Lecture 23: Cell-Cycle Regulation and the Genetics of Cancer II

Checkpoints and aneuploidy

Phenotypes of cancer cells

Cancer is caused by accumulation of mutations

Oncogenes and tumor suppressors

Read: 627-639

Fig: 18.16-18.24

Table: 18.3, 19.4

Three classes of error lead to aneuploidy in tumor cells

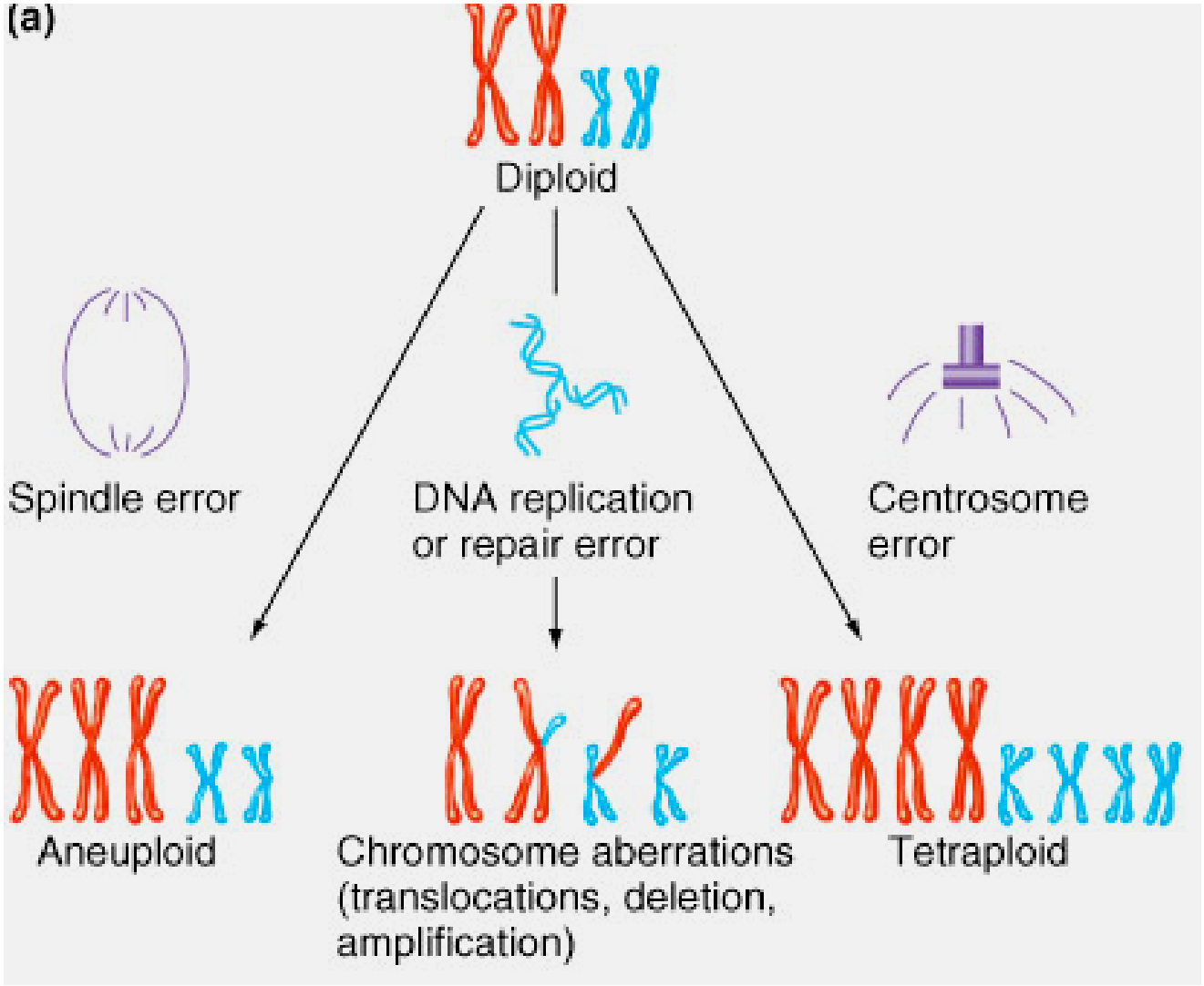
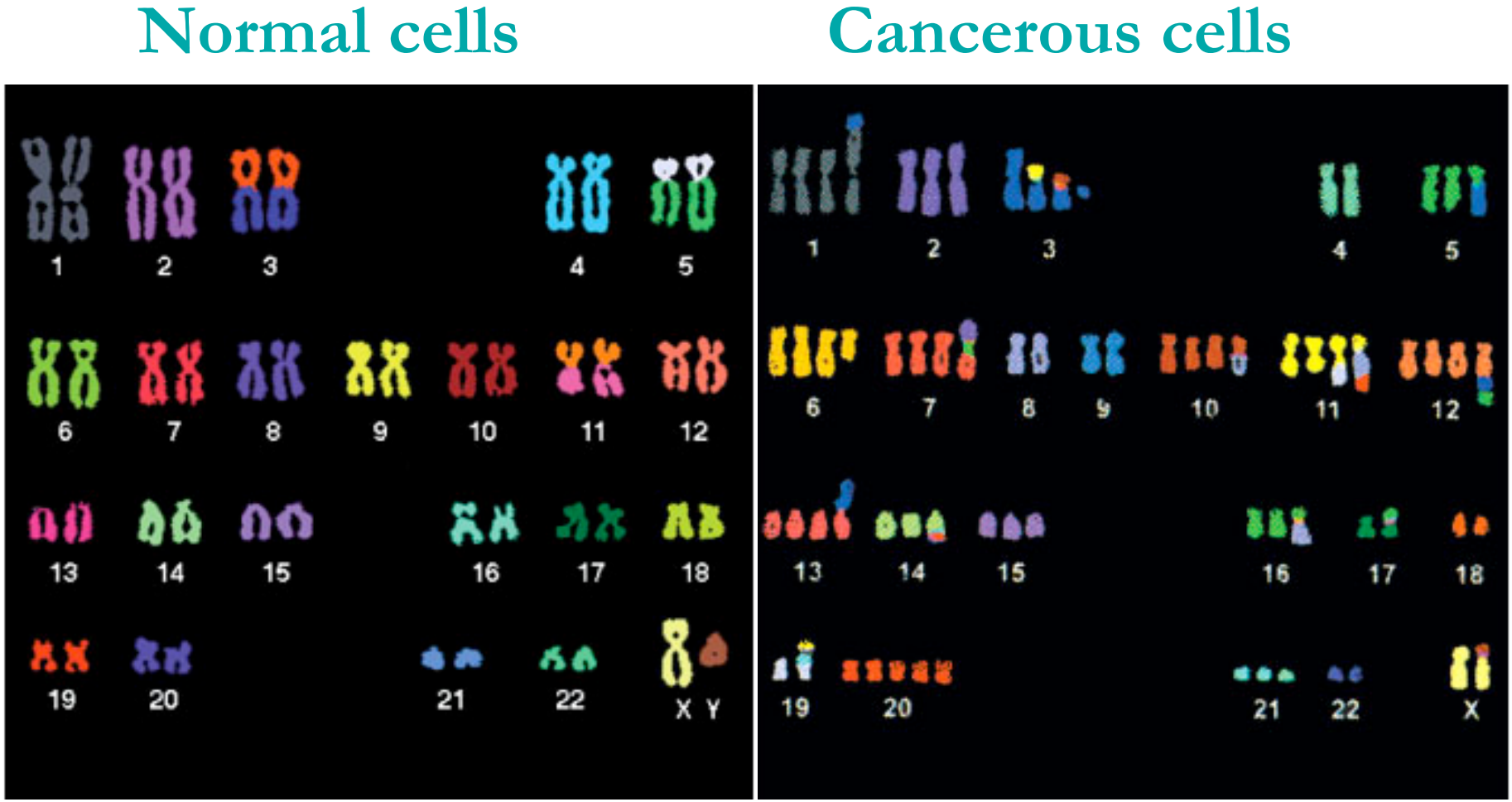


