Molecular basis of oncogenesis

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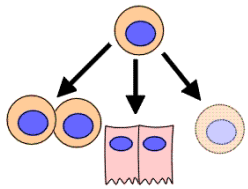
Cancer Biology : definition

Somatic cell fates :

Division in 2 identical sister-cells = self-renewal



Cellular programmed death = apoptosis

Division and cellular differentiation = acquisition of specialised functions

Cancer :

- disruption of the cellular homeostasis
  Imbalance between proliferation / differentiation / apoptosis

- monoclonal proliferation
  Abnormal proliferation of cells originating from a same ancestral cell

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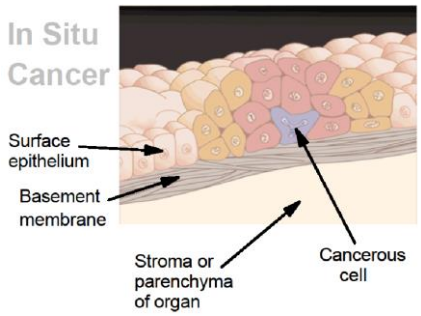
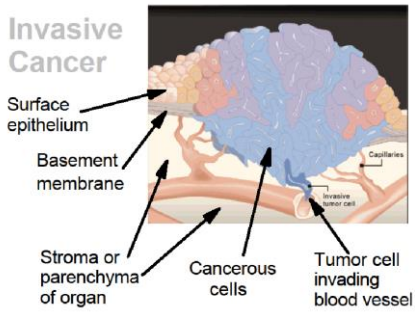
Cancer Biology : multi-step process

Normal tissue → in situ tumor → locally invasive cancer → metastases





Malignant tumors = capable of invading neighboring tissues
and/or spreading to more distant sites (metastasizing)

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Cancer : heterogeneous disease

- 3 main forms of cancer according to the cell of origin :
  - Carcinomas : tumor arising in epithelial tissue *80-90%*
    - Intestine, bronchi, mammary ducts, epiderma,…
  - Sarcomas : tumor arising in mesenchymal tissue
    - tumor derived from muscle, bone, cartilage, fat or connective tissues,…
  - Hematological malignancies :
    - Leukemia : derived from bone marrow hematopoïetic precursors
    - Lymphoma : derived from lymphocytes responsible for the immune response

- Classification within each major group :
  - By site, tissue type, histological appearance, biological characteristics, degree of malignancy,…

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Genetic basis of oncogenesis

1. Tumorigenic retrovirus
2. Transfection of tumoral DNA
3. Cytogenetics
4. Inherited cancers

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Tumorigenic retrovirus

- *1900 : "filtrable" agents may induce chicken tumors*
  - *discovery of the Sarcoma Roux virus*
- *1970 : transforming properties of viral DNA (v-SRC)*
- *1976 : Nobel Prize Varmus & Bishop (Stehelin)*
- Retrovirus : may induce cellular transformation
  - Sarcoma Rous virus → Sarcoma (chicken)
  - Abelson murine leukemia virus → Sarcoma, Leukemia (mouse, cat)
- Isolation of viral oncogenes v-SRC, v-ABL,…
- v-SRC, v-ABL derived from host cellular sequences (SRC, ABL)
- Viral **oncogenes** have cellular normal counterpart named cellular **proto-oncogenes**, which may become tumorigenic when mutated
- Oncogenes induce dysregulation of normal cellular functions

