Molekular tumor biology 3.
The genetic background of cancer

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(based on lectures of András Matolcsy, SOTE)

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22 March 2018.

Introduction

- **Proto-oncogenes**:
  - Involved in the signalling pathways of **cell division, cell growth:** stimulatory action
  - **Mutation or increased expression** → transformed to **oncogenes** → **oncogenesis (tumorigenic transformation)**
- **Tumor suppressor genes**:
  - Main **functions**:
    - Cell division, DNA replication: inhibitory action
    - Stimulating cell differentiation
    - Inducing apoptosis
  - **Mutation or decreased expression → inactivation** → lack of protective action against cancer

Introduction

- Genetic defects in tumor cells
  - In onkogens/tumorsupressor gens - qualitative
    → **mutation**
  - In their regulatory system - quantitative
    → **changes in expression**

Introduction

- Genetic defects
    1. Translocation
    2. Chromosomal imbalance
    3. Point mutations
    4. Genetic instability
    5. Hereditary genetic defects
    6. Mikro-RNA differences
    7. Epigenetic effects

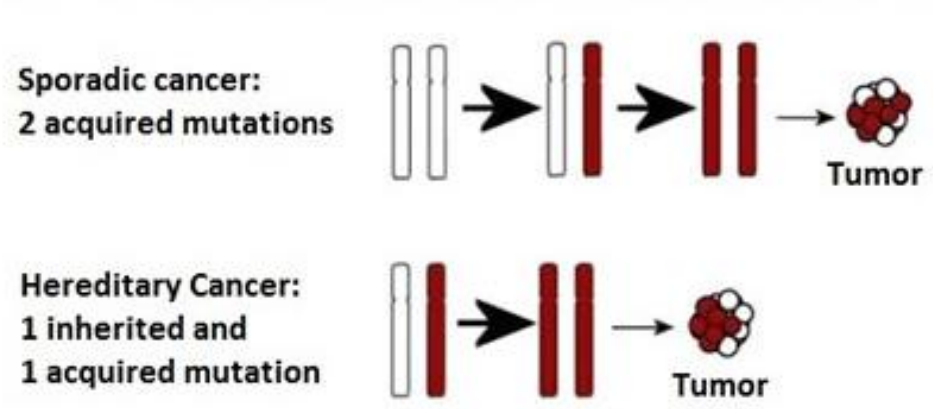
Introduction

- Genetic defects can participate in
  - The develop of tumors
  - The progression of tumors

- It is important to know them
  - Diagnostics
  - Prognosis
  - Therapeutic target

