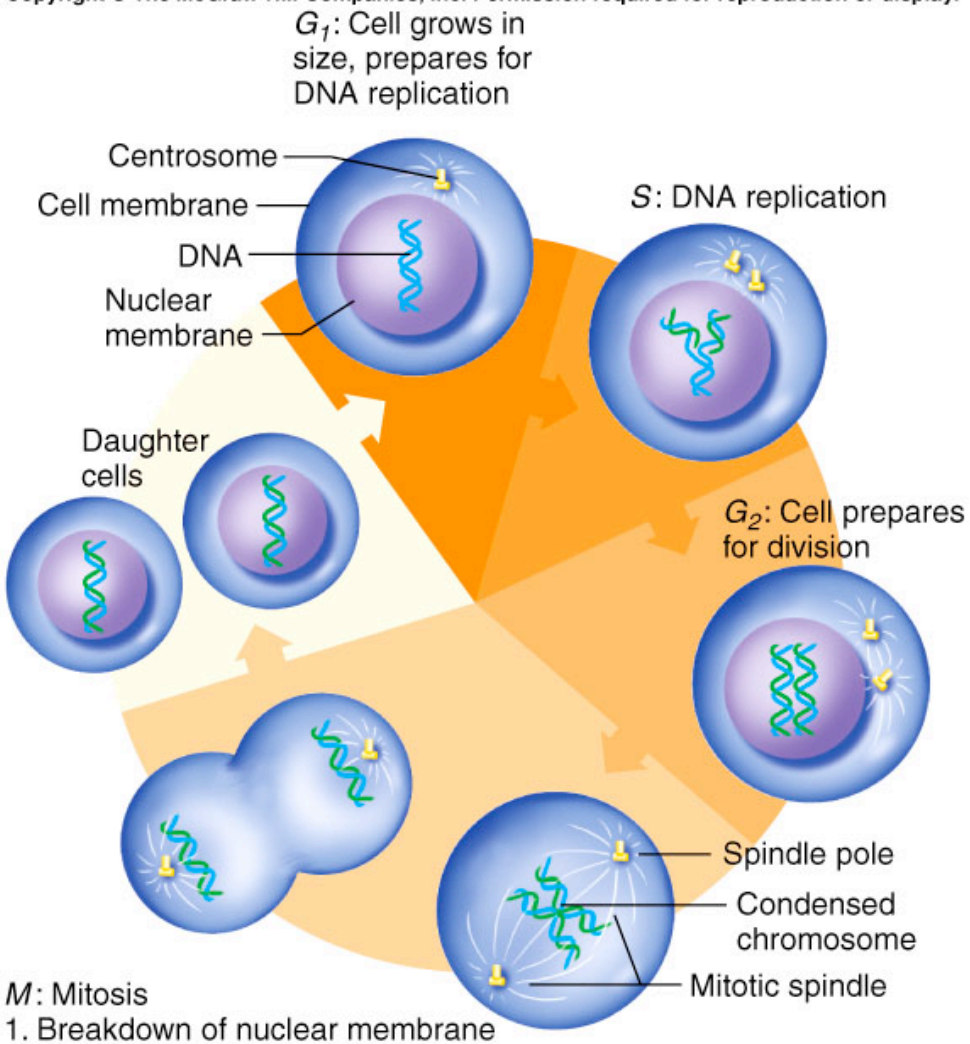
Lecture 20: Cell-Cycle Regulation and the Genetics of Cancer

Read chapter 15.1-6
(642-675)

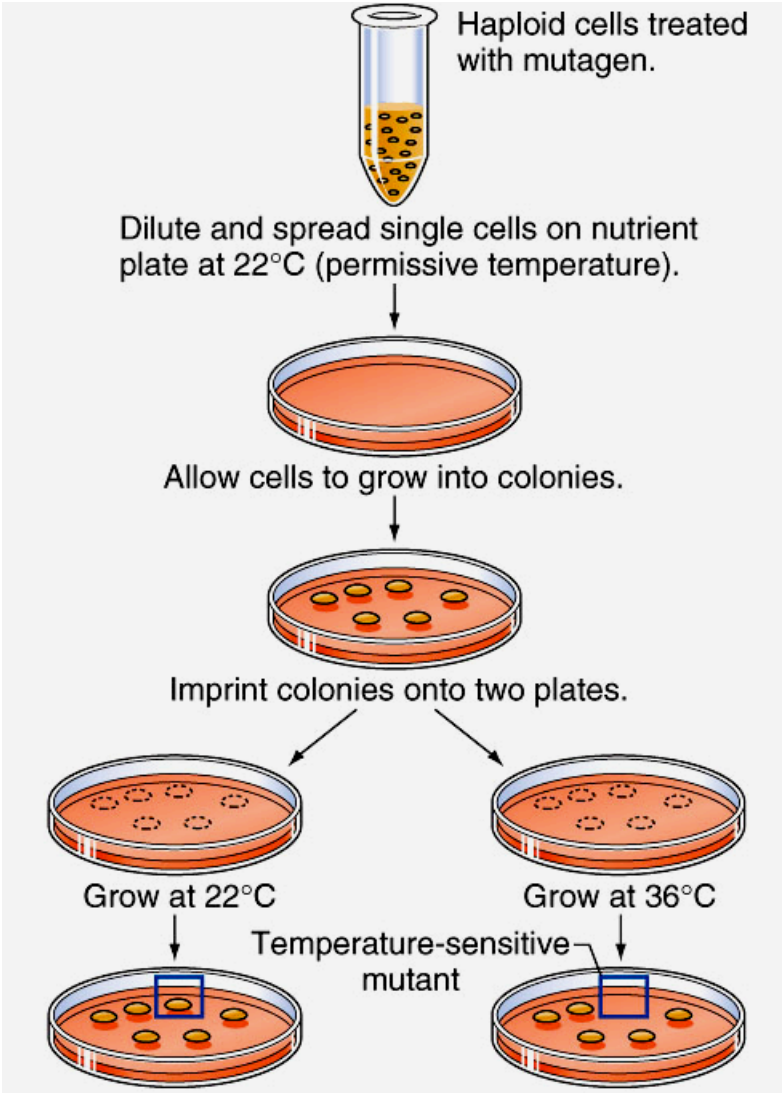
The normal cell division



The cell cycle has four phases:

