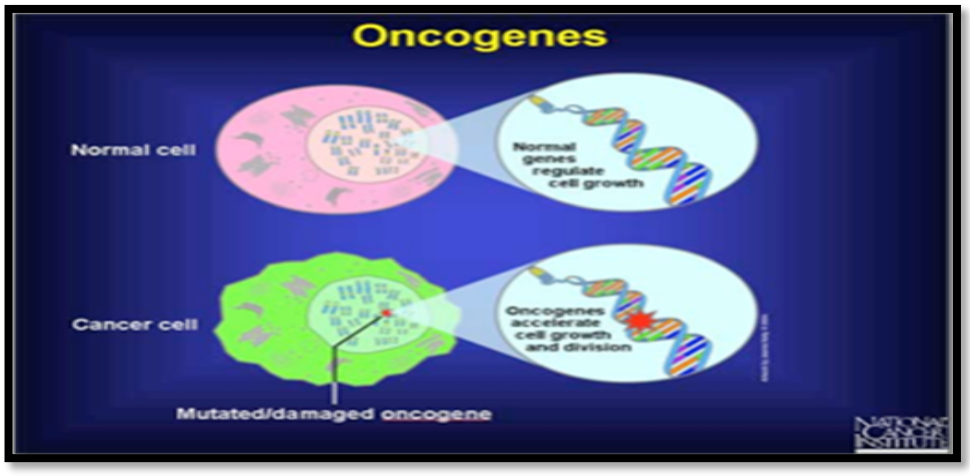
**Cell cycle is regulated by a balance between

growth stimulating genes = proto-onco genes and

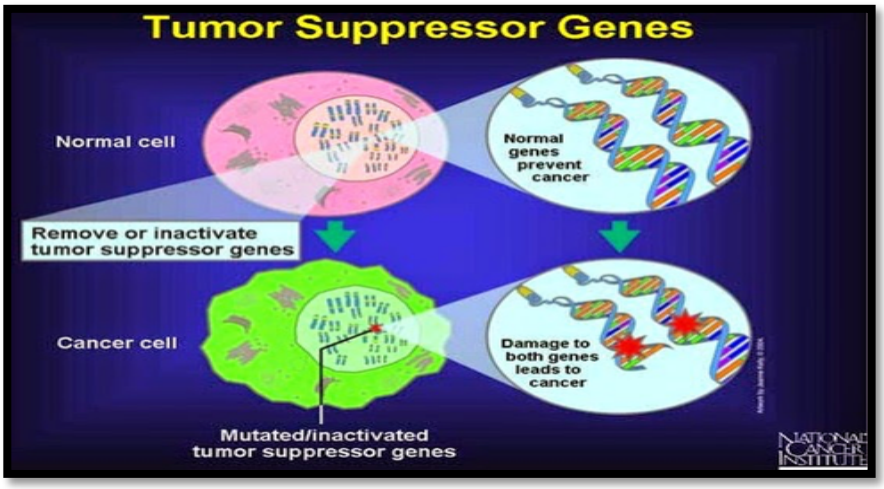
growth inhibiting genes= tumor suppressor genes.

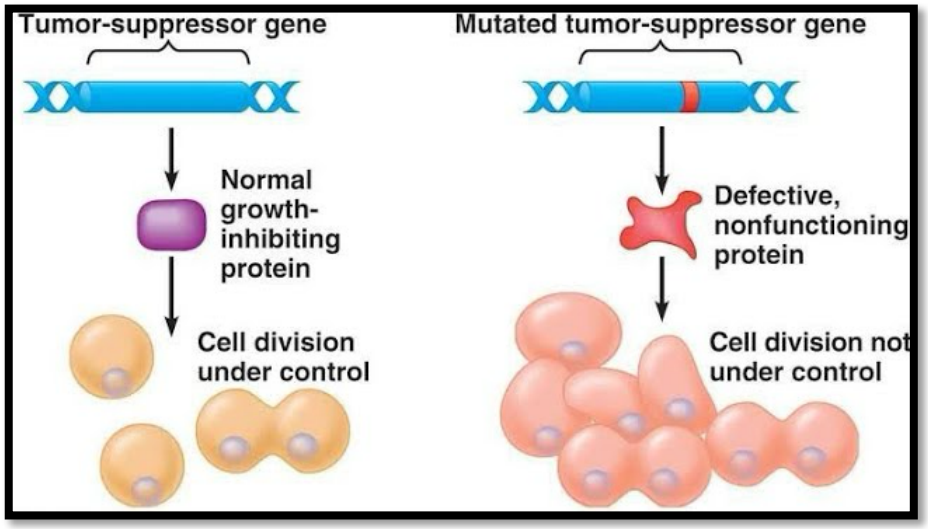


- Proto-oncogenes normally stimulate growth in a controlled manner. **If they are mutated**, they cause **uncontrolled growth (cancer).**