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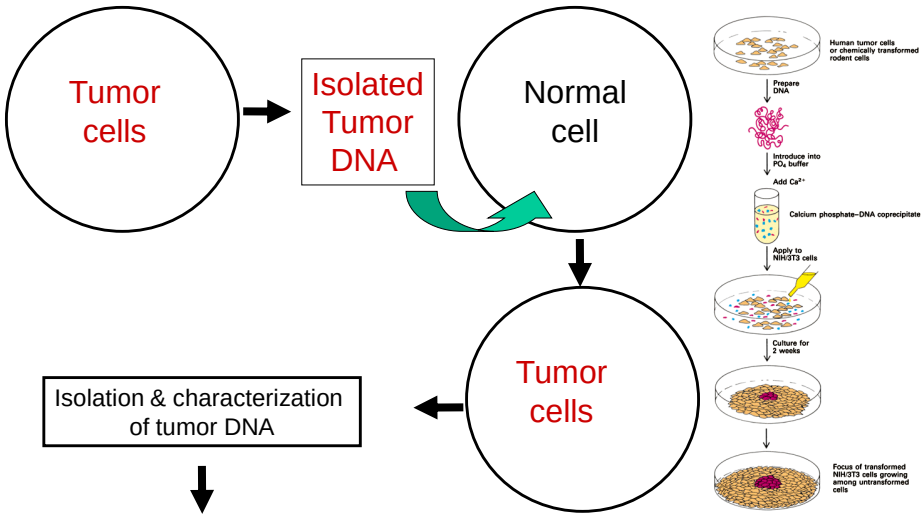
Tumor phenotype transfer to normal cells due to DNA transfection



Identification of activated oncogenes in human tumor
(*RAS* family : *HRAS, KRAS, NRAS*)

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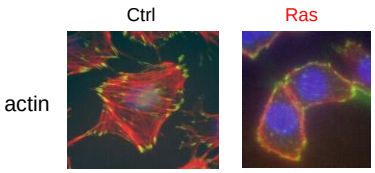
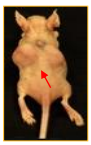
Activation of the *RAS* oncogenes involved in multiple cellular processes

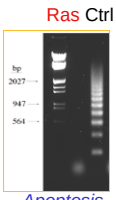
- *RAS* mutations in 15-20% of human tumors
  50% colorectal cancer
  95% pancreatic cancer



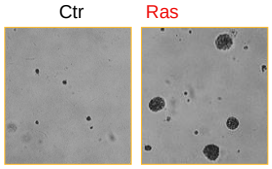
actin depolymerization
Cytoskeleton



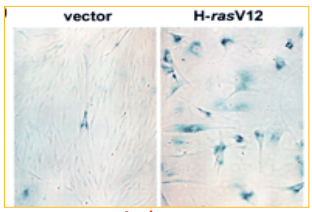
Tumor induction
Proliferation



Apoptosis
Survival



Anchorage-independent Growth
Adhesion



Aging

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Genetic basis of oncogenesis (3)

Chromosome rearrangements

- 1890: nuclear and mitotic alterations in cancer cells (Von Henseman)
- 1914: assumption that clonal chromosomal anomalies induce cellular malignant transformation (Boveri)
- 1956: human chromosome number (Tijo & Levan)
- 1960: marker chromosome – Philadelphia - in chronic myeloid leukemia – CML- (Nowell & Hungerford)
- 1970: chromosome bands (Caspersson)
- 1970-…: discovery of multiple recurrent cytogenetic alterations, correlations between karyotypic aberrations, diagnosis and prognosis
- 1975-…: expansion of molecular biology, cloning of involved genes, functional studies (genes, proteins)
- 1990-…: therapeutic applications
- 2001: human genome cartography