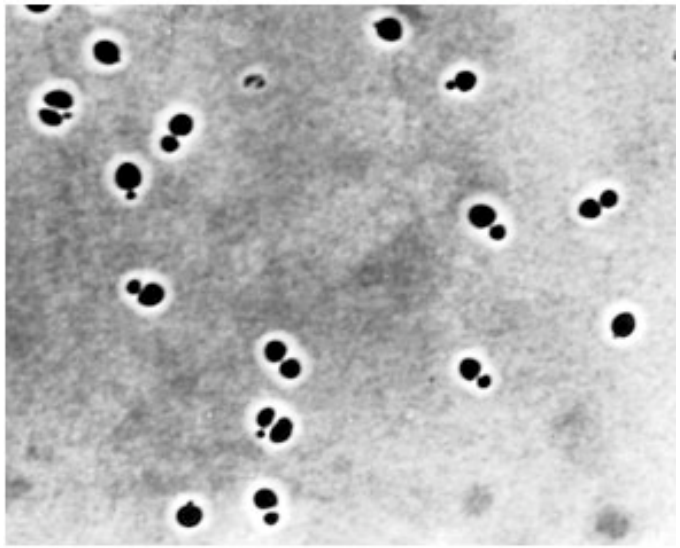
G_1, S G_2, and M

Isolation of temperature-sensitive mutants in yeast

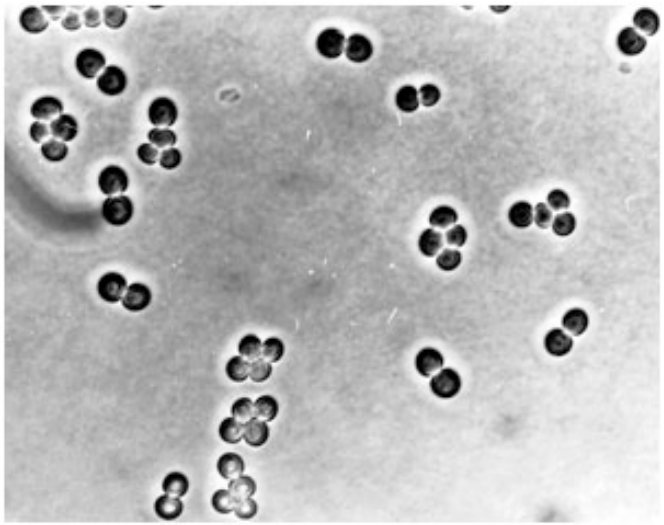


- Mutants grow normally at permissive temperature
- Mutants loses gene function at restrictive temperature
- Thousands of cell cycle mutants have been identified

A cell-cycle mutant in yeast



(a)

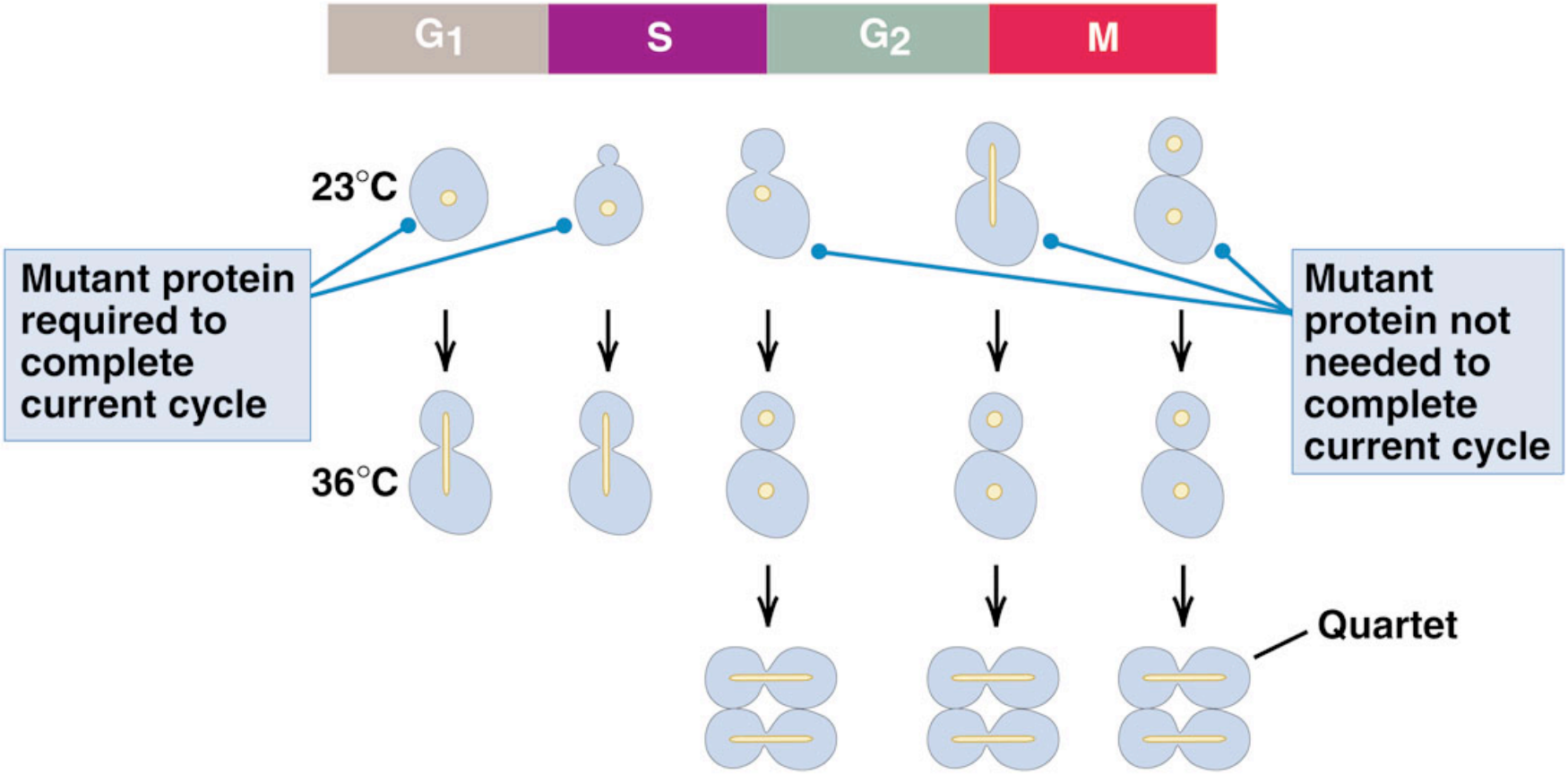


(b)

