CANCER
An INTRODUCTION

a reference book:

The Molecular Biology of Cancer
S-Pelengaris and M. Khan
(Wiley-Blackwell edition)

Terminology

- CANCER – derived from the Greek word *karkinoma* and the Latin word *cancer* that means ***CRAB***
- Cancer is a "malignant" ***TUMOUR***
- Tumour – is a greek word for "swelling" of the tissue caused by inflammation
- Neoplasia – means "new growth" (neoplasm = new tumour)
- Oncology – Greek *oncos* = tumour

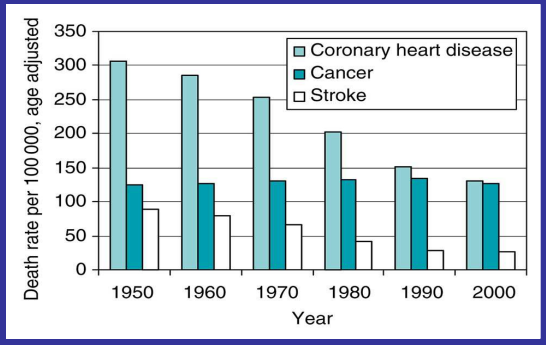
The Burden of CANCER

- In year 2000: 5.3 million men + 4.7 million women affected; 6.2 million deaths
- Incidence (new cases) expected to increase up to 15 million by year 2020
- 10-25 % of deaths worldwide
- Most frequent cancers: non-melanoma skin cancers, lung cancer, breast and colon cancers

The Burden of CANCER (2)

- In year 2008 (IARC data):
- 12.7 million of new cases;
- 7.6 million deaths (1.6 million LUNG; 1.4 million BREAST; 1.2 million COLORECTAL
- Influence of Geographical area (environmental factors; life style; nutritional factors)
- Influence of Gender (role of hormones, habits)
- Influence of etnia: prostate cancer more frequent in Afro-carribean men; lung and colorectal cancers more frequent in 'white' women, while Multiple Myeloma is more frequent in Afro-carribean women.

Cancer incidence in US is NOT declining when compared to Heart diseases and Stroke



Neoplasia

- **is an abnormal mass of tissue**
- **its growth is uncoordinated with that of normal tissues**
- **Its growth persists after the cessation of initial stimulus**
- **loss of responsiveness to normal growth controls**
- **NOT SIMPLY hyperplasia, metaplasia and dysplasia.**

WHAT IS CANCER

- HYPERPLASIA
- DYSPLASIA
- ANAPLASIA
- METAPLASIA

and more…

- INVASIVE GROWTH
- RESISTANCE TO CELL DEATH
- CACHEXIA

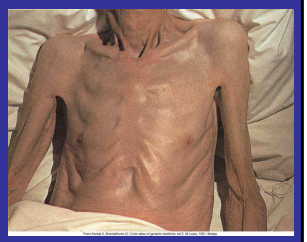
Clinical manifestations of Cancer

Fatigue
sleep disturbances
biochemical changes
loss of muscle function
malnutrition

(bone marrow alterations):
Anemia
Laeukopenia
Thrombocytopenia (chronic bleeding)
Lymphopenia (infection susceptibility)

Clinical Features of Malignancy

- **Cachexia**
  - Decreased body fat, weight loss, early satiety, anorexia, taste alterations
  - marked weakness, fatigue, anemia
  - persistent febricula (T= 38°C)
  - Increased infections
  - increased metabolic rate
  - Correlates with size and spread of tumuor



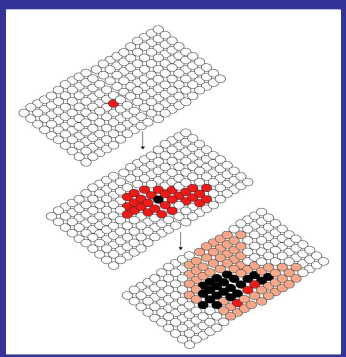
Clinical Features of Malignancy

- **Paraneoplastic Syndromes**
  - 10-15% of cancer patients
  - Symptoms that can't be explained by spread of the tumor or by indigenous hormones
    - Endocrinopathies (Hypercalcemia, secretion of ADH, etc)
    - Nerve and muscle disorders
    - Vascular and hematologic changes (thrombosis)

WHAT CAUSES CANCER ?

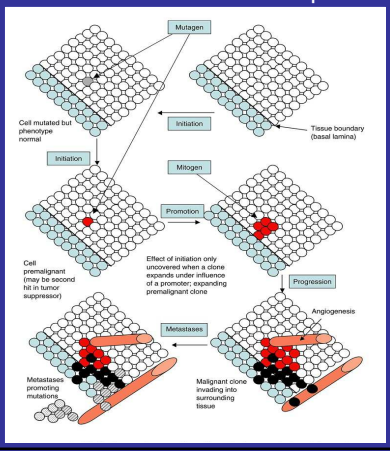
- Cancer arises from mutational expression of key genes regulating cell proliferation, cell death, cell differentiation, cell metabolism, cell adhesion, cell migration.
- Altered expression of these genes occurs as a consequence of GENETIC and/or EPIGENETIC events.
- MUTATIONS and EPIMUTATIONS may occur in differentiated ADULT (somatic) cells or in undifferentiated CANCER STEM cells.

CANCER is a CLONAL disease



Cancer begins as a 'mono-clonal' and then progresses to become a 'poly-clonal' disease through accumulation of new / random genetic and epigenetic alterations.

