

## **Neoplasia lec3**

Cancer is caused by DNA mutations, in this 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.

**\*\*Carcinogenesis is a multistep process, at a molecular level tumor progression and heterogeneity 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 a 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 = protooncogenes 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**

- - 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.
- - 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.
- Recently, genes that affect the interaction between tumour 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, 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 oncogenes overexpressed??**

- 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 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: 1.subtle: point mutations, insertions, point deletions.  
2. Large, karyotypic change: translocations, large deletions, gene amplification, aneuploidy
- Non mutational: MicroRNAs and epigenetic modifications

## **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 expression of a 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 influence of a highly active promoter.
  - 2. Translocation forms a new fusion gene that encodes a novel (new) protein.
- Occur mainly in haematogenous 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!

### Examples:

- the translocation created a new gene ABL-BCR from 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) that increased expression of the MYC gene resulting in increased cell proliferation

Philadelphia chromosome: an example of a translocation causing a new protein (a kinase) that increases cell proliferation. So it 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) = increased copies of the gene present within the chromosome
  - 2. Double minutes: extra copies of the gene separated from the chromosome.

## **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).
- Result from errors of the mitotic checkpoint

## **microRNAs (miRNAs)**

- Noncoding, micro RNA segments (22 nucleotides) that are negative regulators of the genes.
- They inhibit gene expression post-transcriptionally = repress translation or cleave mRNA.
- SO: transcription occurs = messenger RNA formed. But mRNA is not translated to a 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 increased 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 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. In cancer cells:
  - 1.Global DNA hypo methylation: increases expression of genes. Also causes chromosomal instability
  - 2.Selective promoter hyper methylation of tumor suppressor genes: silenced
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### **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 promoters.