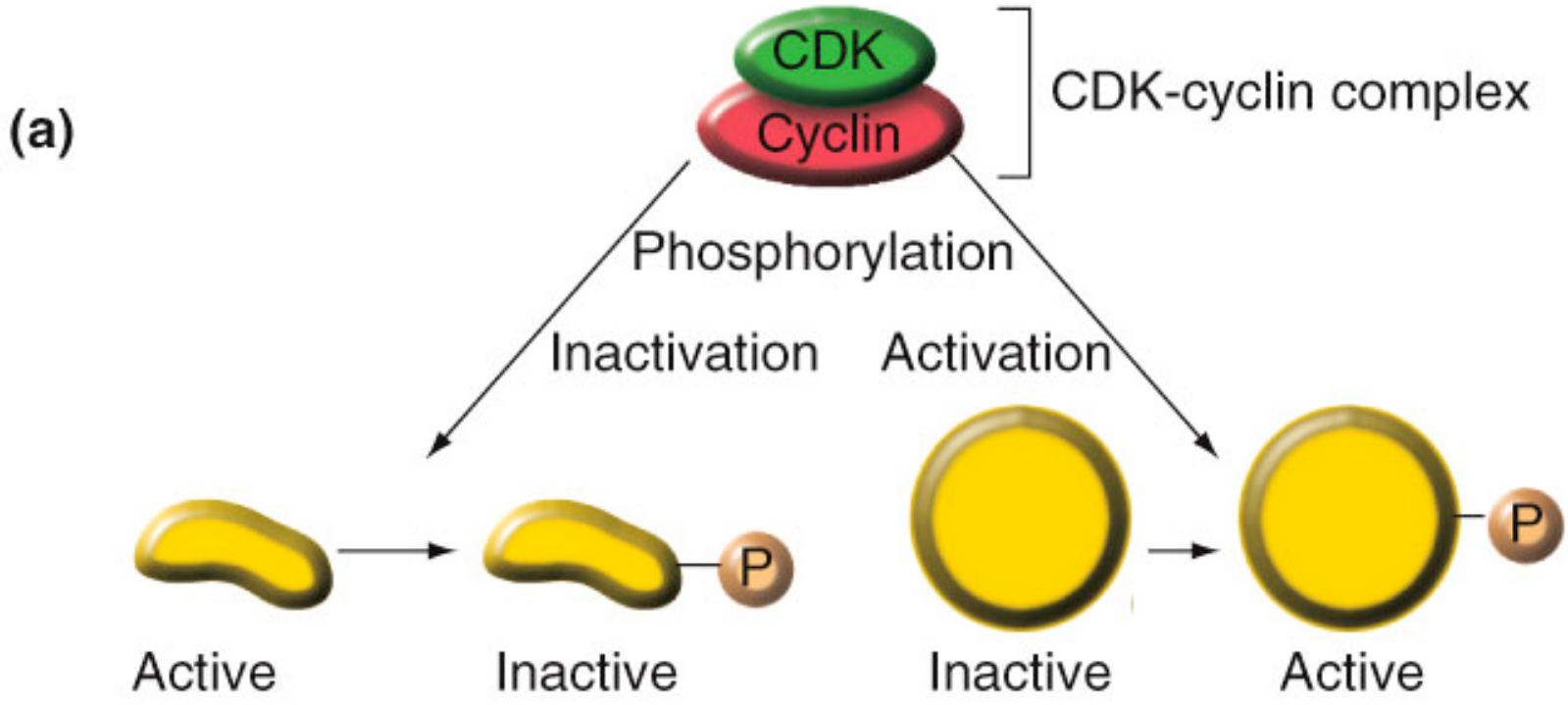
- (a) growth at permissive temperature displays buds of all sizes
- (b) growth at restrictive temperature shows cells have finished first cell cycle and arrested in the second