CARCINOGENESIS is a Multistep PROCESS

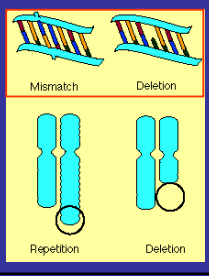


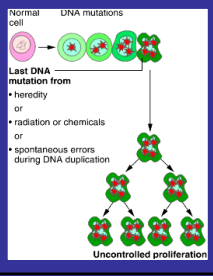
Cellular and Molecular Mechanisms in Multistage Carcinogenesis: INITIATION

Initiating event involves cellular genome – MUTATIONS

Target genes:
- oncogenes/tumor suppressor genes
- signal transduction
- cell cycle/apoptosis regulators

"Simple" genetic changes





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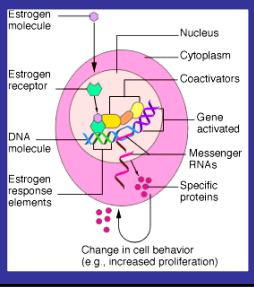
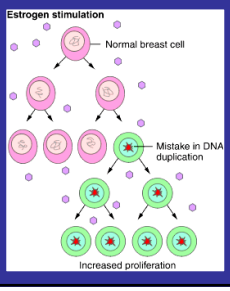
Cellular and Molecular Mechanisms in Multistage Carcinogenesis: PROMOTION

Reversible enhancement/repression of gene expression:
- increased cell proliferation
- inhibition of apoptosis

No direct structural alteration in DNA by agent or its metabolites





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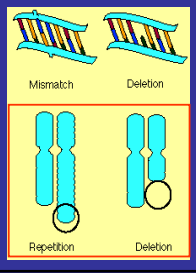
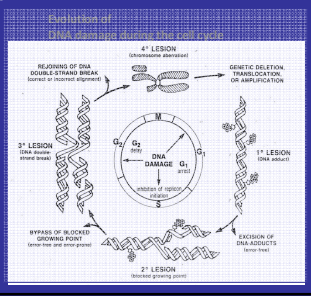
Cellular and Molecular Mechanisms in Multistage Carcinogenesis: PROGRESSION

- Irreversible enhancement/repression of gene expression
- Complex genetic alterations (chromosomal translocations, deletions, gene amplifications, recombinations, etc.)
- Selection of neoplastic cells for optimal growth genotype/phenotype in response to the cellular environment

"Complex" genetic changes





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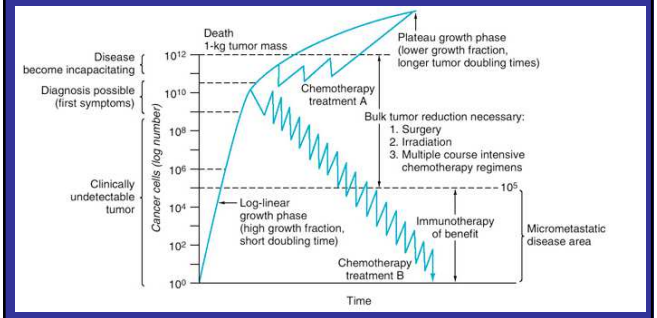
- CANCER CELL TRANSFORMATION is (theoretically) a 'relatively' HIGH probable event;
- Yet, in terms of diagnosed and symptomatic disease, CANCER is RARE, VERY RARE !
- In fact: consider that at autopsy is frequent to detect cancers (mostly thyroid cancers) which were asymptomatic and undiagnosed during the lifetime

At cellular level, CANCER is VERY RARE

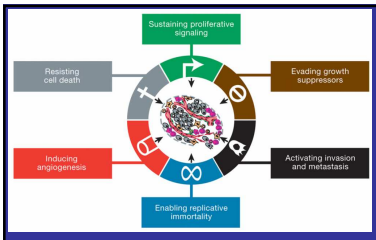
- A human adult is made up of approx 10 (to 14) cells (theoretically, each could become 'cancer'; however only replicating cells are susceptible to introduce DNA errors and can 'fix' and transmit to the progenie the genetic and epigenetic alterations)
- > 10 (to 11) cells die every day and are substituted through replication of existing cells or differentiation of stem cells.
- cancer is diagnosed in 1/3 of individuals and occurs mainly at the age >60 years : despite the high potential of introducing gene mutations in so many dividing cells and for such a long time ! (this implies the existence of BARRIERS that include: DNA repair, oncosuppressors, immune response)

Tumor growth kinetics



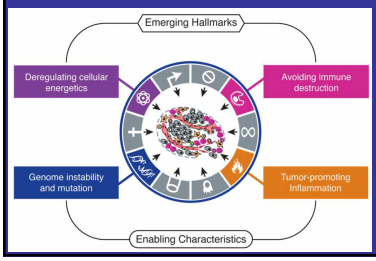
The role of cancer-stroma cell interplay

- Considering that any of the 10(to14) cell could theoretically be transformed and give rise to a Cancer, considering the so many tissues and organs present in a human adult, it is surprising that of the >200 different types of cancers recognized, the most common ones (accounting altogether for > 50% of the new cases) are essentially five: Lung, Breast, Colorectal, Prostate and Non-Melanoma skin cancers !
- (in children, Laeukemia is the most frequent cancer)
- Also metastases do not involve indiscriminately any of the potential organs traversed by the cancer cells (Seed and Soil Theory)



HALLMARKS OF CANCER

1. Sustaining proliferative signaling
2. Evading growth suppressors
3. Resisting cell death
4. Enabling replicative immortality
5. Inducing aberrant angiogenesis
6. Activating invasion & metastasis



Emerging Hallmarks

- Reprogramming energy metabolism
- Evading immune destruction

Enabling Characteristics

- Genomic instability and mutation
- Inflammation

Hanahan and Weinberg 2011 (Cell)