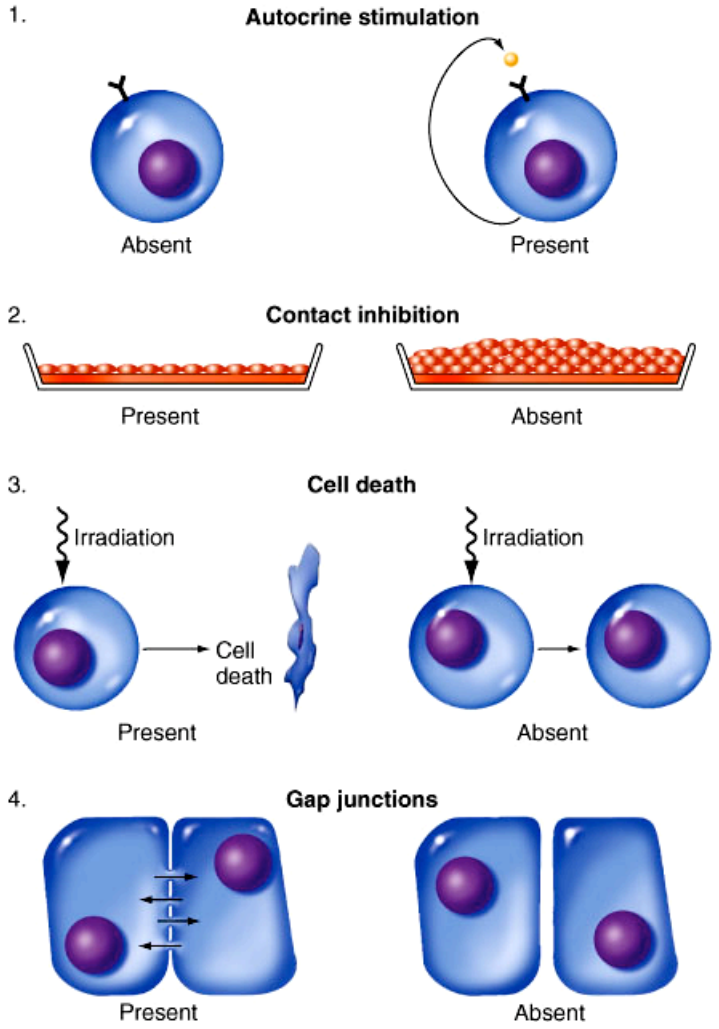
Fig. 18.13a

Fig. 18.13 b



Chromosome painting (multiplex-FISH or multi-color FISH or M-FISH)

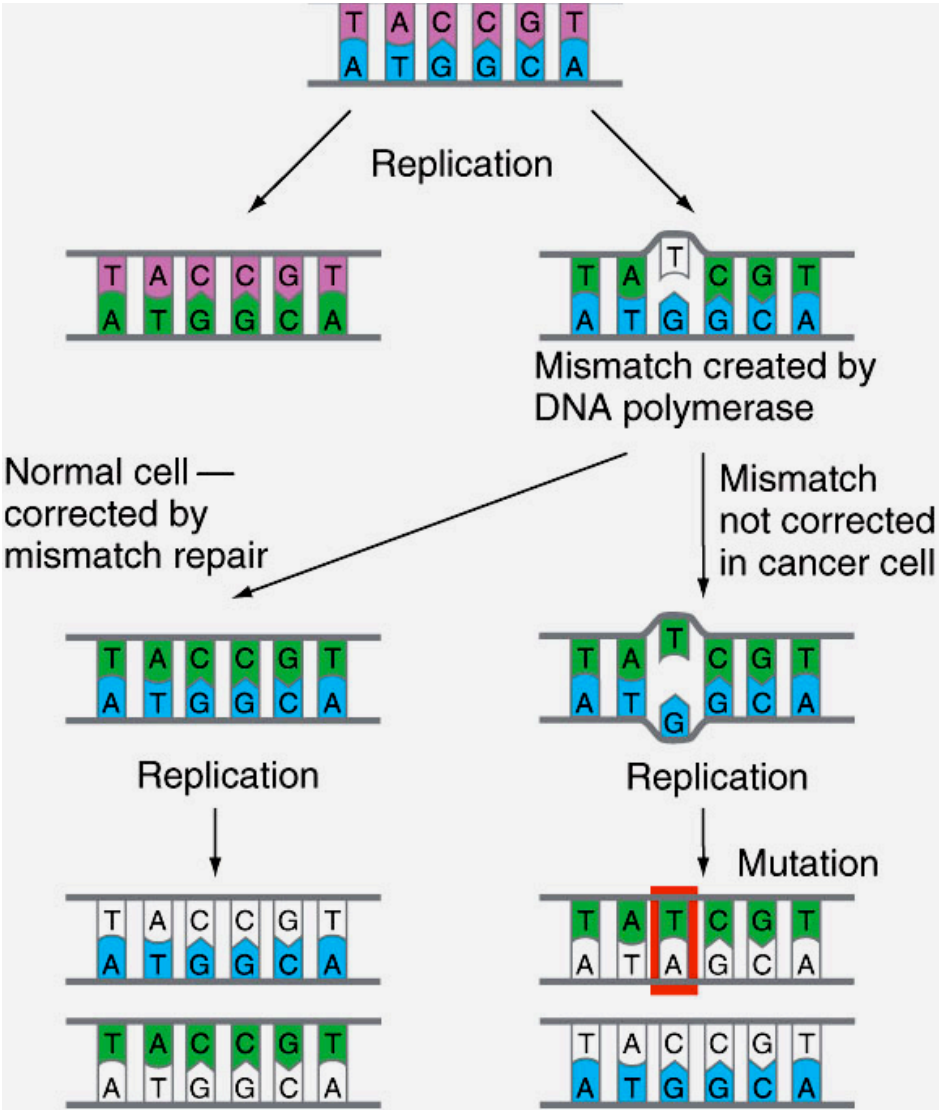
General cancer phenotype includes (1) many types of cellular abnormalities