Fig. 15.6

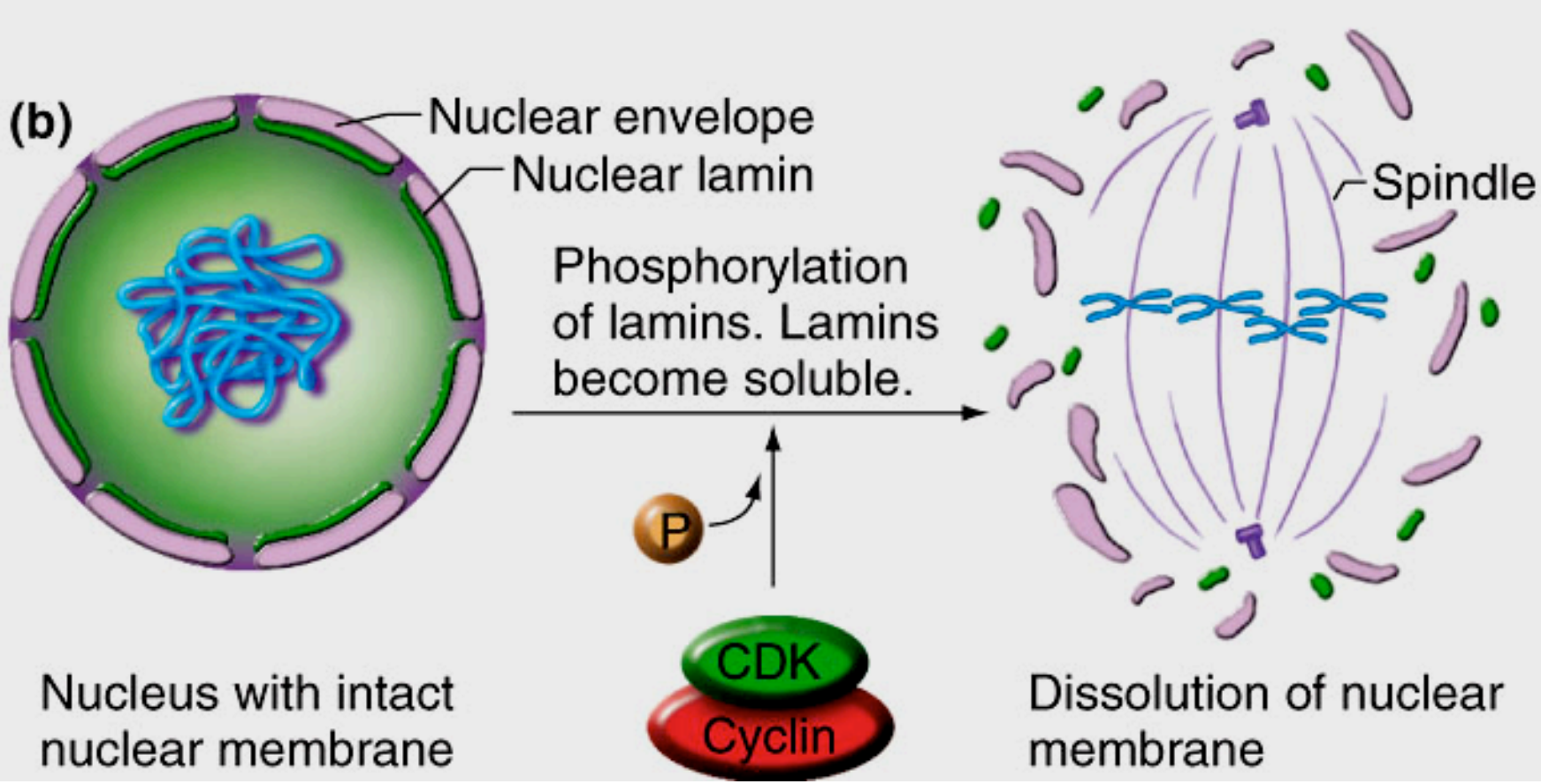
Use of heat-sensitive mutations to decipher the timing of a gene's function in the cell cycle



Cyclin-dependent kinases (CDK) control the cell cycle by phosphorylating other proteins