Tumor suppressor genes **counteract the function of the oncogenes**. **If they are inhibited by a mutation**, then cells **can proliferate without this "braking" effect of the tumor suppressor genes.**





Other genes involved in cancer

1) ***Genes that regulate apoptosis:*** these are very important because if the damaged cell dies by apoptosis, then no proliferation is possible. So, these genes are frequently mutated in cancers to keep cells alive and block apoptotic messages.
2) ***DNA repair genes also play a role in carcinogenesis.*** If DNA damages are repaired, then no cancer will occur. If DNA repair genes become nonfunctioning, then there is a chance of DNA damages to accumulate in cells.

3) Recently, ***genes that affect the interaction between tumor cells and host cells (surrounding normal cells)*** are thought to play a role in carcinogenesis...Especially genes which affect immune response of the host to cancer cells

So: five types of regulatory genes are mainly affected:

1. **Growth promoting proto-oncogenes**
2. **Growth inhibiting tumor suppressor genes**
3. **Genes that regulate apoptosis**
4. **Genes involved in DNA repair.**
5. **Genes that regulate interactions between tumor cells and host cells .**

Particularly important are genes that enhance or inhibit recognition of tumors cells by the host immune system

Oncogenes

- **Normally:** our cells **have proto-oncogenes.** These cause cell proliferation in a regulated manner
- **If the proto-oncogenes are mutated or overexpressed:** they **are called oncogenes**
- **Proto-oncogenes encode for proteins:** proto-oncoproteins, or oncoproteins
- These oncoproteins include **transcription factors, growth regulating proteins, and proteins involved in cell survival.**
- When **proto-oncogenes are mutated into Oncogenes**, this causes **overexpression of proteins involved in cell growth.**
- **If one allele is mutated or overexpressed:** there **will be increase in the growth proteins**, **which is enough to increase cell growth.**
- So, mutations of oncogenes act **in a dominant manner.**
- Important oncogenes: **RAS and ABL.**

How are oncogenes over expressed ?

1. **point mutation resulting in activation**
2. **amplification: increased number of copies of the oncogenes**
3. **Translocations**
4. **Epigenetic modification**

Tumor suppressor genes

- They normally **inhibit cell growth.**
- If **mutated or lost loss of growth inhibition**: so, **tumors occur.**
- Both **alleles need to be lost or mutated for the tumors to develop**, because **if only one allele is lost**, the other can compensate! so no cancer occurs.

✓ So, these are **recessive mutations.**

Most important examples :

1) **RB gene (retinoblastoma gene).** Called the Governor of the genome **controls growth and puts a brake in cellular proliferation.**
2) **TP53 gene.** Guardian of the Genome. **It senses genetic damage.**

✓ So, if there is damage, it causes cessation of proliferation or if the damage cannot be repaired, it causes apoptosis.

Genetic lesions in cancer

We now know the types of genes that **should be damaged for cancer to occur.**
But how they are damaged?

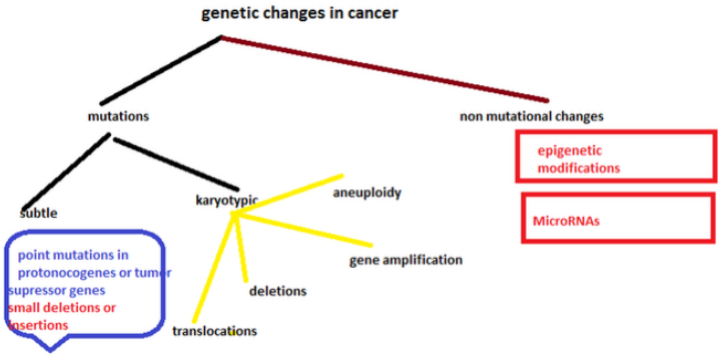
They can be damaged by **Mutational or non-mutational damages.**