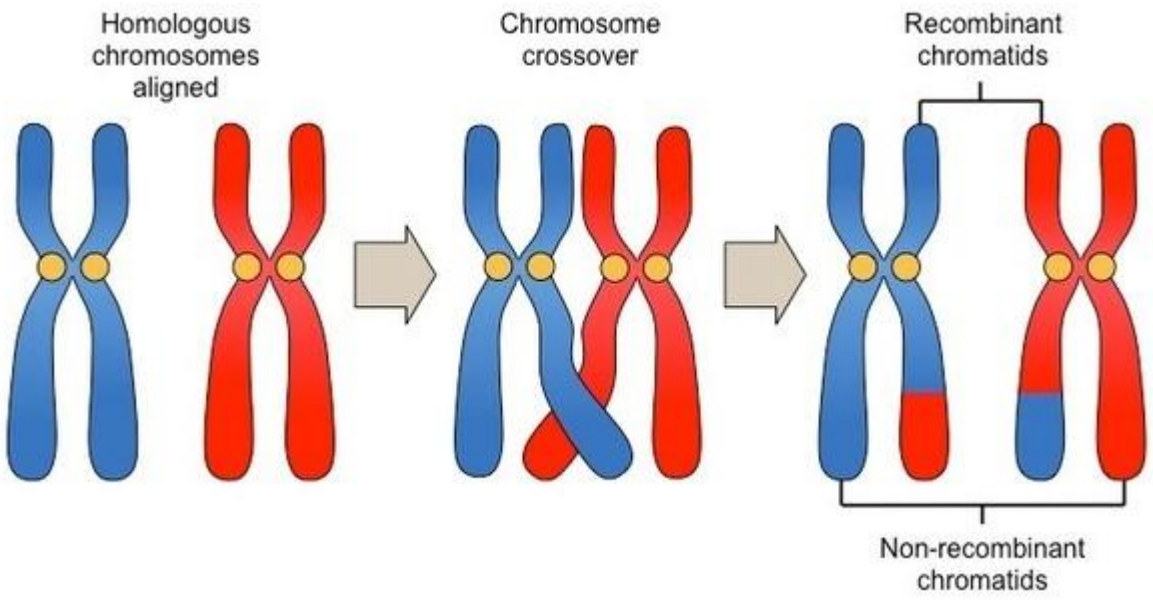
Knudson's two hit hypothesis

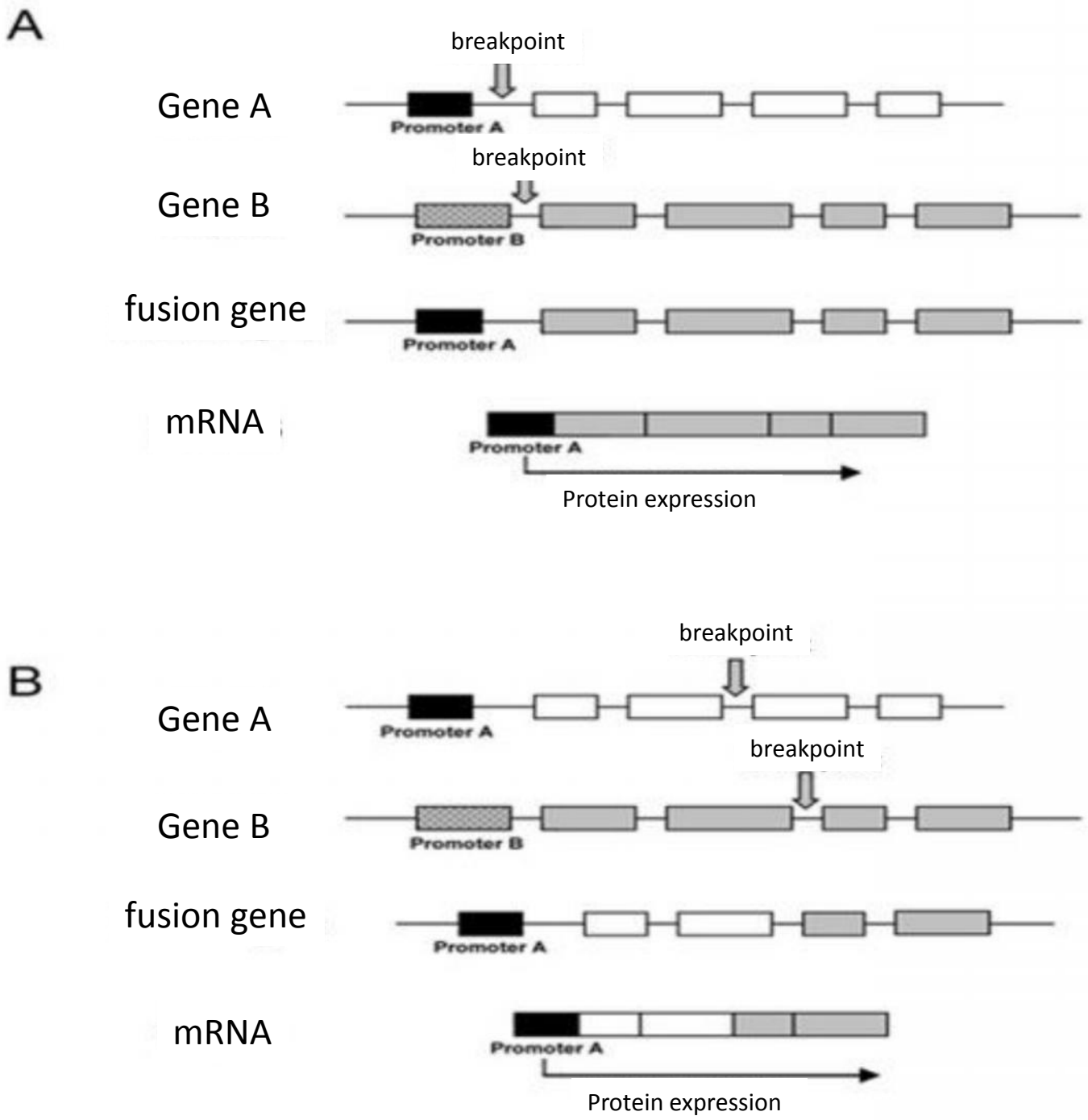
- Genes have two allels
- Both of them have to be defective for malignus transformation
  (The defects may have different origin)
- Somatic mutation: sporadic cancer
- Germ cell mutation : hereditary cancer