Nuclear lamins are one of the substrates of CDK

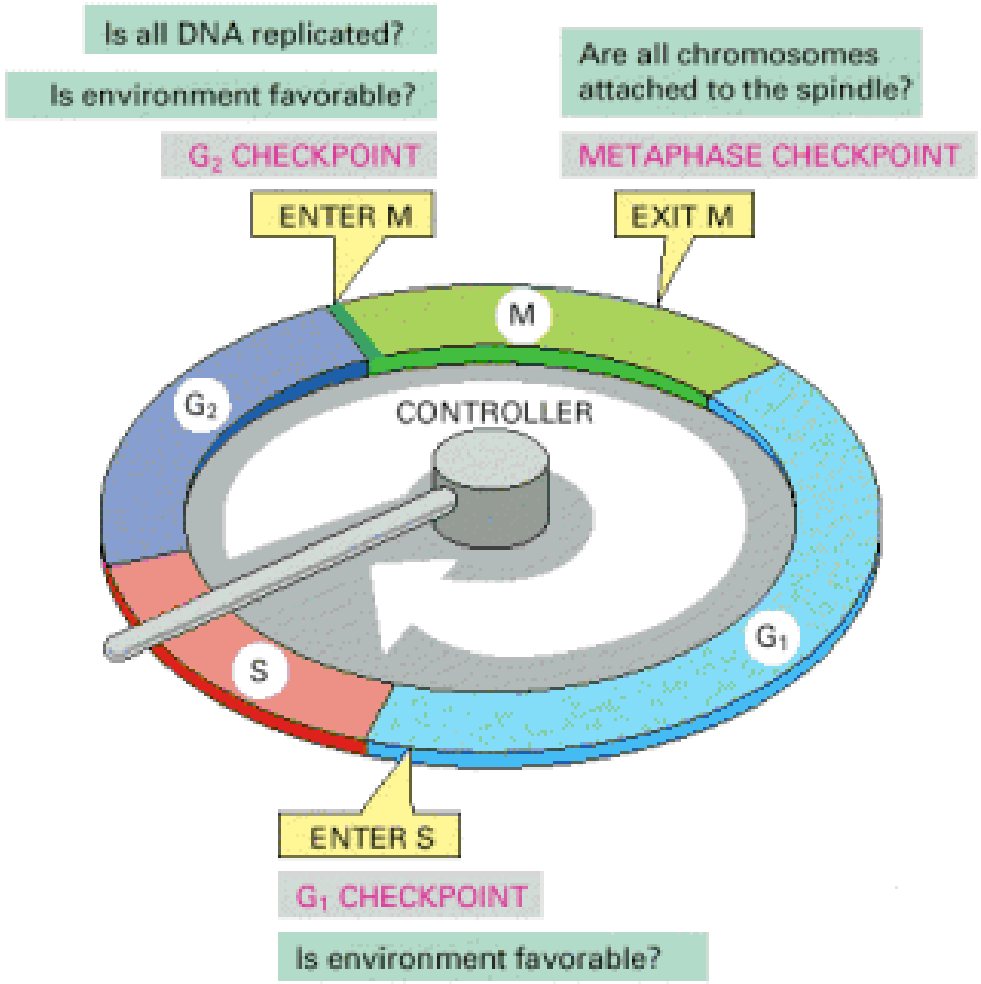


Three cell cycle check points ensure genomic stability

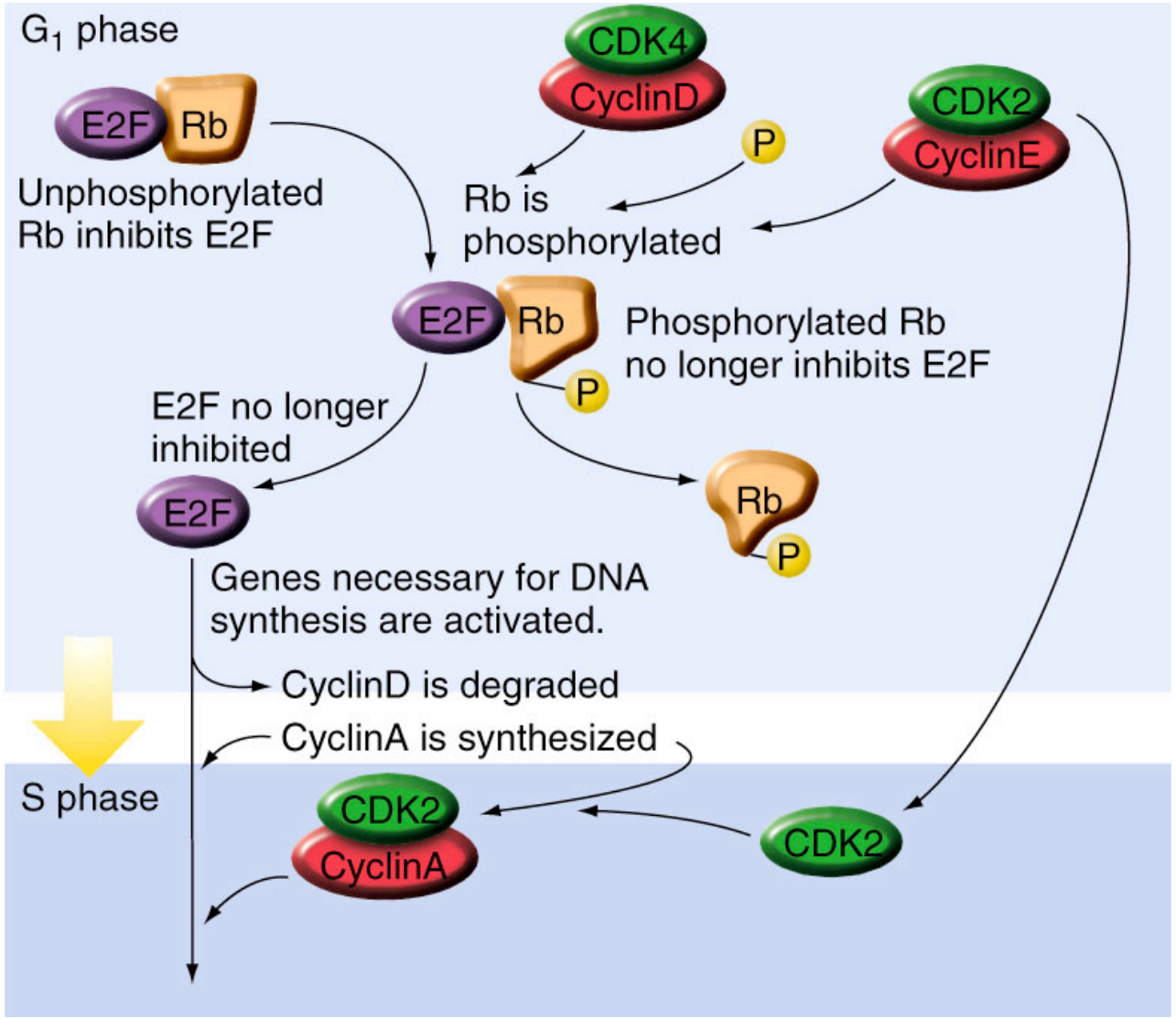
G1 to S (start) check points

G2 to M check points

Metaphase-anaphase check points



CDKs mediate the transition from the G_1-to-S phase in human cells



Interactions between various tumor suppressors and proto-oncogenes in growth control of a cell