❖ **Mutations (effect on the actual sequence of the DNA):**

1. ***subtle***: point mutations, insertions, point deletions.
2. ***Large, karyotypic change***: translocations, large deletions, gene amplification, aneuploidy

❖ **Non mutational (expression of the gene change): MicroRNAs andepigenetic modifications:**

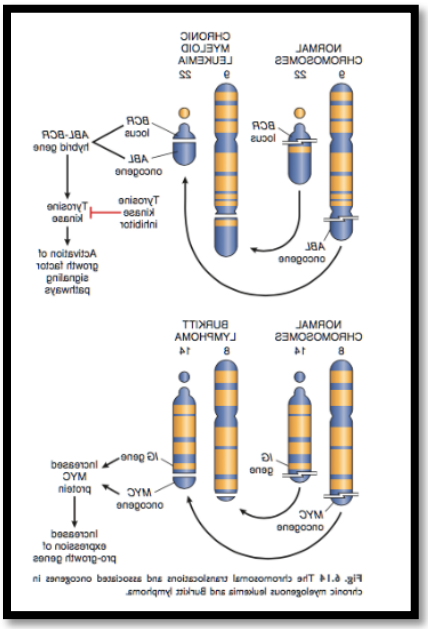
Mutational changes



Point mutations

- These are **single changes in nucleotides**
- Point mutations that **stimulate an oncogene or inhibit both alleles of a tumor suppressor gene can result in cancer.**

Balanced translocations



- Translocations **can cause cancer if they increase the expression of protooncogene.**
- This can happen by **two mechanisms:**

1) **Removing** the proto-oncogene from its normal, regulated locus **to a new position where it becomes under the influence of a highly active promoter.**

2) Translocation forms a **new fusion gene that encodes a novel (new) protein.**

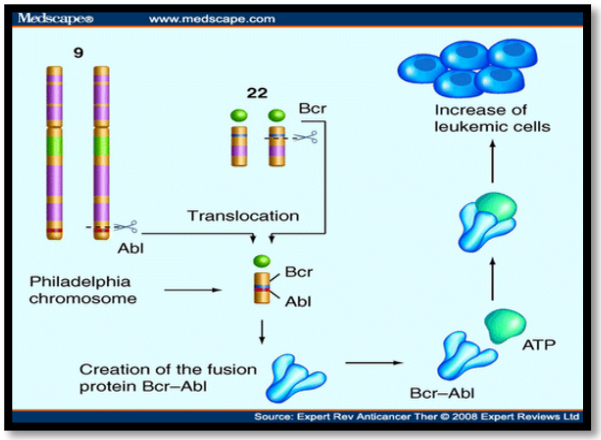
Examples:

- The **translocation** created a **new gene ABL-BCR** from a **fusion of two genes (ABL and BCR).** This created a new tyrosine kinase that **can activate cell proliferation resulting in leukemia**.
- the translocation moved the MYC oncogene to a new locus (near the IG gene; **active gene**) that increased expression of the MYC gene (over activation) resulting in increased cell proliferation.

Philadelphia Chromosome

(translocation9:22):

- an example of a <u>translocation causing a new protein (a kinase) that increases cell proliferation</u>. So, it is the chromosome **where gene fusion happens, and a new gene is formed encoding for a new protein.**



Gene amplifications

- **Proto-oncogenes can be amplified** and **overexpressed**. Converted to **oncogenes**.
- This is seen in karyotyping as **two patterns :**
  1) ***Homogenously stained region (HSR)*** = <u>increased</u> copies of the gene <u>present within the chromosom</u>.
  2) ***Double minutes:*** <u>extra copies of the gene separated from the chromosome.</u>

❖ Occur mainly in hematogenous neoplasms, why?

- Because lymphoid cells **make DNA breaks during antibody or T cell receptor recombination.** (Loads of cutting and rearrangements of the genes) so there is more chance that a gene that was cut will be "pasted "in a new locus!

This table shows examples of tumors caused by translocations. Don't memorize it!!