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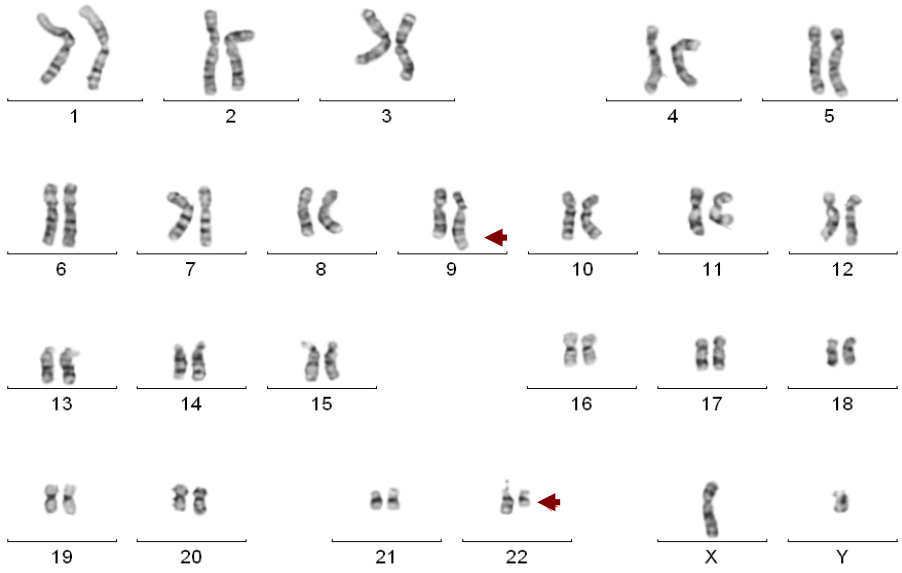
Translocation leading to a chimeric gene
t(9;22)(q34;q11) in CML



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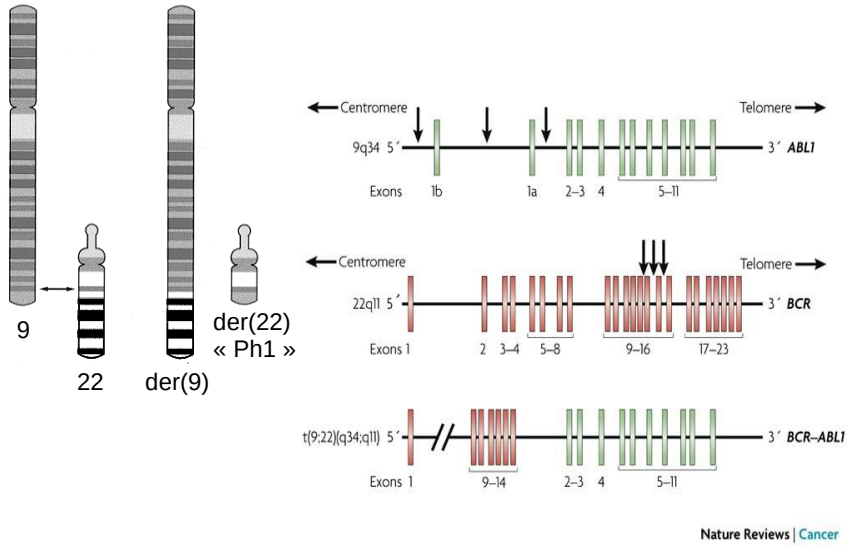

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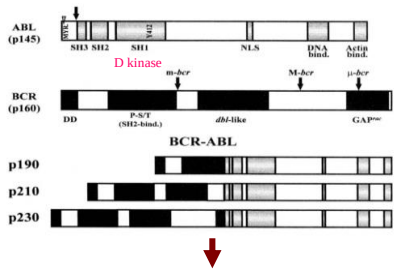
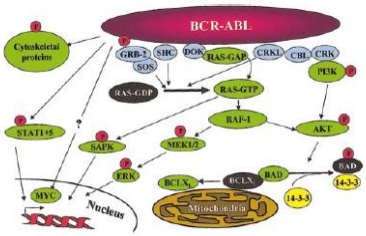
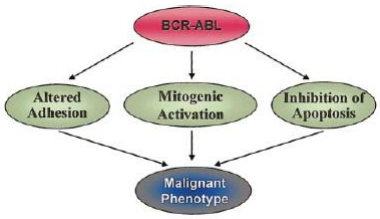