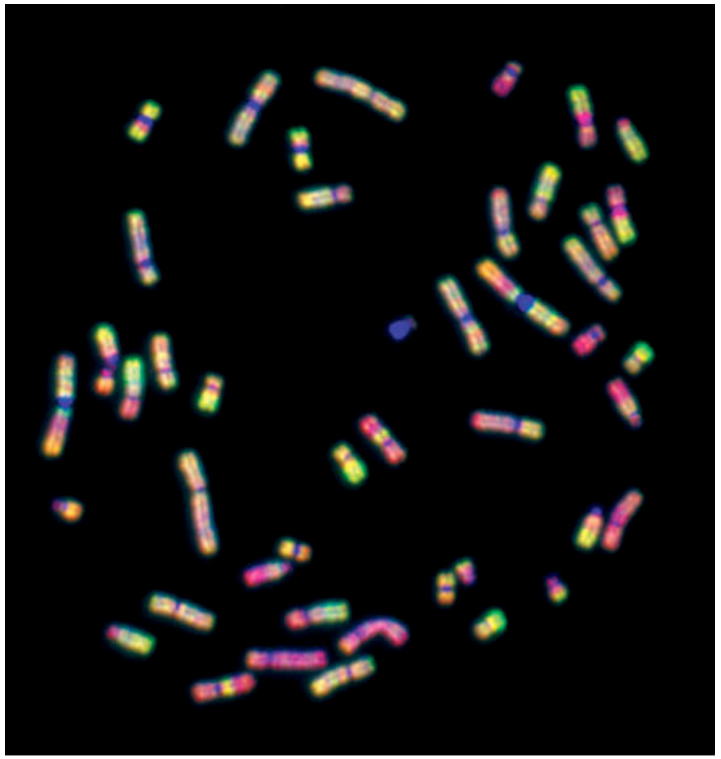


- Autocrine stimulation – tumor cells make their own signals to divide
- Loss of contact inhibition – lost property to stop dividing when contacted by another cell
- Loss of cell death – resistance to programmed cell death
- Loss of gap junctions – no channels for connecting to neighbor cell

Feature Figure 18.16 a

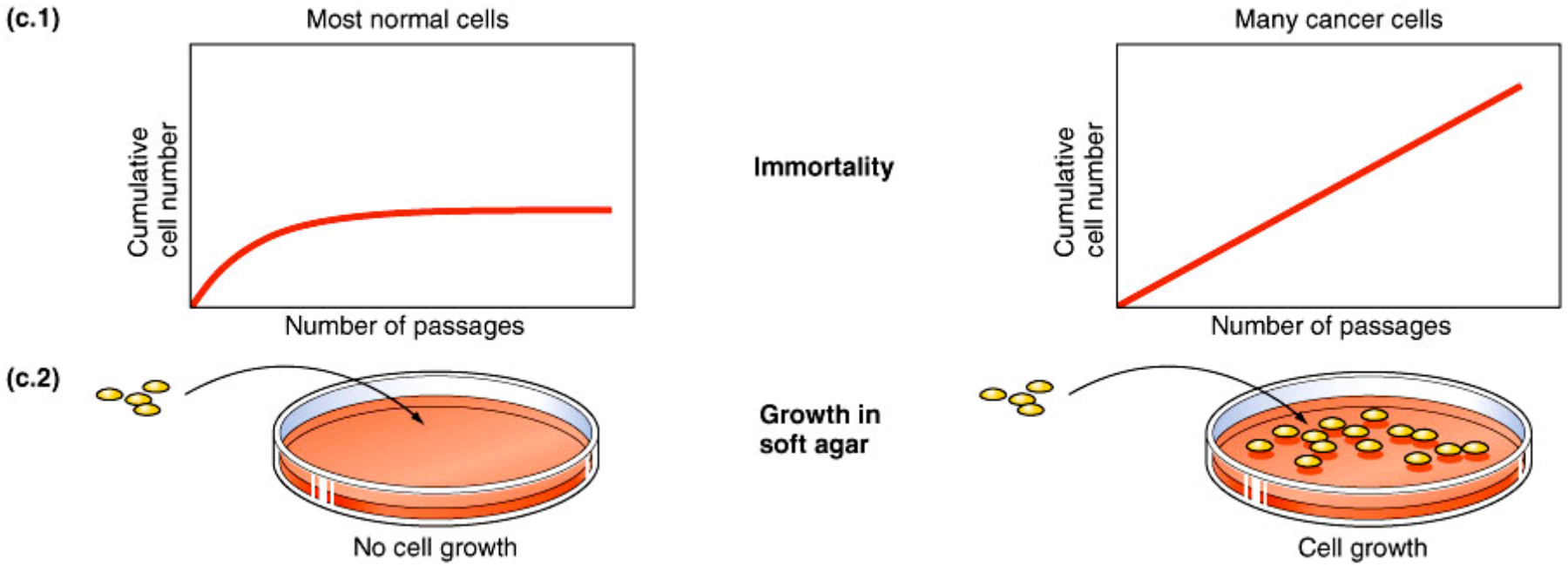
(2) Changes that produce genomic and karyotypic instability





Feature Figure 18.16 b (1) (2)