Tumor type	translocation	Oncogene affected	mechanism	notes
BURKITT lymphoma	t(8;14)	MYC	MYC becomes under stimulation of heavy chain gene elements	90% of Burkitt cases have the mutation overexpression
Follicular B cell lymphoma	t(14,18)	BCL2 (antiapoptotic)	Overexpression of BCL2 by immunoglobulin gene elements	overexpression
Chronic myelogenous leukemia (CML)	t(9;22)	BCR-ABL rearrangement	New fusion gene (Philadelphia chromosome)	90% of cases. More details on next slide!
Ewing sarcoma	t(11;22)	EWS – Fli 1 fusion	Fusion gene	EWS is a transcription factor Fusion product
Prostate carcinoma		ETS	Fusion gene	
Lung cancer		ALK	Fusion gene causing activation of ALK kinase	Only 4% of lung tumors have this fusion...these respond to ALK kinase inhibitors

Deletions

- **More** in **non-hematopoietic solid tumors.**
- Result in **loss** **of tumor suppressor genes.**
- **2 copies** of the **tumor suppressor gene need to be lost**, usually **one by point mutation and another by deletion.**

Aneuploidy

- number of chromosomes **not multiple of the haploid state (23).**
- Results from **errors of the mitotic checkpoint.**

NON-Mutational mutations

microRNAs (miRNAs)

- Noncoding, micro-RNA segments (22 nucleotides) are *negative regulators* of the genes.
- They **inhibit** gene expression **post-transcriptionally (don't interfere in the transcription) = repress translation or cleave mRNA.**
- So, Transcription occurs = messenger RNA formed. **But mRNA is not translated into protein.**
- microRNA can **inhibit translation or cleave the messenger (tears the message before it is read)**
- Cause cancer by increasing **oncogene expression or decreasing tumor suppressor gene expression.**
- miRNAs that target oncogenes. If reduced, then inhibition caused by microRNA is lost, causing **overexpression of oncogenes.**
- miRNAs that target tumor suppressor genes. **If increase,** they cause **downregulation of tumor suppressor genes**, resulting in **cancer** (as if we are functionally reducing the tumor suppressor genes)

Epigenetics

- **Epigenetics are reversible**, heritable changes in gene expression that **occur without mutation.**
- **Two types: *Histone modifications*** (over expression of oncogene or under expression of tumor suppressor gene) and ***DNA methylation***.
- Functionally relevant changes to the genome that do not involve a change in the nucleotide sequence.

❖ Examples of mechanisms that produce such changes are ***DNA methylation and histone modification,*** each of which **alters how genes are expressed without altering the underlying DNA sequence.**

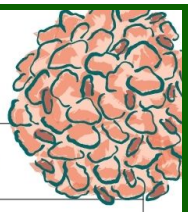
Epigenetics and cancer

- Gene expression is silenced by **DNA methylation= more methyl groups lead to more silencing (suppression).** In cancer cells:

1) Global DNA hypo methylation **increases expression of genes**. It also causes **chromosomal instability.**
2) Selective promoter hyper methylation of tumor suppressor genes: **silenced.**

Summary

- Changes in those genes can be mutational (point mutations, deletions,amplifications, translocations) or non mutational (epigenetic changes or microRNA changes)
- microRNAs are posttranscriptional inhibitors of gene expression.
- Epigenetic changes are changes that do not affect the DNA sequence but change gene expression through stimulating or inhibiting gene promotors.



Gene Category	Normal Function	What Goes Wrong in Cancer	Genetic Mechanism	Key Examples
Proto-oncogenes → Oncogenes	Promote controlled cell growth	Gain of function → uncontrolled proliferation	Point mutation, amplification, translocation, epigenetic activation	RAS, MYC, ABL
Tumor suppressor genes	Inhibit cell cycle, induce repair/apoptosis	Loss of growth inhibition	Point mutation + deletion, promoter hypermethylation	RB, TP53
Apoptosis genes	Eliminate damaged cells	Cells survive despite DNA damage	Mutation or overexpression of anti-apoptotic genes	BCL-2
DNA repair genes	Repair DNA damage	Genomic instability, mutation accumulation	Loss of function	BRCA1/2, MSH2
Tumor–host interaction genes	Immune recognition of abnormal cells	Immune evasion	Epigenetic or mutational changes	MHC-related genes

منقول عن أحد الأخوة :

يومٌ وُلدتُ فيه من جديد!