Constitutive activation of a chimeric tyrosine kinase





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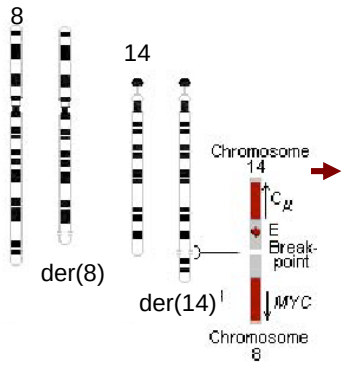
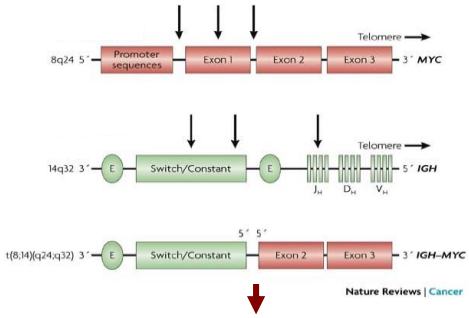
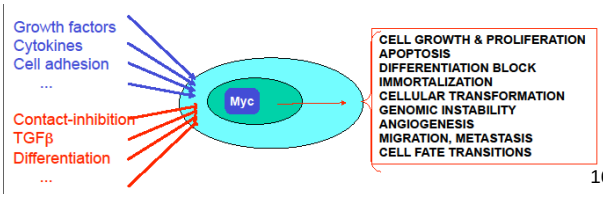
Translocation leading to upregulation t(8;14)(q24;q32) in Burkitt lymphoma





Constitutive activation of a normal MYC protein driven by immunoglobulin enhancers



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Inherited cancers

- Most cancers sporadic
- +/- 5% of all cancers inherited
- Autosomal dominant inheritance

- Positional cloning (80's-90's) :
  - identification of new cancer genes
  - usually, loss of function mutations
    - recessive
    - (dominant negative)
  - 2 types of tumor suppressor genes :
    - "Gatekeeper" = Cell control *(TP53, RB) = tumor suppressor genes*
      - Cell cycle control
      - Programmed cell death
    - "Care-taker" = Genome stability *(ATM, MMR complex)*
      - DNA repair
      - Carcinogen metabolism

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Gatekeeper gene : Retinoblastoma

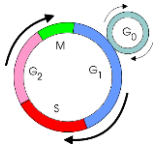
Sporadic retinoblastoma	Inherited retinoblastoma (30%)
Unilateral tumor	Bilateral tumor
Single tumor	Multiple tumors
Late-onset	Early-onset
	Inherited as a dominant trait
	High penetrance

1983 : 13q14 loss of heterozygosity
1986 : RB gene
Bi-allelic inactivation of RB gene

2 somatic mutations

1 germline predisposing mutation
1 somatic mutation (risk : x1000)

RB = gatekeeper tumor suppressor gene which controls the G1-S checkpoint
Loss of RB : uncontrolled proliferation



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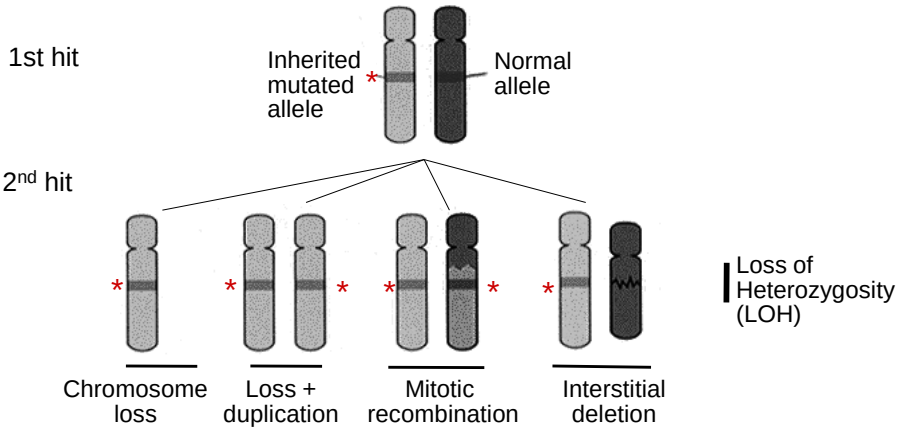
Tumor suppressor genes
Two-hit Knudson model (1971)



- Germline mutation → cancer predisposition (autosomal dominant inheritance)
- Second somatic mutation → tumor development

