Molecular Biology of Cancer Introduction



Carcinogenesis

Nonlethal genetic damage + Clonal expansion

Involved gene classes

- Oncogenes
- Tumor suppressors
- Genes regulating apoptosis
- DNA repair genes

Carcinogenesis is a multistep process

Definitions

Oncogene

- Mutation/over-expression of a proto-oncogene
 - Transcription factors
 - Growth regulation
 - Cell survival
 - Cell-cell-matrix interactions
- Cellular transformation
- Dominant (one damaged allele enough)

Tumor suppressor gene

- Mutation = uncontrolled growth/transformation
- Both alleles/LOH/haploinsufficiency
- Governors (growth control e.g. RB)
- Guardians (sensing DNA damage e.g. *TP53) mutator phenotype*

Genetic Lesions in Cancer



Balanced Translocations

Proto-oncogene activation by:

- 1. Over-expression - t(8;14) *MYC* - t(14;18) *BCL2*
- 2. Fusion products

 t(9;22) BCR-ABL
 t(11;22) EWS-Fli-1
 TMPRSS-ETS*

 from deletion on chr. 21 or translocation





Deletions

2nd most prevalent karyotypic abnormality

Karyotypic deletions are more common in nonhematopoietic solid tumors

- 13q14 deletions (RB)
- 17p deletions (TP53)
- 21q deletions



Gene amplifications

Proto-oncogene activation by overexpression

- *NMYC* neuroblastomas 25-30% poor prognosis
- ERBB2 (HER2/NEU)
 breast cancer
 20%
 α-ERBB2 antibody Tx





Aneuploidy

Chromosomal number not a multiple of the haploid state

Human haploid number 23

Frequently due to abnormal mitotic checkpoint

Cause vs consequence?

miRNA





miRNA

In cancer:

↑ oncogene expression↓ tumor suppressor

BCL2: Leukemia/Lymphoma

RAS: Lung

MYC: B cell leukemia

Epigenetic Changes in Cancer

Epigenetics





Cancer epigenetics

Global DNA hypomethylation

Selective promoter hypermethylation (e.g. tumor suppressor genes)



Epigenetic context

Same genetic material - wildly different cell types

Cellular epigenetic context (e.g. *NOTCH1*)

Molecular Biology of Cancer Initiation & Progression

Carcinogenesis is a multistep process