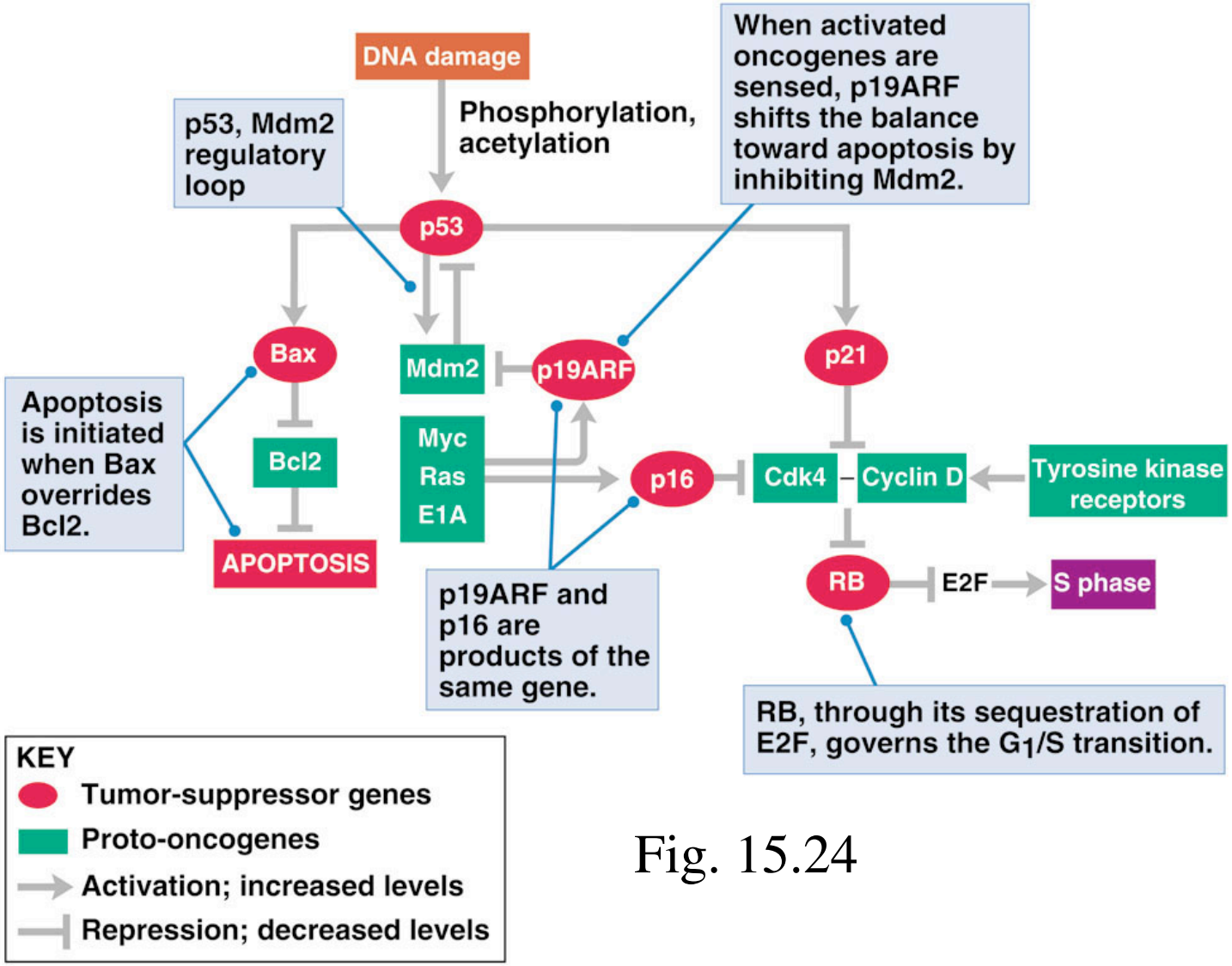


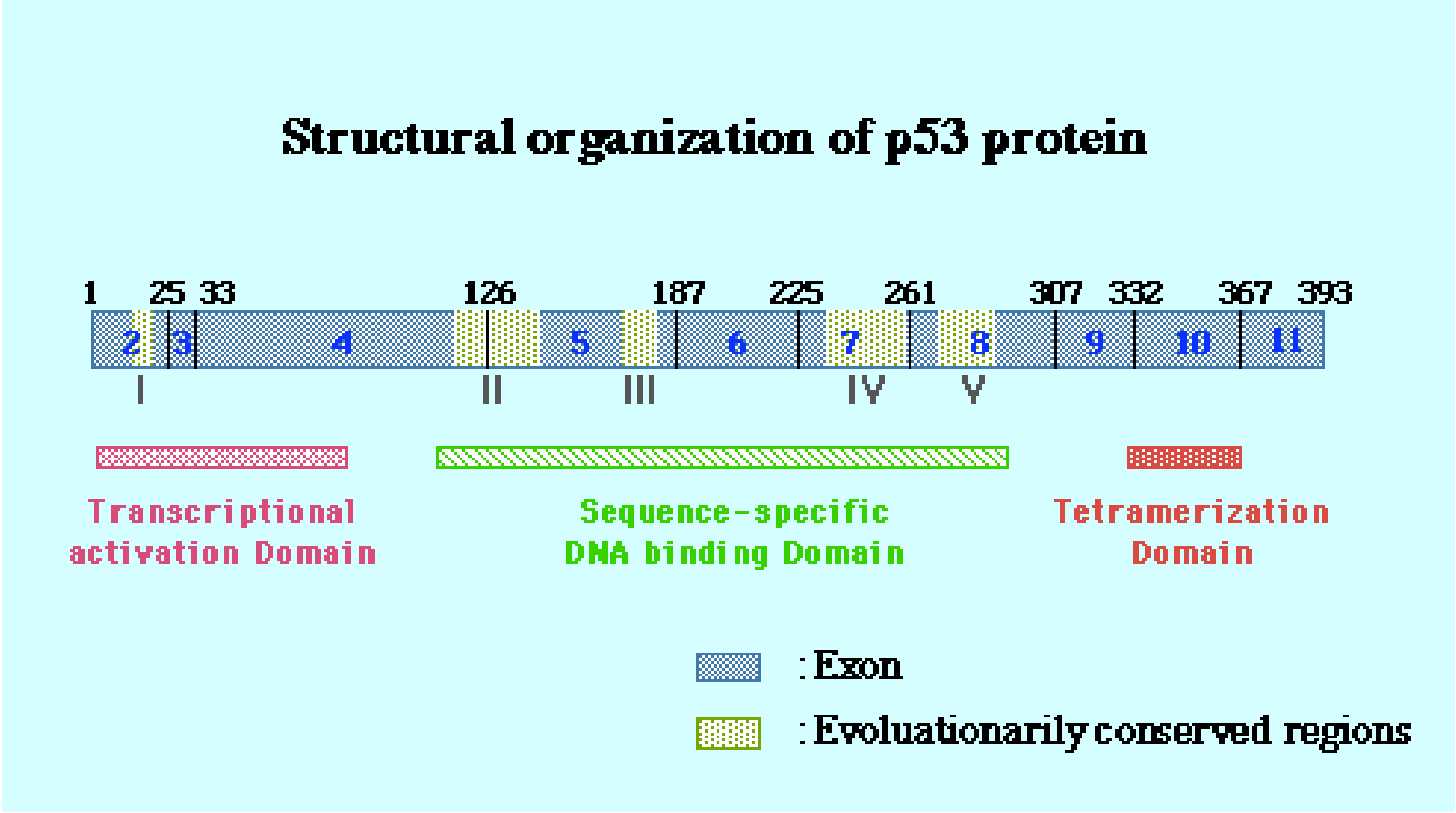
Fig. 15.24

70 cell-cycle genes identified through temperature-sensitive mutation screens

TABLE 18.1 Some of the Cell-Cycle Genes in Which Mutations Contribute to Cancer

Genes	Gene Products and Their Function
CDKs	Enzymes known as cyclin-dependent protein kinases that control the activity of other proteins by phosphorylating them
CDC28	A CDK discovered in the yeast *Saccharomyces cerevisiae* that controls several steps in the *S. cerevisiae* cell cycle
CDC2	A CDK discovered in the yeast *Schizosaccharomyces pombe* that controls several steps in the *S. pombe* cell cycle; also the designation for a particular CDK in mammalian cells
CDK4	A CDK of mammalian cells important for the G_1-to-S transition
CDK2	A CDK of mammalian cells important for the G_1-to-S transition
cyclins	Proteins that are necessary for and influence the activity of CDKs
cyclinD	A cyclin of mammalian cells important for the G_1-to-S transition
cyclinE	A cyclin of mammalian cells important for the G_1-to-S transition
cyclinA	A cyclin of mammalian cells important for S phase
cyclinB	A cyclin of mammalian cells important for the G_2-to-M transition
E2F	A transcription factor of mammalian cells important for the G_1-to-S transition
RB	A mammalian protein that inhibits E2F
p21	A protein of mammalian cells that inhibits CDK activity
p16	A protein of mammalian cells that inhibits CDK activity
p53	A transcription factor of mammalian cells that activates transcription of DNA repair genes as well as transcription of *p21*
RAD9	A protein that inhibits the G_2-to-M transition of *S. cerevisiae* in response to DNA damage
E6	A protein of the HPV virus that inhibits p53
E7	A protein of the HPV virus that inhibits Rb

p53: an anti-oncogenic protein



-members of Li-Fraumeni cancer-prone families were shown to carry germ-line p53 mutations.
-mice that are homozygous null for p53 are highly predisposed to tumors.