1, Translocation

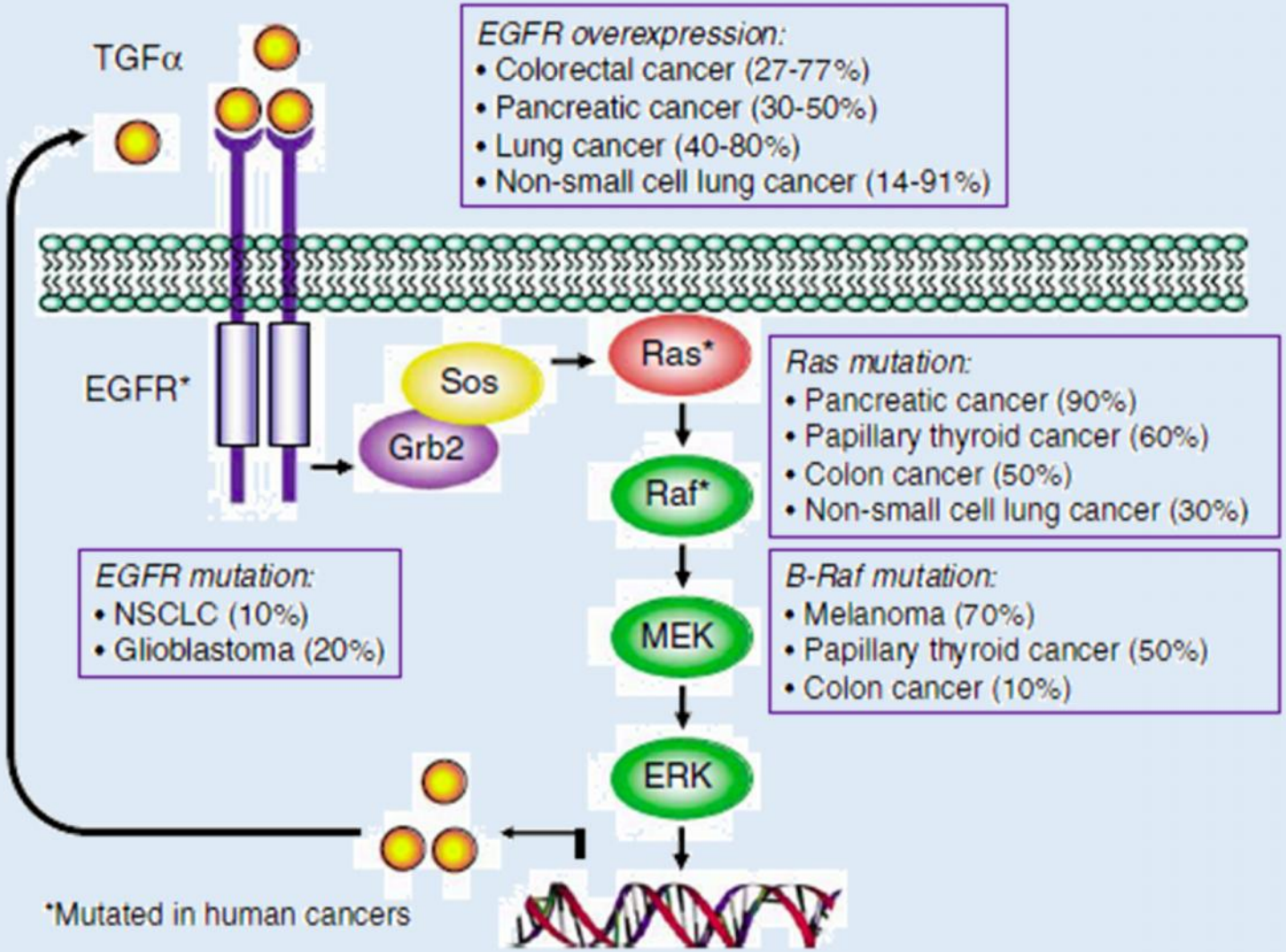
- The whole gene migrates in the genome
- Mainly the activation of oncogens
- A, to the promoter of the gene
- B, incorporated in another protein gene → chimeric genes