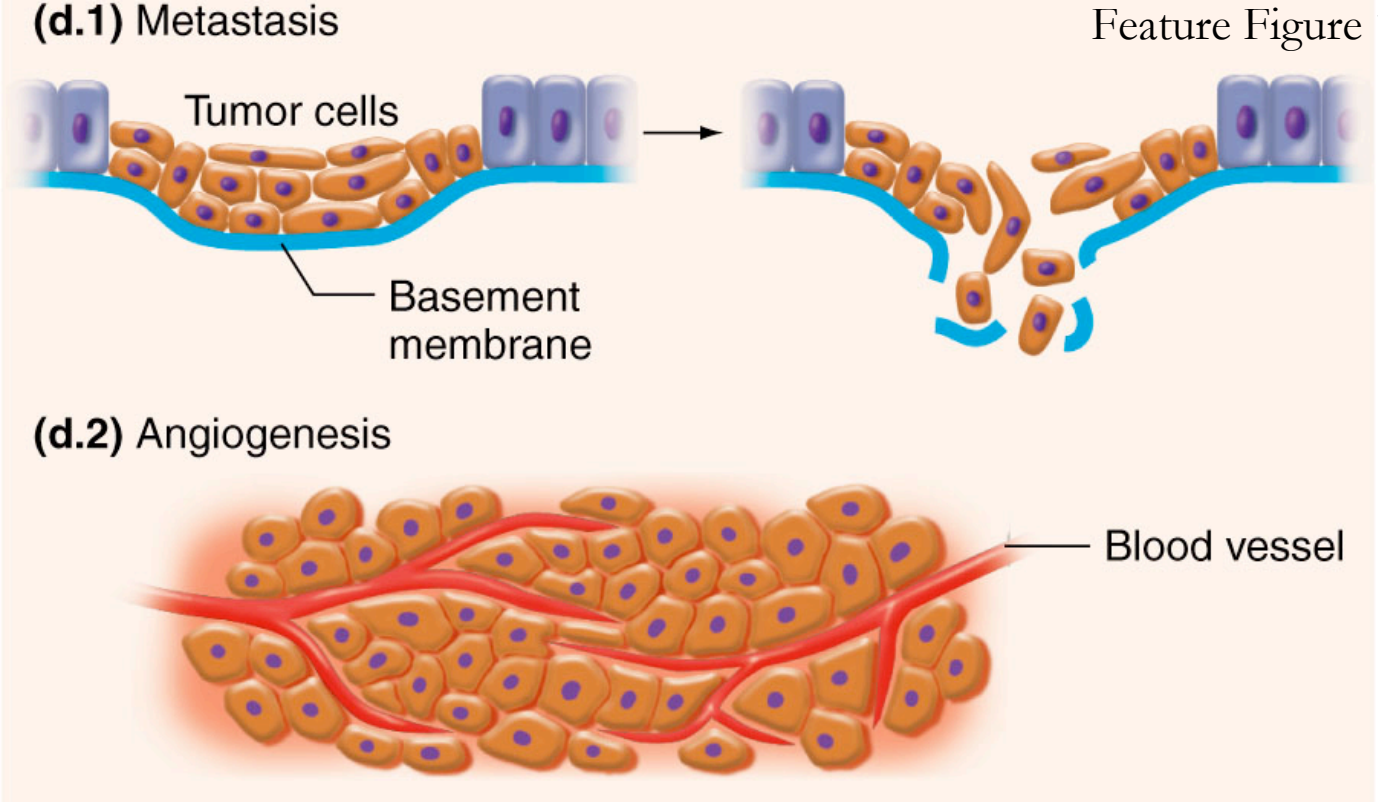
(3) Changes that produce a potential for immortality



- Loss of limitations on the number of cell divisions
- Ability to grow in culture – normal cells do not grow well in culture
- Restoration of telomerase activity

Feature Figure 18.16 c

(4) Changes that enable tumor to disrupt local tissue and invade distant tissues



Feature Figure 18.16 d

- Ability to metastasize
- Angiogenesis – secrete substances that cause blood vessels to grow toward tumor
- Evasion of immune surveillance

A. Cancer phenotype results from accumulation of multiple mutations in the clonal progeny of cells

B. Most cancers result from exposures to mutagens

- If one sib or twin gets cancer, other usually does not
- Populations that migrate – profile of cancer becomes more like people indigenous to new location