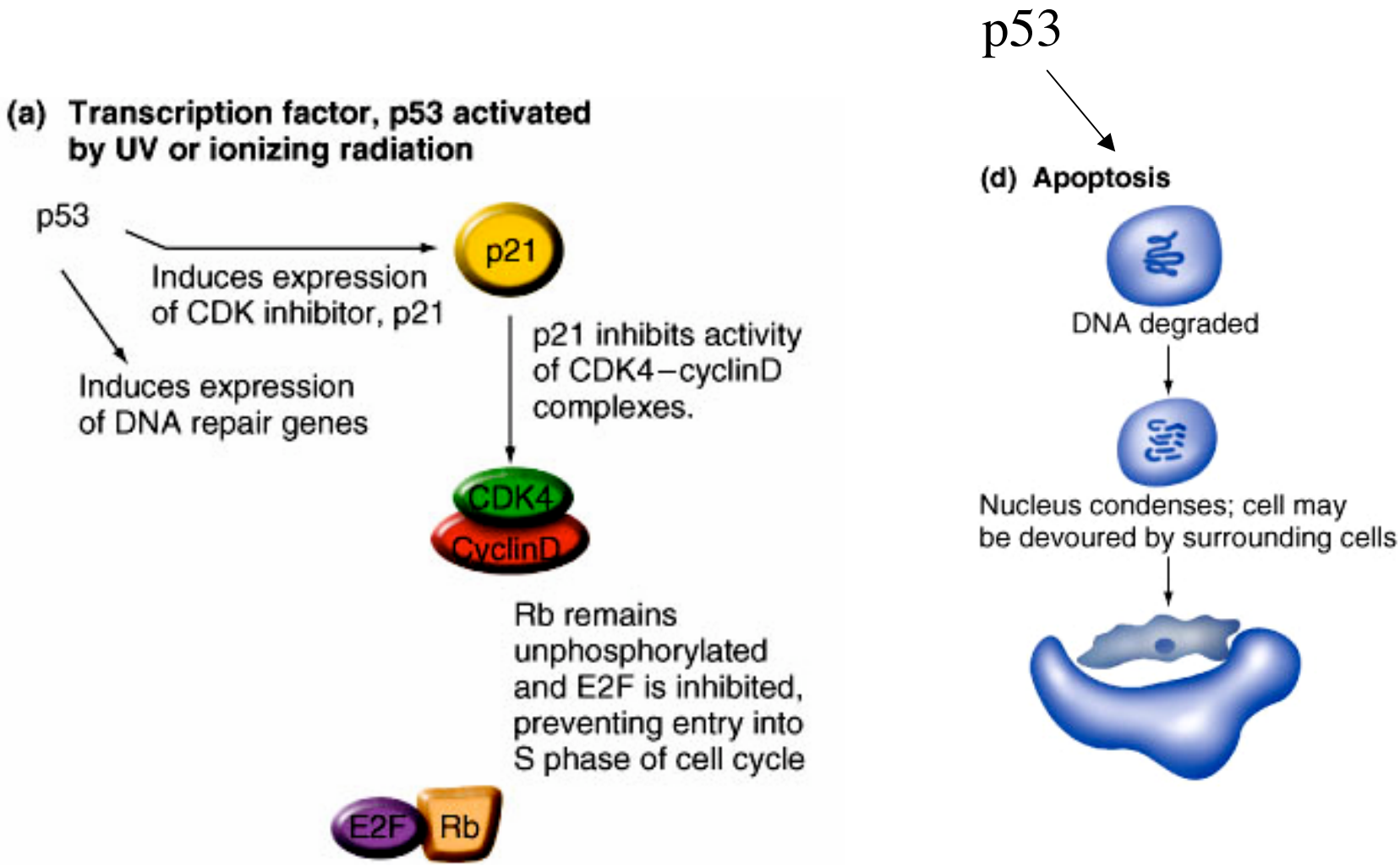

(a) Transcription factor, p53 activated by UV or ionizing radiation
p53
p21
Induces expression of CDK inhibitor, p21
Induces expression of DNA repair genes
p21 inhibits activity of CDK4–cyclinD complexes.
CDK4
CyclinD
Rb remains unphosphorylated and E2F is inhibited, preventing entry into S phase of cell cycle
E2F
Rb
p53
(d) Apoptosis
DNA degraded
Nucleus condenses; cell may be devoured by surrounding cells