A
breakpoint
Gene A
Promoter A
breakpoint
Gene B
Promoter B
fusion gene
Promoter A
mRNA
Promoter A
Protein expression
B
breakpoint
Gene A
Promoter A
breakpoint
Gene B
Promoter B
fusion gene
Promoter A
mRNA
Promoter A
Protein expression

Transzlokáció	Fúziosgén	Daganat
Deregulation of genes with normalstructure (promoter switch)		
t(14;18)(q32;q21)	BCL2/IgH	Follicularis lymphoma
t(8;14)(q24;q32)	IgH/c-MYC	Burkitt lymphoma
t(11;14)(q13;q32.33)	CCND1/IgH	Köpenysejtes lymphoma
t(12;13)(p13;q12.3)	ETX6/CDX2	Akut myeloid leukaemnia
Fusion chimeric genes With Tirozin kinase activity		
t(2;5)(p23;q35)	NPH1/ALK	Anapláziás nagysejtes lymphoma
t(9;22)(q34;q11)	BCR/ABL	Krónikus myeloid leukaemia
inv(2)(p21;p22p23)	EML4/ALK	Nem-kissejtes tüdőcarcinoma
inv(10)(q11.2;q112.2)	RET/NCOA4	Papillaris pajzsmirigycarcinoma
With Transcriptional factor activity		
t(15;17)(q22;q21)	PML/RARA	Akut prolyelocytás leukaemia
t(8;21)(q22;q22)	RUNX1/RUNX1T1	Akut myeloid leukemia
t(12;21)(p13;q22)	ETV6/RUNX1	Gyermekkori akut lymphoblastos leukemia
t(2;3)(q13;p25)	PAX8/PPARG	Follicularis pajzsmirigy carcinoma
t(11;22)(q24;q21)	EWSR1/FLI1	Ewing sarcoma

The role of the Ras / MAP kinase cascade in the oncogenesis



Roberts and Der (2009): Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene, 26, 3291-3310.

2, Chromosomal imbalance

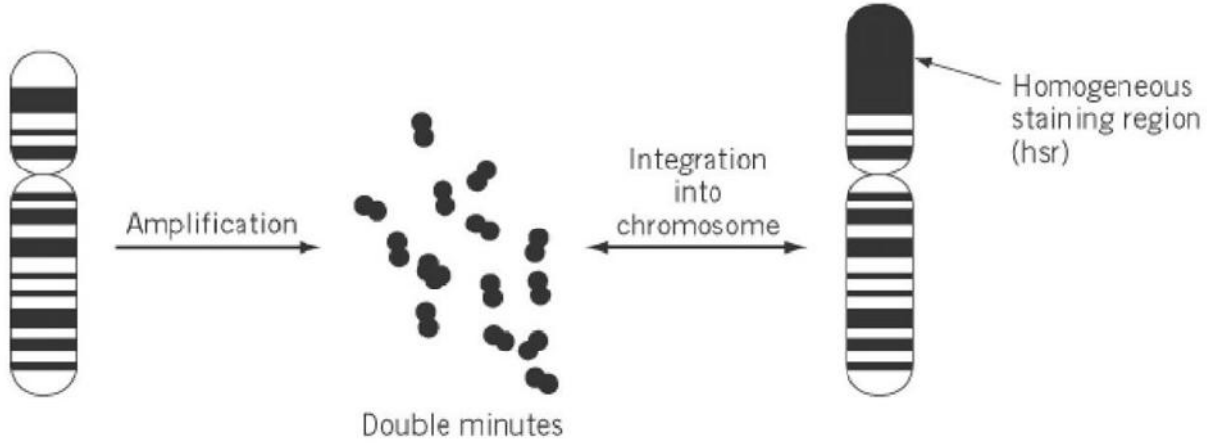
- Amplification or deletion of chromosome segments of different sizes