Cancer develops over time

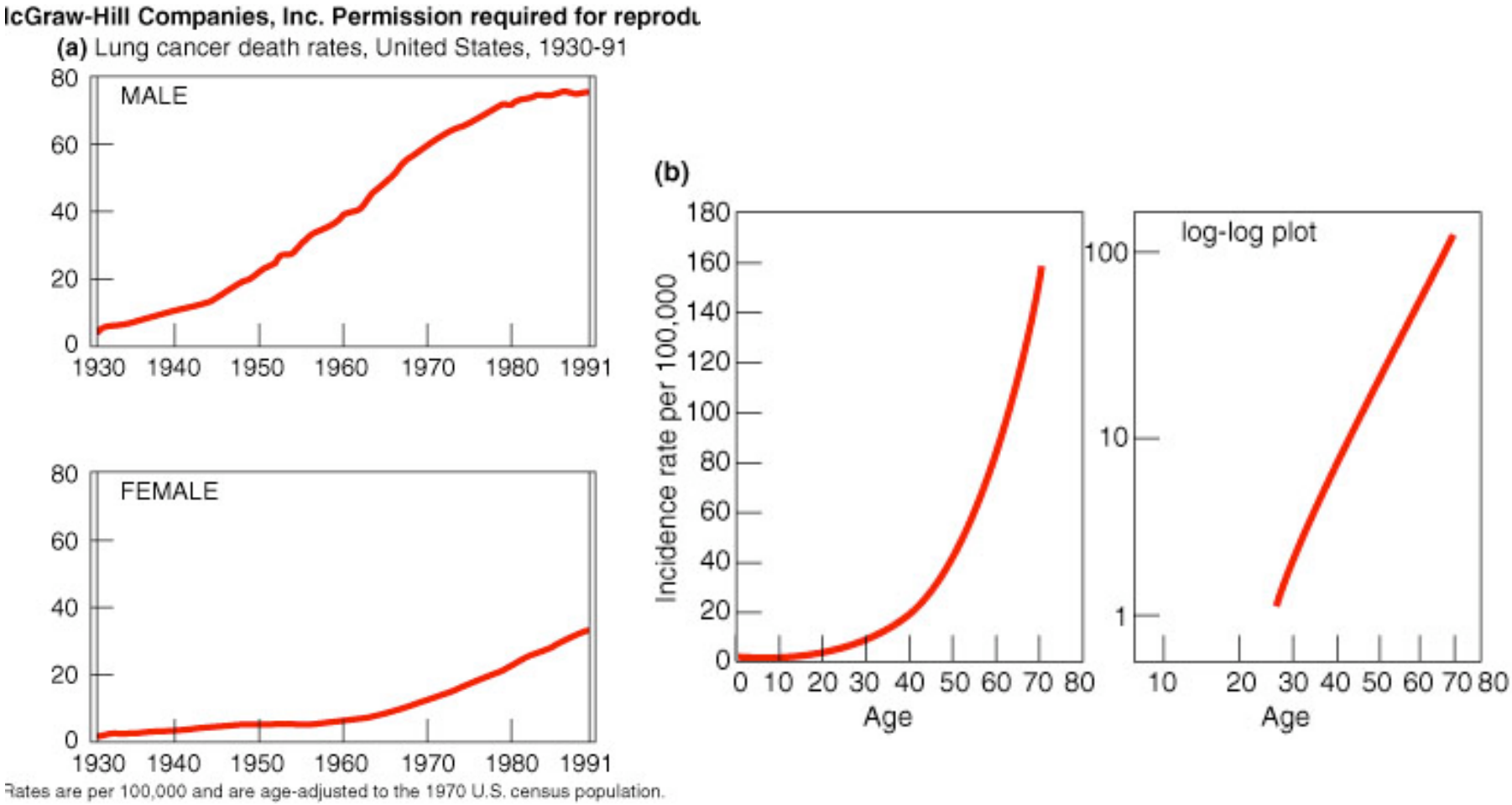


Fig. 18.19

Cancer arises by successive mutations in a clone of proliferating cells

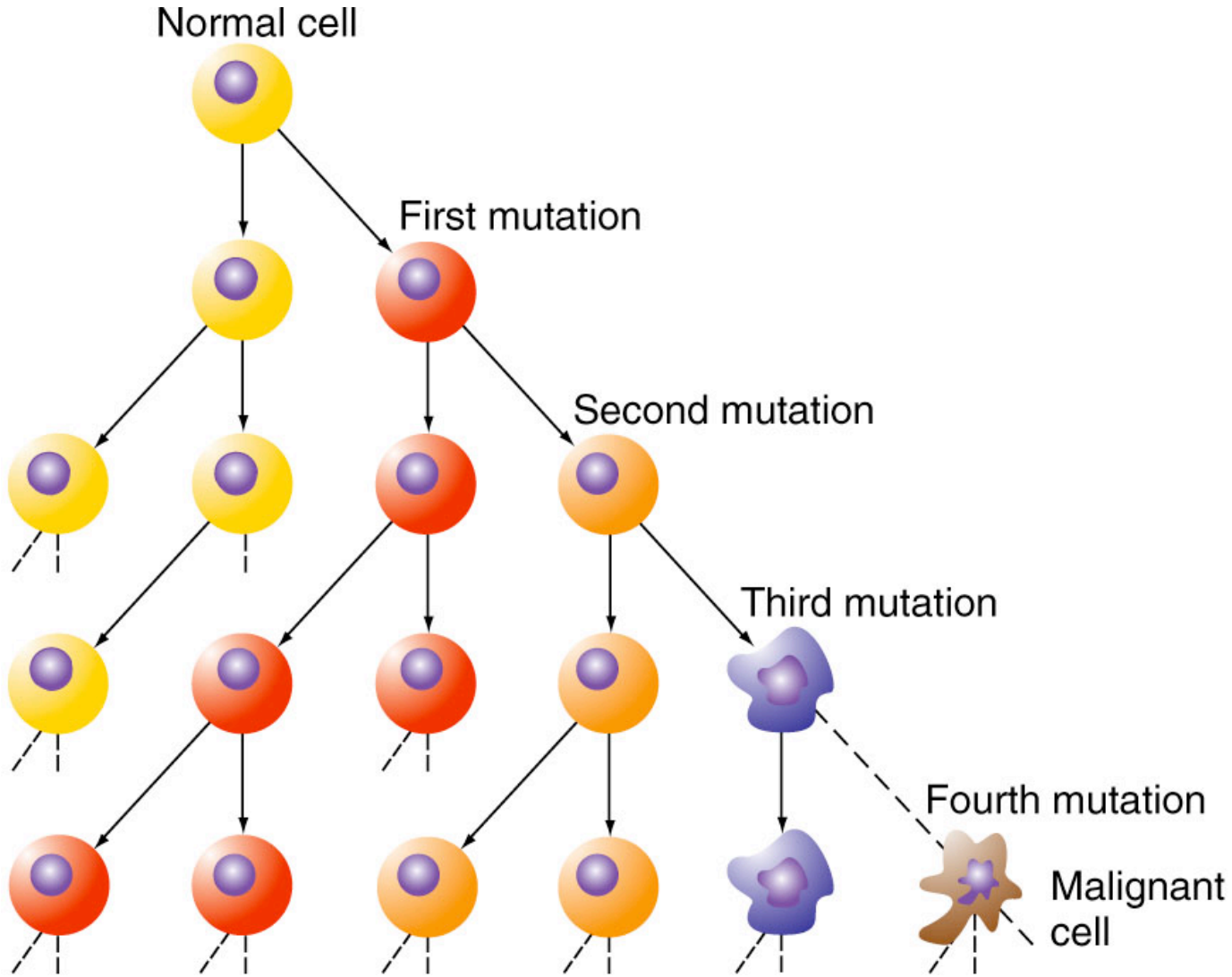
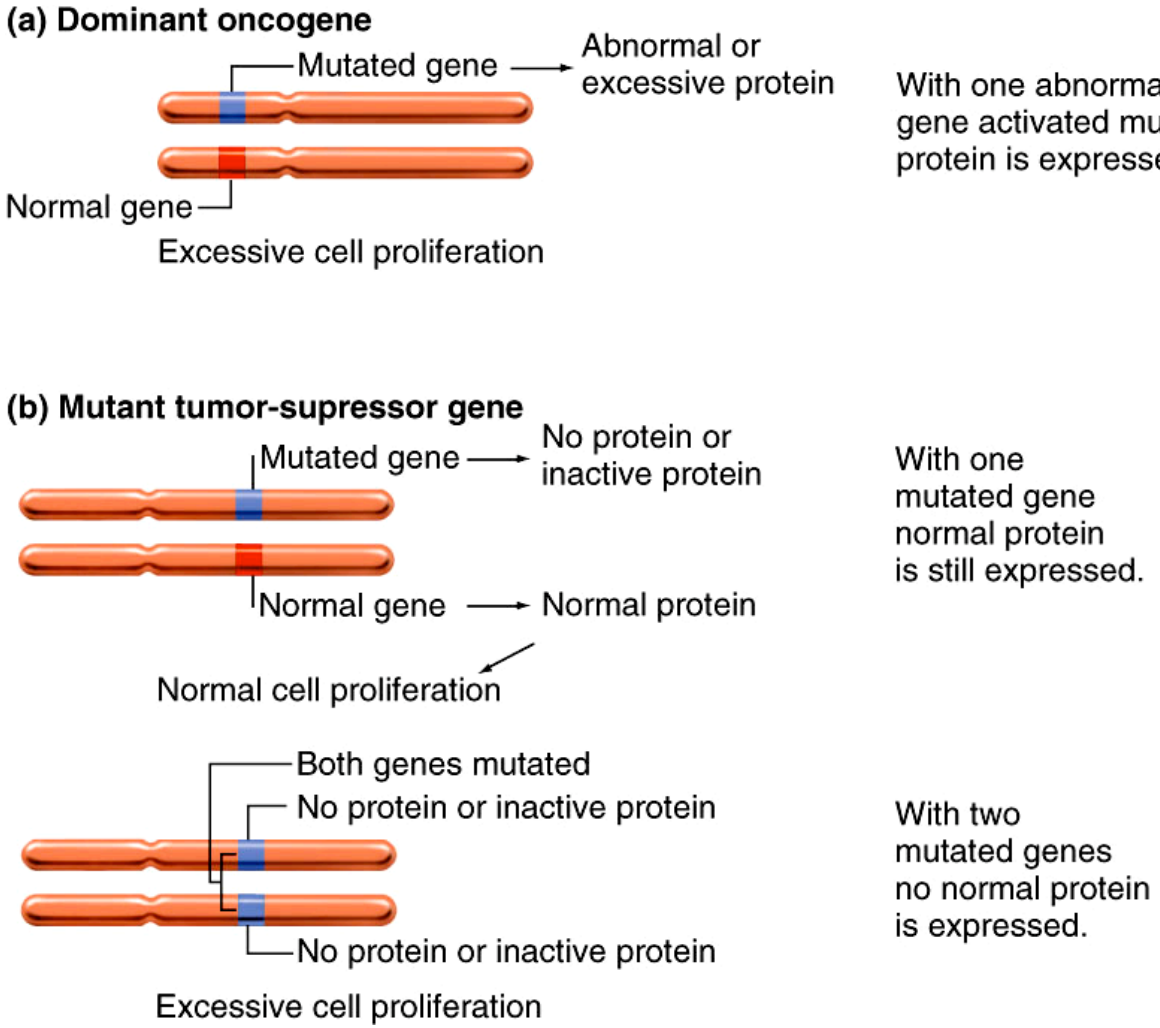