- Theory expanded to sporadic cancer : 2 somatic mutations

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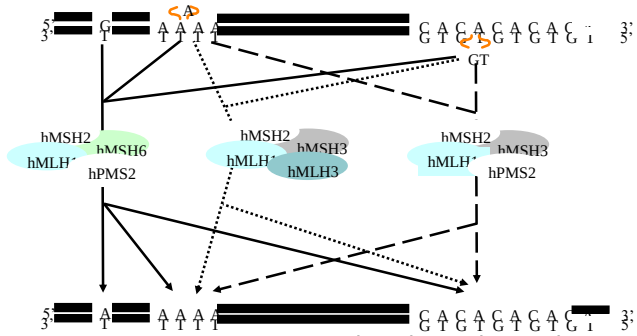
Caretaker gene : MMR

- Hereditary nonpolyposis colon cancer (HNPCC)
- High increase in
  - point mutations
  - instability of repeated nucleotidic sequences
- Mutations in genes responsible for DNA repair



The Mismatch Repair System in human

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Main genes involved in inherited cancers

Cancer	Gene	Type of gene
Familial adenomatous polyposis	*APC*	Gatekeeper
Li-Fraumeni syndrome	*TP53*	Gatekeeper
Retinoblastoma	*RB*	Gatekeeper
Wilms tumor	*WT1*	Gatekeeper
Ataxia telengiectasia	*ATM*	Caretaker
Fanconi anemia	*FCA complex*	Caretaker
Xeroderma pigmentosum	*ERCC complex*	Caretaker
HNPCC	*MLH1, MSH2, MSH6, PMS1, PMS2*	Caretaker
Breast cancer (familial form)	*BRCA1, BRCA2, PALB2*	Caretaker
Multiple endocrine neoplasia	*RET*	Oncogene
Papillary renal cancer	*MET*	Oncogene
GIST	*KIT*	Oncogene

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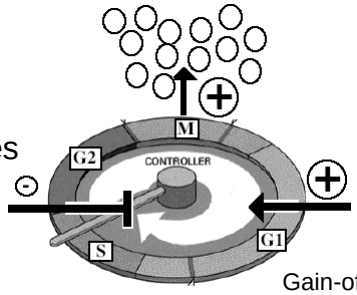
2 categories of genes involved in cancer



Tumor suppressor genes

Oncogenes

Loss-of-function mutation

Recessive effect

Gain-of-function mutation

Dominant effect

Gatekeepers	Caretakers
→ directly regulate cellular checkpoints	→ maintain genome integrity
e.g. : RB, TP53	e.g. : MMR complex, ATM

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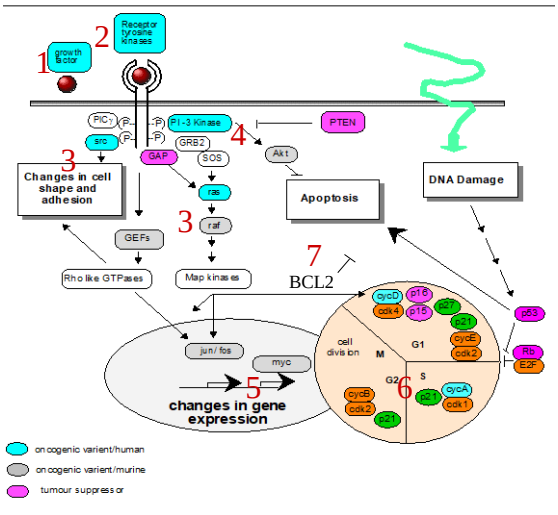
Alteration of master genes for cellular homeostasis

1. Growth factors (GF) and cytokines
2. GF receptors
3. (Sub-)membrane proteins
4. Cytosolic / sub-membrane kinase proteins
5. Nuclear transcription factors
6. Cellular cycle regulator proteins
7. Apoptosis regulator proteins