- Oncogene – amplification
- Tumor supressor gene – deletion
- Regulatory function (eg micRNA)

2, Chromosomal imbalance

<u>Amplification</u> (up to 100x copy)

- Proto-oncogenes become oncogenes
- It plays a role in tumor progression
- It can be chromosomal or extrachromosomal (double minutes)



Kromoszóma	Gén	Tumor
Unknown genes		
+ 7	?	Astrocytoma, glioblastoma
+ 8	?	Akut myeloid leukemia, myelodysplasia
+12	?	Krónikus lymphocytás leukemia
+12p	?	Here germinalis tumorok
+17p	?	Különböző daganatok
Known genes		
amp(1)(32.1)	IKBKE	Emlőcarcinoma
amp(2)(p24.1)	N-MYC	Neuroblastoma
amp(3)(p14.2-p14.1)	MITF	Melanoma
amp(6)(q25.1)	ESR1	Emlőcarcinoma
dup(6)(q22-23)	MYB	Akut lymphoblastos leukaemia, colorectalis carcinoma
amp(8)(q24.21	MYC	Különböző daganatok
amp(11)(q13)	CCND1	Különböző daganatok (emlő, eosophagus, máj)
amp(12)(12.1)	K-RAS	Különböző daganatok
amp(14)(q13)	NKX2-1	Nem-kissejtes tüdőcarcinoma
amp(17)(q21.1)	ERBB2	Különböző daganatok

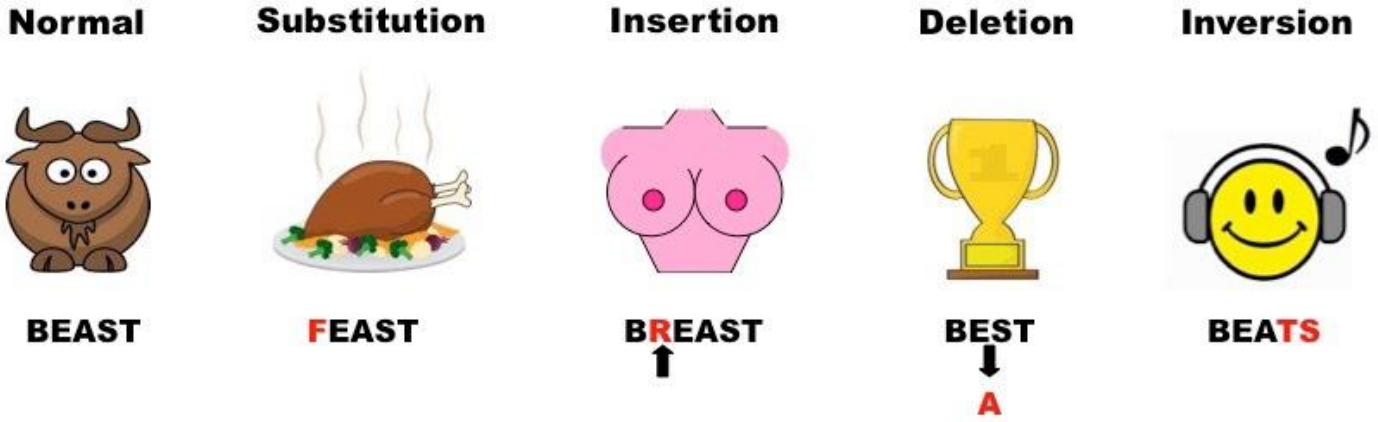
2, Chromosomal imbalance

Deletion

- Losing suppressor genes
  (on one allele – on the other allele could be another mutation)