Fig. 18.21

Cancer mutations occur in two forms



- Oncogenes
  - dominant mutations
- Mutant tumor-suppressor genes
  - recessive mutations

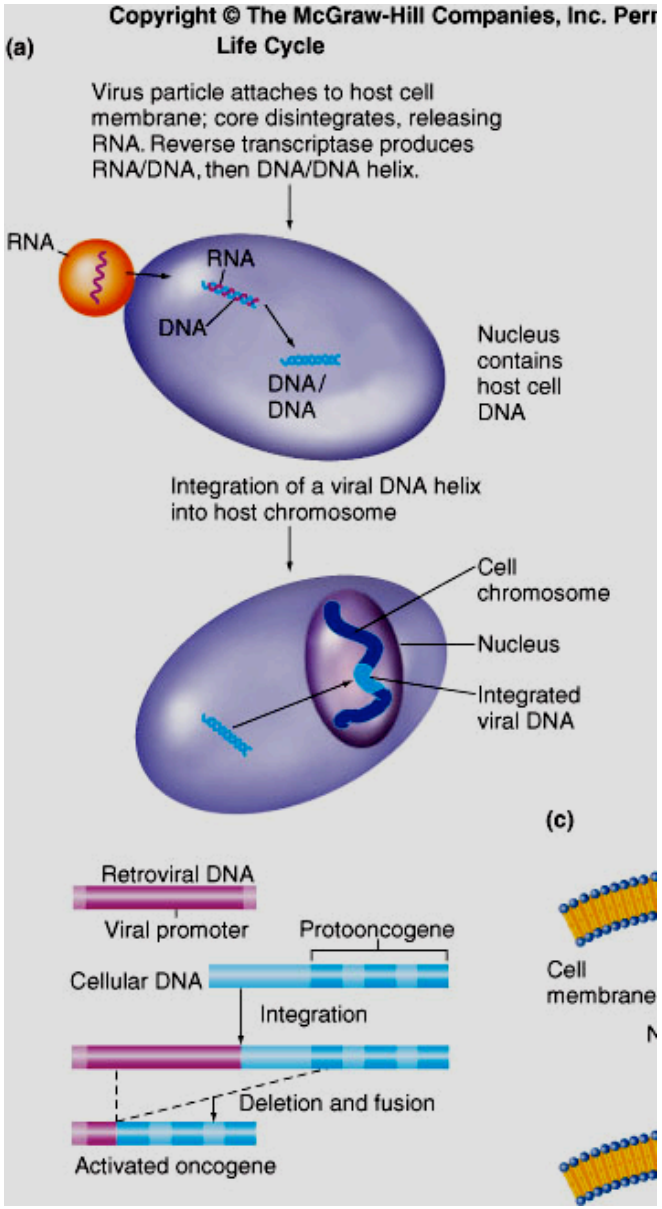
Fig. 18.22

Oncogenes

TABLE 18.3 Retroviruses and Their Associated Oncogenes*

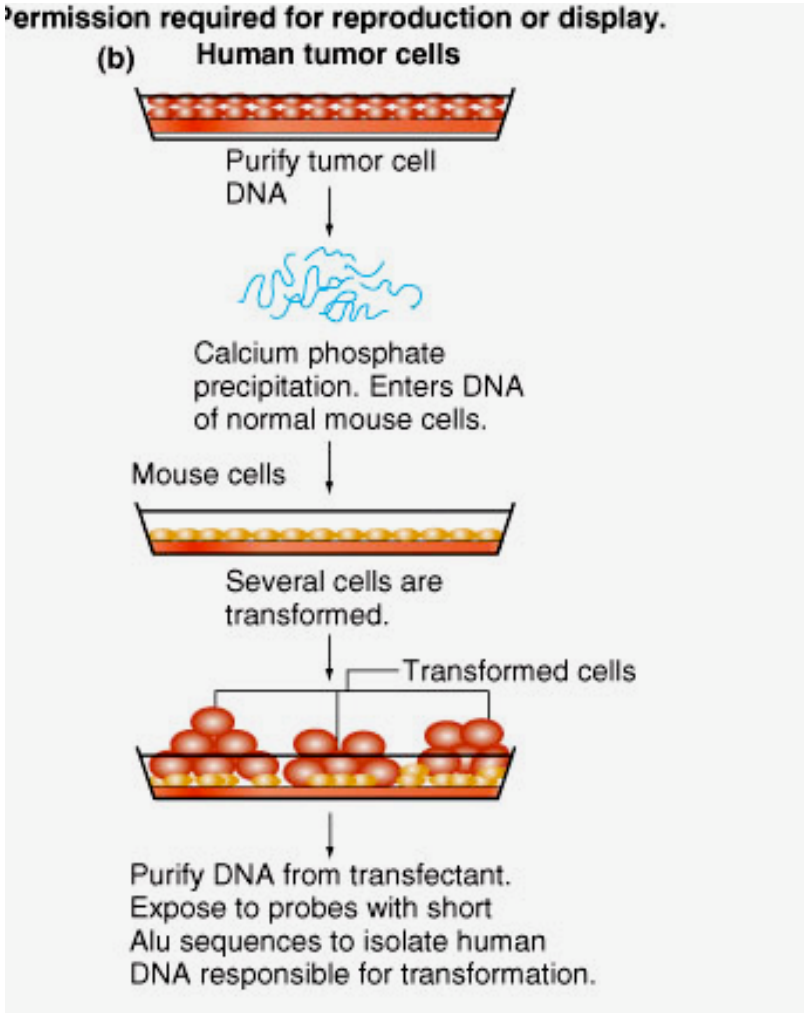
Virus	Species	Tumor	Oncogene
Rous sarcoma	Chicken	Sarcoma	*src*
Harvey murine sarcoma	Rat	Sarcoma and erthyroleukemia	*H-ras*
Kristen murine sarcoma	Rat	Sarcoma and erthyroleukemia	*K-ras*
Moloney murine sarcoma	Mouse	Sarcoma	*mos*
FBJ murine osteosarcoma	Mouse	Chondrosarcoma	*fos*
Simian sarcoma	Monkey	Sarcoma	*sis*
Feline sarcoma	Cat	Sarcoma	*sis*
Avian sarcoma	Chicken	Fibrosarcoma	*jun*
Avian myelocytomatosis	Chicken	Carcinoma, sarcoma, and myleocytoma	*myc*
Ableson leukemia	Mouse	B cell lymphoma	*abl*