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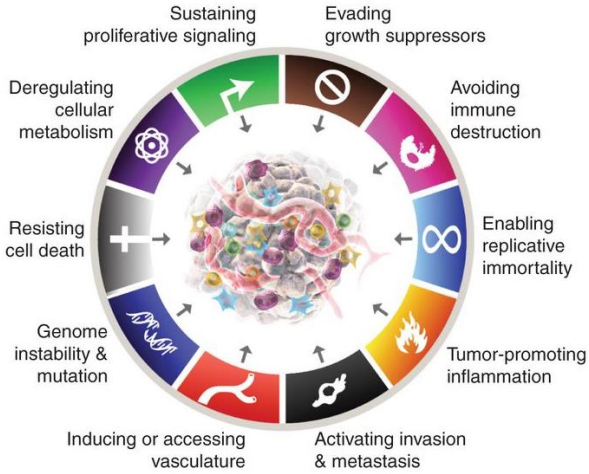
Cancer Biology : Multistep tumorigenesis
Not always in the same order



Hanahan D, Cancer Discovery 2022 25

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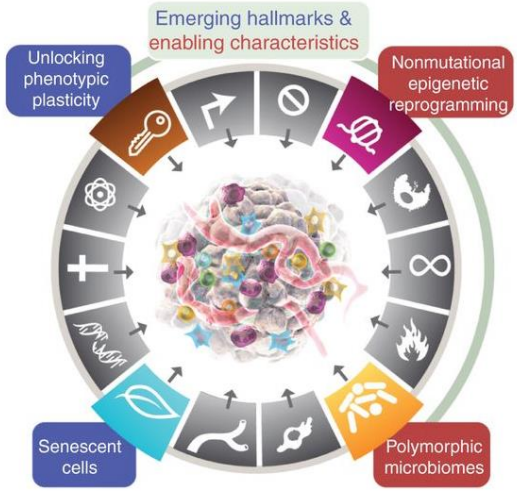

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Mutations of these genes :
tumor initiation and progression

- Usually mutation on a single somatic cell
  - that then divides into daughter cells
  - present only in the tumoral cells
  - * monoclonality (subclonal)
  - * acquired mutation
- More rarely inherited mutation through germline
  - present in every cell of the body

→ Strong positive selection for cell proliferation and survival caused by the mutations

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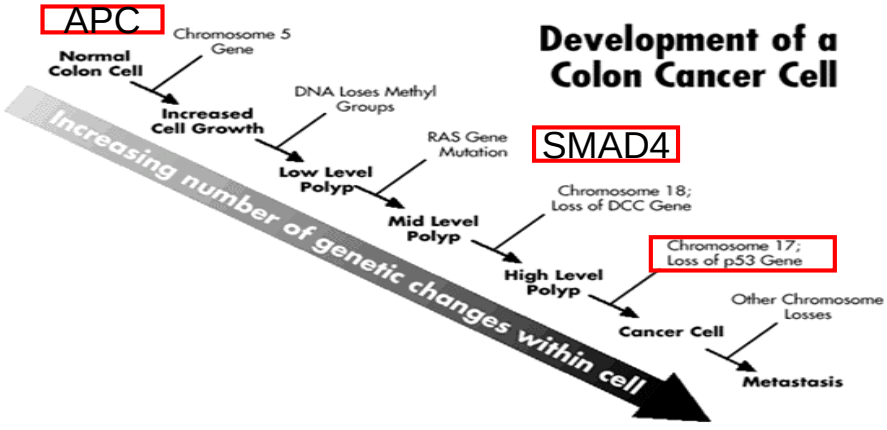
Multistep genetic defects

- Accumulation of synergistic genetic damages through mutation in master genes



http://medic.med.uth.tmc.edu/edprog/Path/Neo1/neo-24.jpg

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Cancer and the environment

- The risk of cancer varies
  - Among different populations
  - In different environments within the same population
- Exposure to mutagens and carcinogens in the environment → somatic mutations → carcinogenesis
  - Radiation
    - Ionizing radiation
    - UV
  - Chemical Carcinogens
    - Tobacco
    - Benzene
    - Components of the diet
    - Role of drug-metabolizing enzymes
  - Infectious agents
    - EBV, HTLV-I, HBV...

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