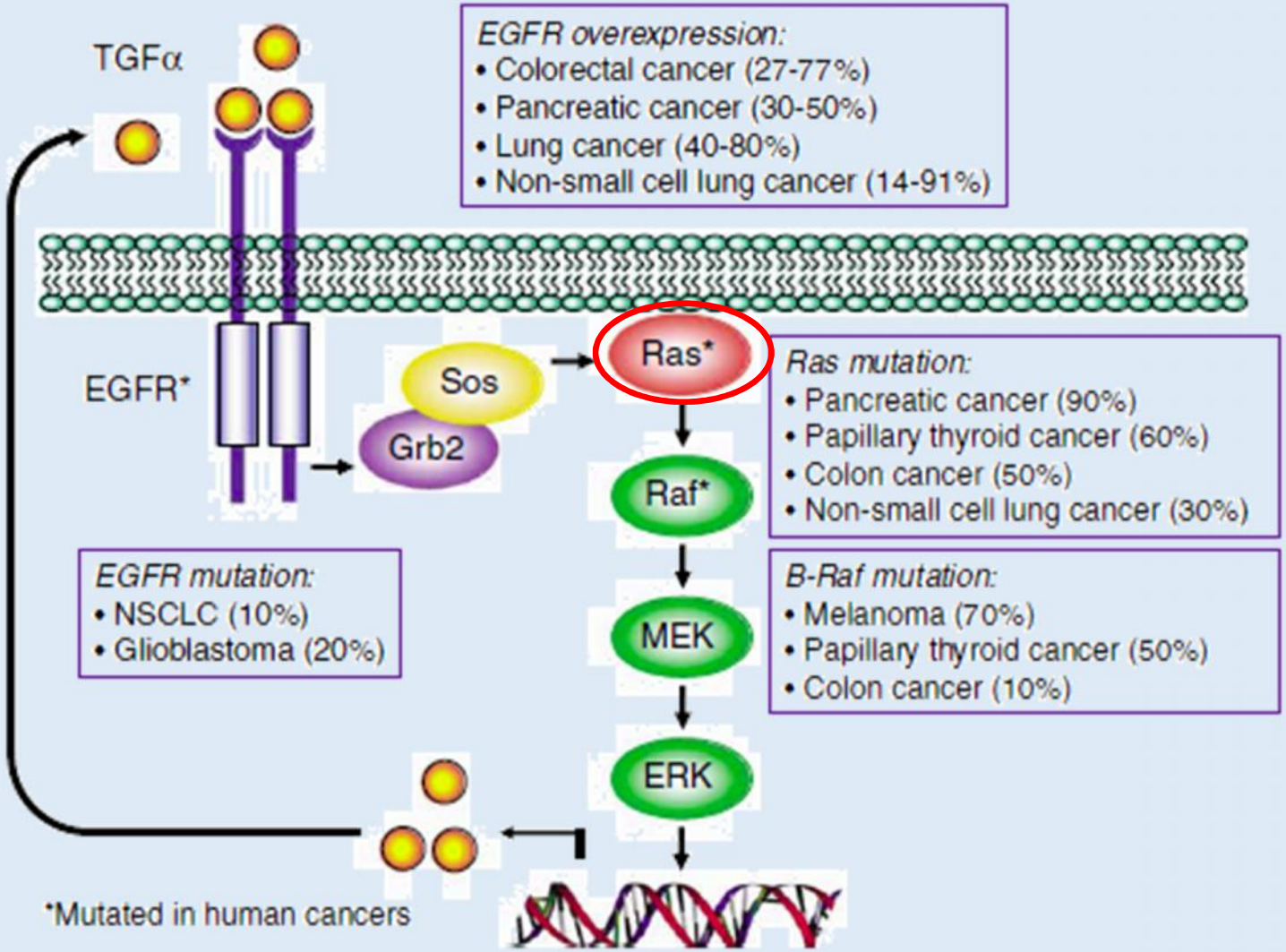
Chromosoma	Gén	Daganat
Unknown genes		
del(1p)	?	Neuroblastoma, oligodendroglioma
del(3p)	?	Különböző daganatok
del(5q)	?	Myelodyslpasia, akut myeloid leukaemia
del(7q)	?	Myelodyslpasia, akut myeloid leukaemia
del(19q)	?	Oligodendroglioma
del(20q)	?	Polycythaemia, myelodysplasia
Known genes		
del(1)(q24)	HPC1	Prostatacarcinoma
del(3)(p26-p25)	VHL	Vesesejtes carcinoma
del(5)(q21-q22)	APC	Colorectalis-, gyomor-, oesophagus-, tüdő-, emlő-, prostata-, ovariumcarcinoma
del(8)(p22)	MSR1	Prostata-, emlőcarcinoma
del (9)(p21-p22)	INK4A	A daganatok ~50%-a; nem-kissejtes, tüdőcarcinoma, melanoma, lymphoma
del(13)(q14.2)	RB	Retinoblastoma, osteosarcoma, tüdő-, eosophagus, prostata-, vese-, cercixcarcinoma
del(17)(p13.1)	TP53	A daganatok ~50%-a; emlő-, colon-, hugyhólyag-, ovarium, vese-, bör-, tüdőcarcinoma
del(17)(q11.2)	NF1	Különböző daganatok
del(X)(11.1)	FAM123B	Wilms tumor