Approaches in identifying oncogenes



- **Analysis of tumor causing retroviruses**

Fig. 18.23 a



- Exposure of noncancerous cells to tumor DNA in culture
  - Human tumor DNA to transform normal mouse cells
  - Human DNA isolated from transformants

Fig. 18.23 b, c

Oncogenic effects of oncogenes

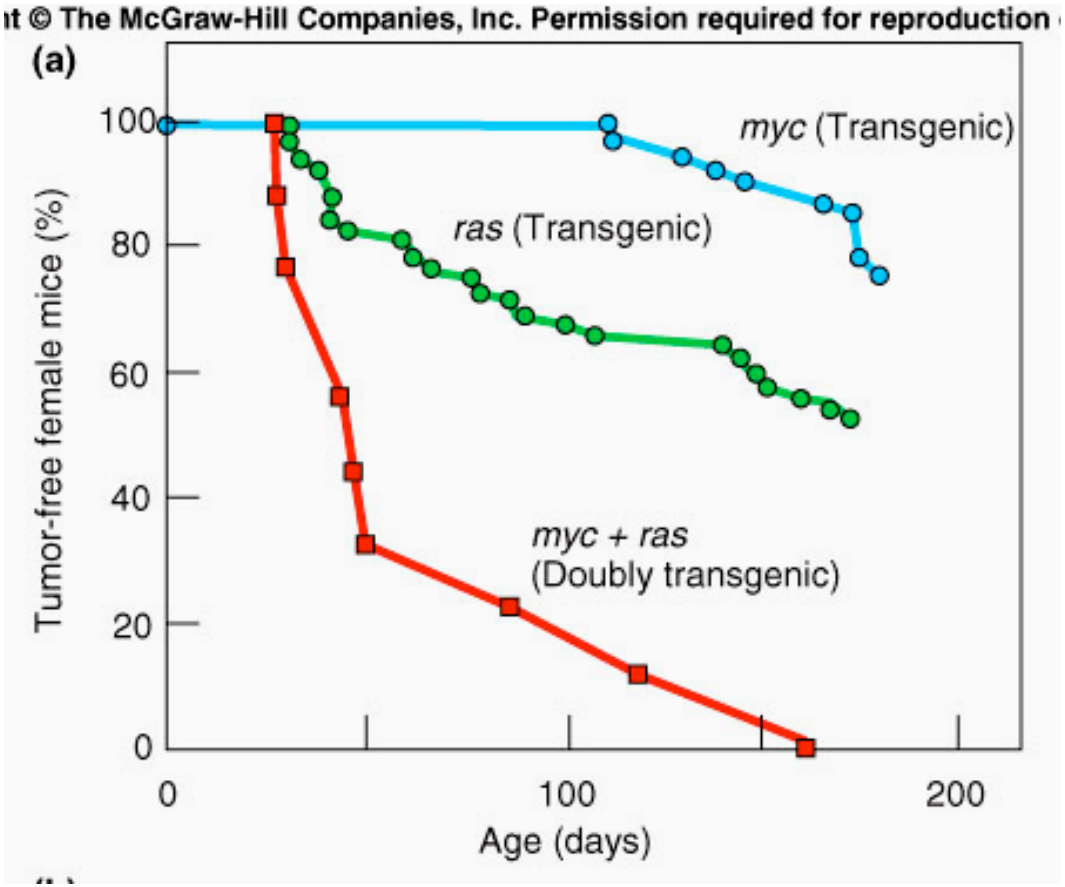


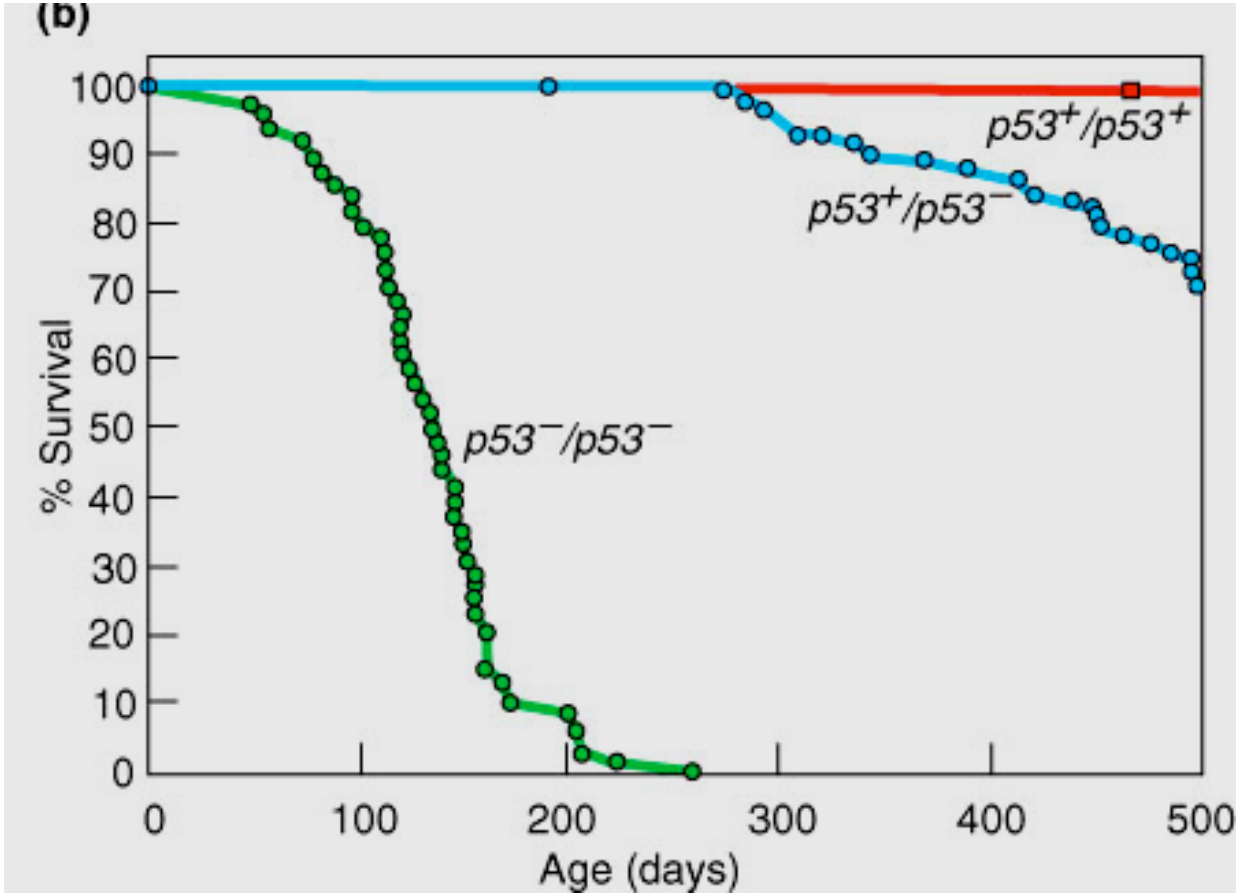
Fig. 18.17

Tumor suppressor genes

TABLE 18.5 **Mutant Alleles of These Tumor-Suppressor Genes Decrease the Accuracy of Cell Reproduction***