تُرى ماذا خسرنا في الطريق؟

"عليّ أن أُسرع كي لا تفوتني صلاة المغرب"

من طبيعة الإنسان أن يذنب، وهذا ليس مما يعيب الإنسان، بل مما يميّزه، وفي إحدى فترات حياتي لم أكن ملتزمًا دينيًا كما أنا عليه اليوم، ولله الحمد، ولكن قد تلمع بنا شرارة التغيير، غير أن الشعلة التي أنبتتها تلك الشرارة تعيش في عالم عاصف، كثائر على الظلم يعيش بين من يرتضي الظلم ويدافع عنه.

يوم الحادي والثلاثين من شهر تموز عام 2023 يومٌ قررتُ فيه أن أتغير، لا أنكر أنه ربما يكون بدافع الحماس لا أكثر، لكنها كانت الشعلة التي أشعلت الثورات على الشيطان في داخلي، فلم يرقَ لي يومًا أن أكون كما أنا، أن يأتي يوم أنظر فيه إلى الخلف فلا يكون هناك مازوت خلفك، فأنت لم تسر إطلاقًا.

قررتُ يومها أن أبدأ الصلاة في المسجد، صليتُ الظهر، والعصر، والمغرب أيضًا، ولم يغب عن بالي الآن مشهد ظل محفورًا. في داخلي، أتذكره من فترة لأخرى، ولا يزال حاملًا لنفس الأثر، فيعيد لي ذلك الشعور الغريب الذي لن أكلّف نفسي عناء وصفه، فلن أستطيع إليه سبيلًا.

في أحد الأيام التي لن أكلّف نفسي عناء ذكرها...

دخلتُ إلى المسجد فتوضأتُ للمرة الثانية.. للمرة الثانية؟! أجل، سنتحدث عن الأمر في قسم "عن الوسواس القهري".
دخلتُ فصليتُ في الصف الأخير.. الصف الأخير؟! نعم، وسنتحدث عن الأمر في قسم "عن الوسواس القهري"
وكنتُ أصلي متجاهلًا ما يأتيني من شعور بخروج الريح، وأقول في نفسي: (لا، لن أترك الصلاة، فهذه وسوسة، لم أسمع صوتًا، ولم أجد ريحًا، لا... لن أغادر).

قاطع حبل أفكاري طفلٌ كان في الحادية عشرة من عمره، دخل المسجد مسرعًا، تقدم ليصل إلى الصف الأول، صارع على المساحة الضيقة المتبقية في الصف الأول، فحشر نفسه فيه، وصلى في الصف الأول. فكرتُ: لماذا صلى في الصف الأول ولم أصلِّ فيه؟ لماذا حارب وقاتل وأنا لم أحاول؟ هل أنا فعلًا... أسوأ من ذلك الطفل؟ هل هو فعلًا أفضل مني؟! لا، هو ليس أفضل مني فحسب، لا مجال للمقارنة...

أثناء عودتي إلى المنزل، فكرتُ مليًا في الأمر، أعجبتُ بتلك الروح القتالية التي صارعت للصف الأول، وتذكرت: هل كنتُ مثله في صغري؟! هل قاومت؟ هل حاربت؟ هل كنتُ مثله؟

سرتُ في الطريق كمن شرب حتى الثمالة، فقد انحرفتُ عن مساري بضع مرات حتى إن كادت سيارة أن تدهسني، فعندما أفكر أشرُد بذِهني، وعندما أشرُد بذِهني فأنا لستُ هنا. فكرتُ وتذكرت:

(نعم، لقد كنتُ مثله، أنا أتذكر... ألم أبكِ لأن والدي لم يسمح لي بالذهاب لصلاة العشاء؟ ألم أكن أوشك على البكاء لأني قد أُمرتُ بعدم الصلاة في الصف الأول فهو "للكبار"؟ وبالطبع هذه فكرة خاطئة مستمرة لليوم، فلا يجب أن نمنع أطفالنا من الصلاة في الصف الأول، ومهما كان السبب، فبذلك يتعلقون به ولا يتركونه ما دامت الأنفاس في الصدور، وهذا طبعًا في حال عدم وجود ما يجر الطفل بعيدًا عن الطريق المستقيم، وسنتحدث عن ذلك في قسم "جيل").

وعند وصولي للمنزل الذي أحمد الله على وجوده، تنهدتُ، فحوقلتُ، فأغلقتُ الباب، ورمى لساني بكلمات: ليتني بقيتُ طفلًا!

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Page # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			