3, Point mutation



- Inactivation of tumor supressor genes
- Activation of oncogenes
  – members od signalling pathways are in a constant active state

The role of the Ras / MAP kinase cascade in the oncogenesis



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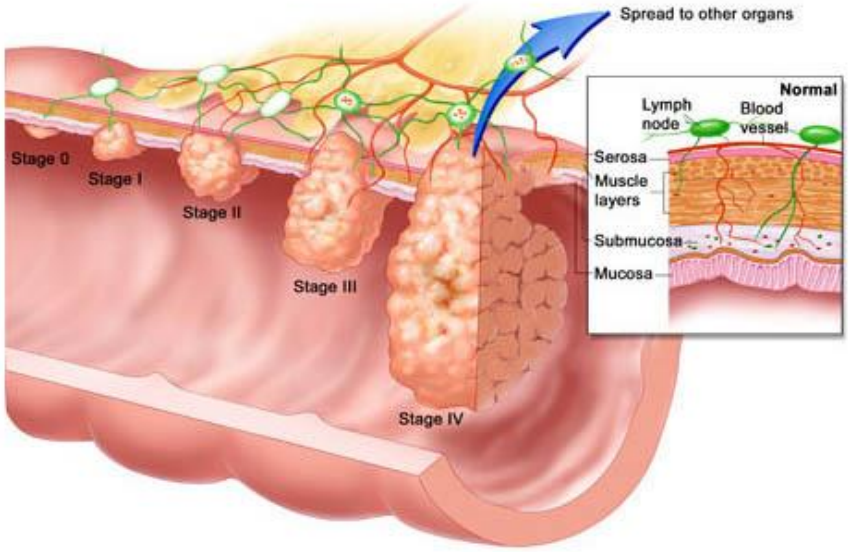
Gén	Daganat
K-RAS	Tüdő-, colon-, pancreas carcinoma
N-RAS	Akut myeloid leukaemia, myelodysplasia
BRAF	Melanoma, colorectalis-, hepatocellularis carcinoma, glioma
JAK-2	Krónikus myeloproliferatív betegségek
EGFR	Tüdőcarcinoma
C-KIT	Gastrointestinalis stromalis tumor, mastocytosis
FLT-3	Akut myeloid leukaemia
RET	Pajzsmirigy carcinoma
NEU	Emlőcarcinoma
ALK	Neuroblastoma

4, Genetic instability

- It affects the whole genome
- Multiplex genetic lesions
- It may also be different in each cell within the tumor
- Types
  - On nucleotide level
  - On chromosome level