Gene	Normal Function of Gene (if known), or Disease Syndrome Resulting from Mutation	Function of Normal Protein Product
p53	Controls G_1-to-S checkpoint	Transcription factor
RB	Controls G_1-to-S transition	Inhibits a transcription factor
p21	Controls G_1-to-S transition	Inhibits CDK
ATM	Controls G_1-to-S phase, and G_2-to-M checkpoint	DNA-dependent protein kinase
BS	Recombinational repair of DNA damage	DNA/RNA ligase
XP	Excision of DNA damage	Several enzymes
hMSH2, hmLH1	Correction of base-pair matches	Several enzymes
FA	Fanconi anemia	Unknown
BRCA1	Repair of DNA breaks	Unknown
BRCA2	Repair of DNA breaks	Unknown

p53 plays a role in preventing tumor formation



Some cancers run in families such as retinoblastoma

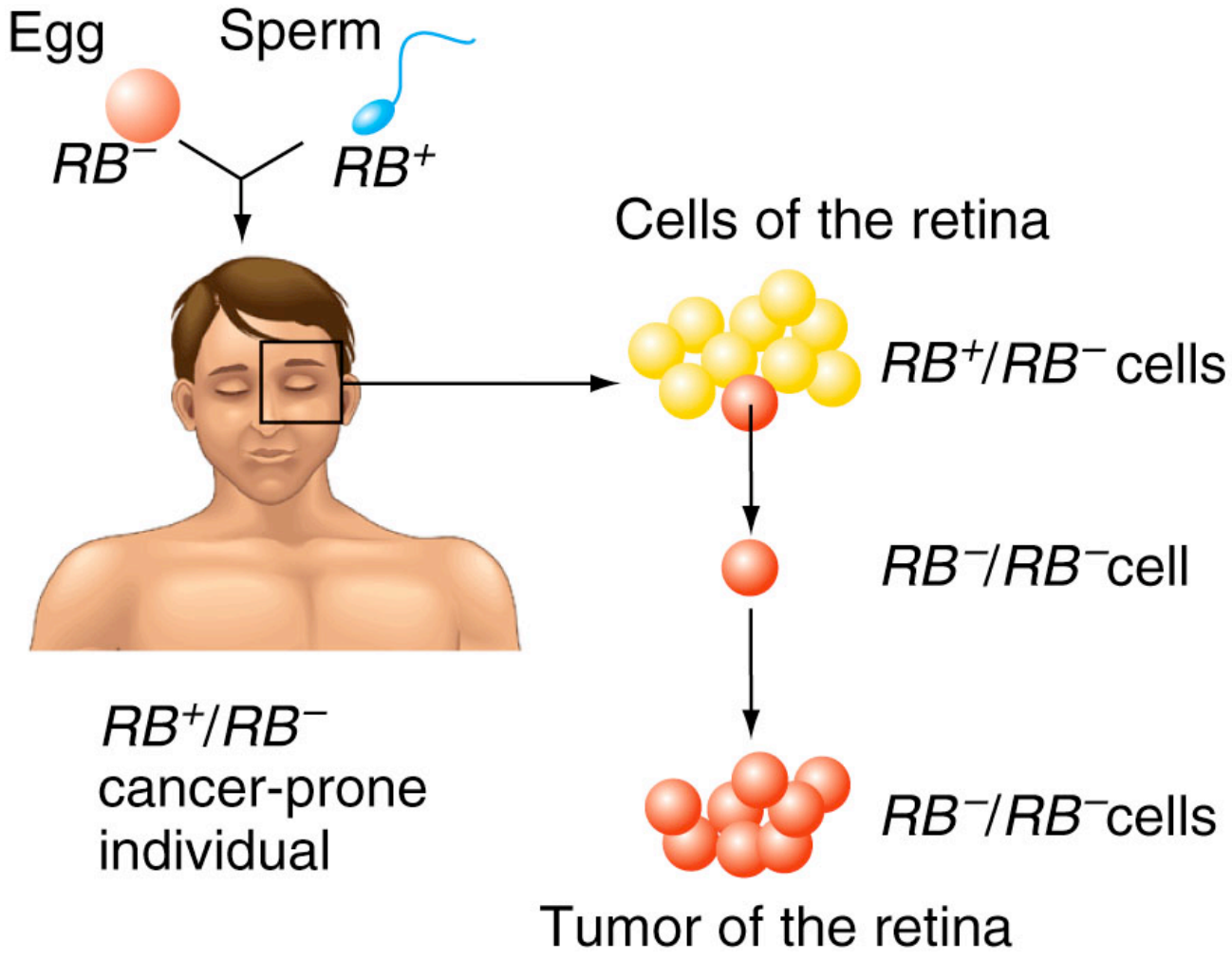
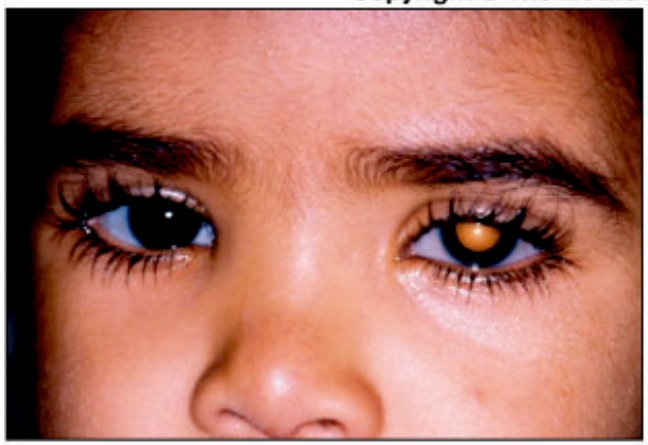


Fig. 18.20

Mutations creating tumor-suppressor alleles release break on cell division and decrease accuracy of cell reproduction e.g., retinoblastoma tumor-suppressor gene



(a)

Pedigree

RB^+/RB^- — RB^+/RB^+

RB^+/RB^-

Chromosome 13 in the normal cells of a person with predisposition to retinoblastoma

Deletion or other mutation at RB^- locus → RB^- RB^+

(b)

Nondisjunction (loss)	Nondisjunction and replication	Mitotic recombination	Gene conversion	Deletion	Point mutation
RB^-	RB^- RB^-	RB^- RB^-	RB^- RB^-	RB^- RB^-	RB^- RB^-

Fig. 18.24