4, Genetic instabili

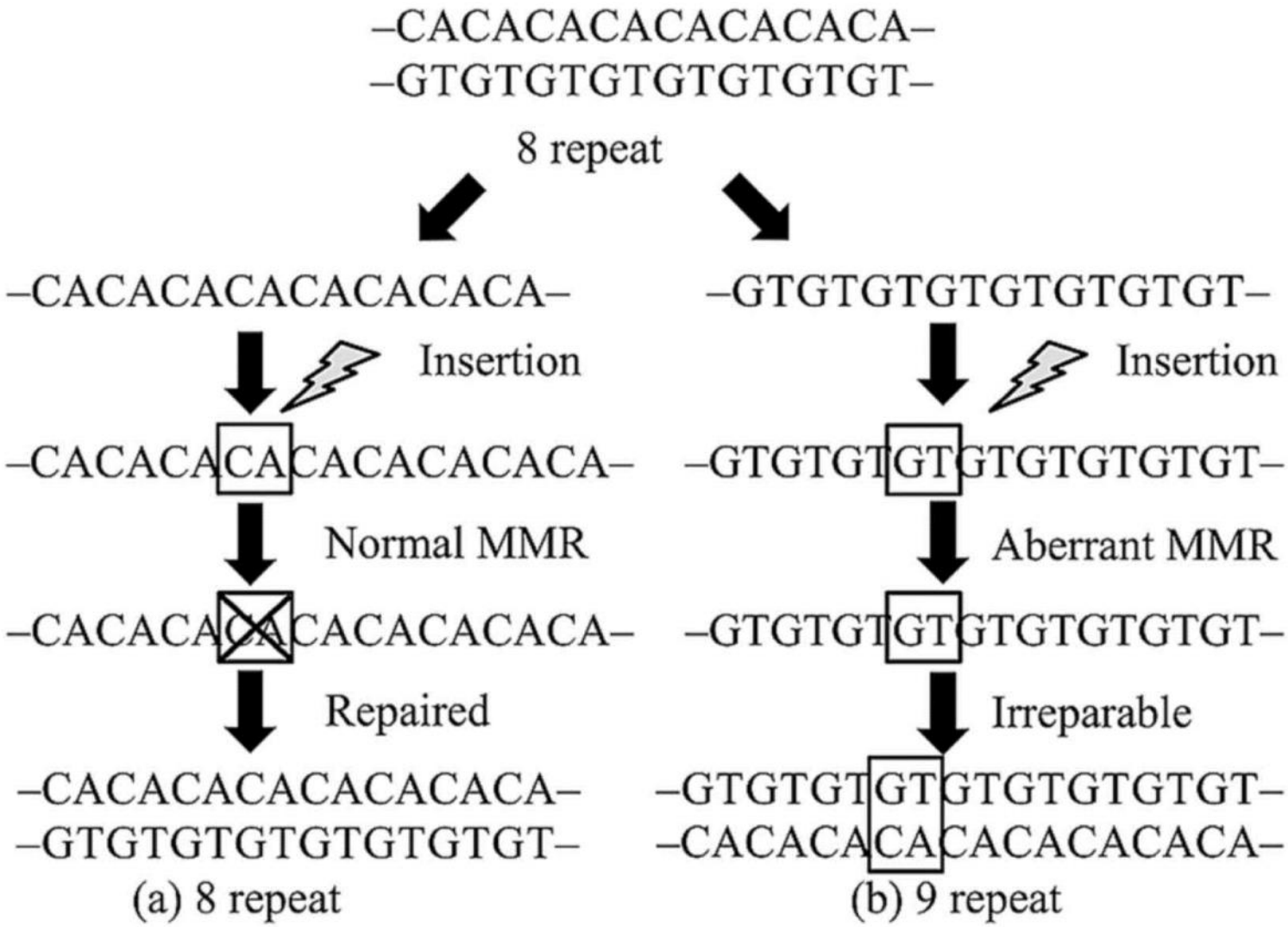


Nucleotide level

- Distuption of the DNA repa

MMR (mismatch repair) system

- repair + inhibits the replication of defective DNA
- Its disorder mainly causes microsatellite instability
- eg.: hereditary nonpolyposis colon carcinomas (HNPCC)


–CACACACACACACACA–
–GTGTGTGTGTGTGTGT–
8 repeat
–CACACACACACACACA–
Insertion
–CACACACACACACACACA–
Normal MMR
–CACACACACACACACACA–
Repaired
–CACACACACACACACA–
–GTGTGTGTGTGTGTGT–
(a) 8 repeat
–GTGTGTGTGTGTGTGT–
Insertion
–GTGTGTGTGTGTGTGTGT–
Aberrant MMR
–GTGTGTGTGTGTGTGTGT–
Irreparable
–GTGTGTGTGTGTGTGTGT–
–CACACACACACACACACA–
(b) 9 repeat