Fig. 18.11 a

Over 50% cancer cells contain mutations in p53

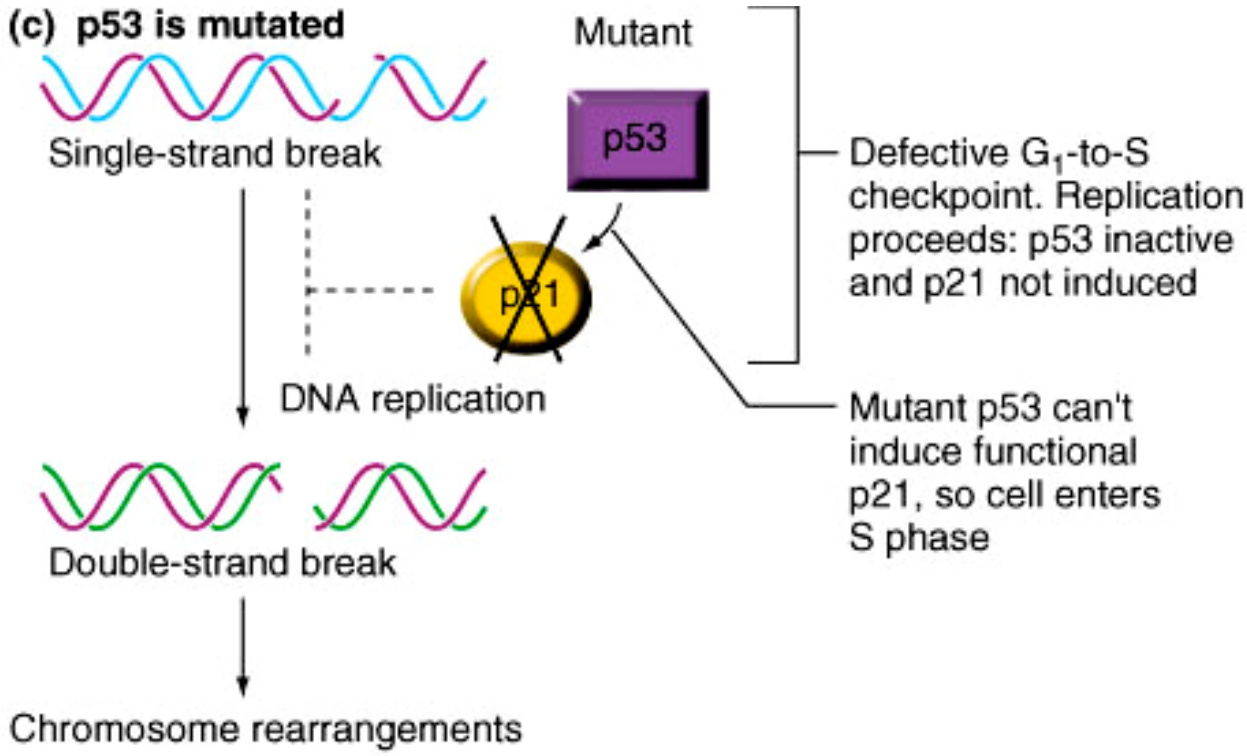


Fig. 18.11 c,d

G2-to-M check points

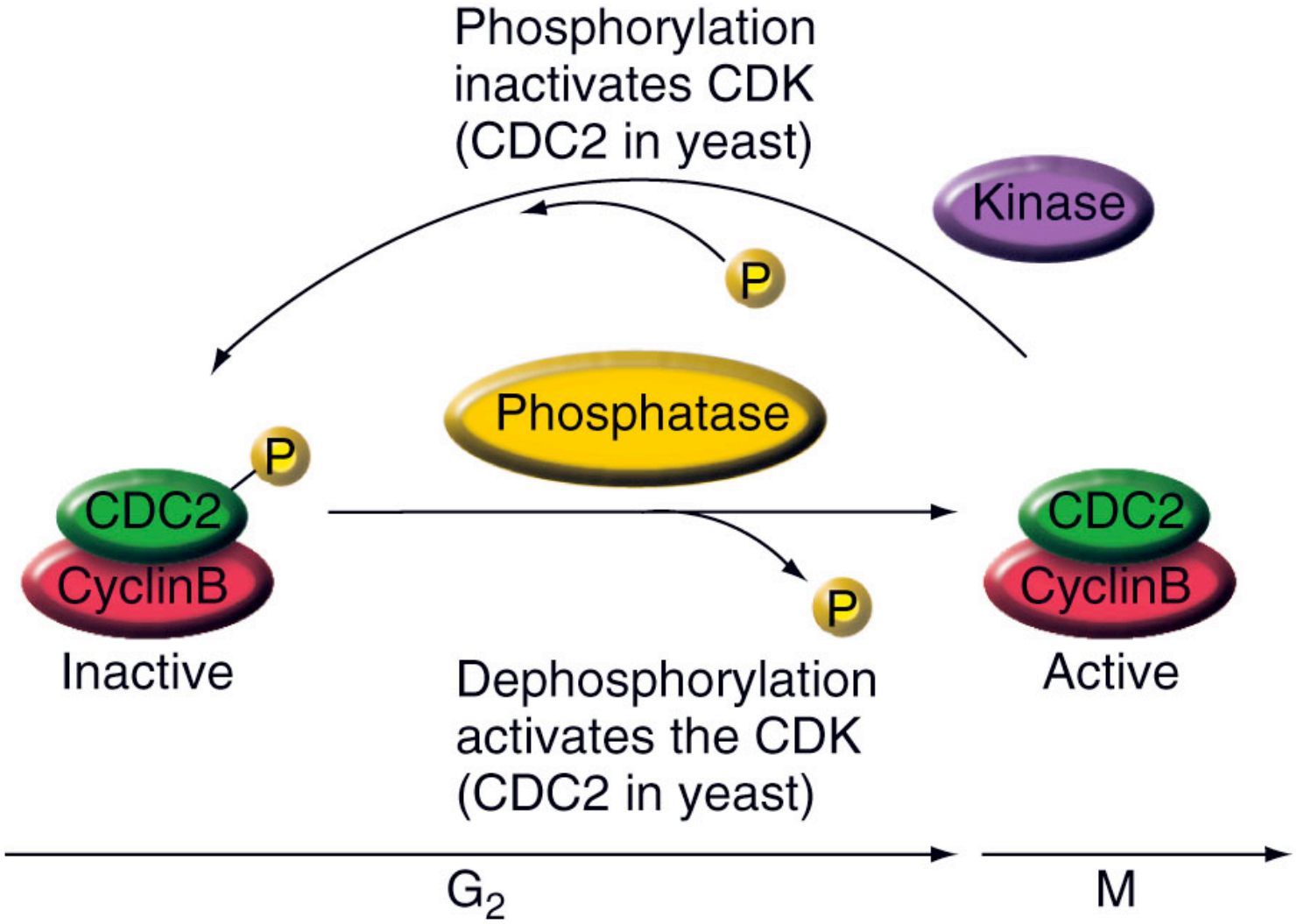


Fig. 18.10

G_2-to-M check points

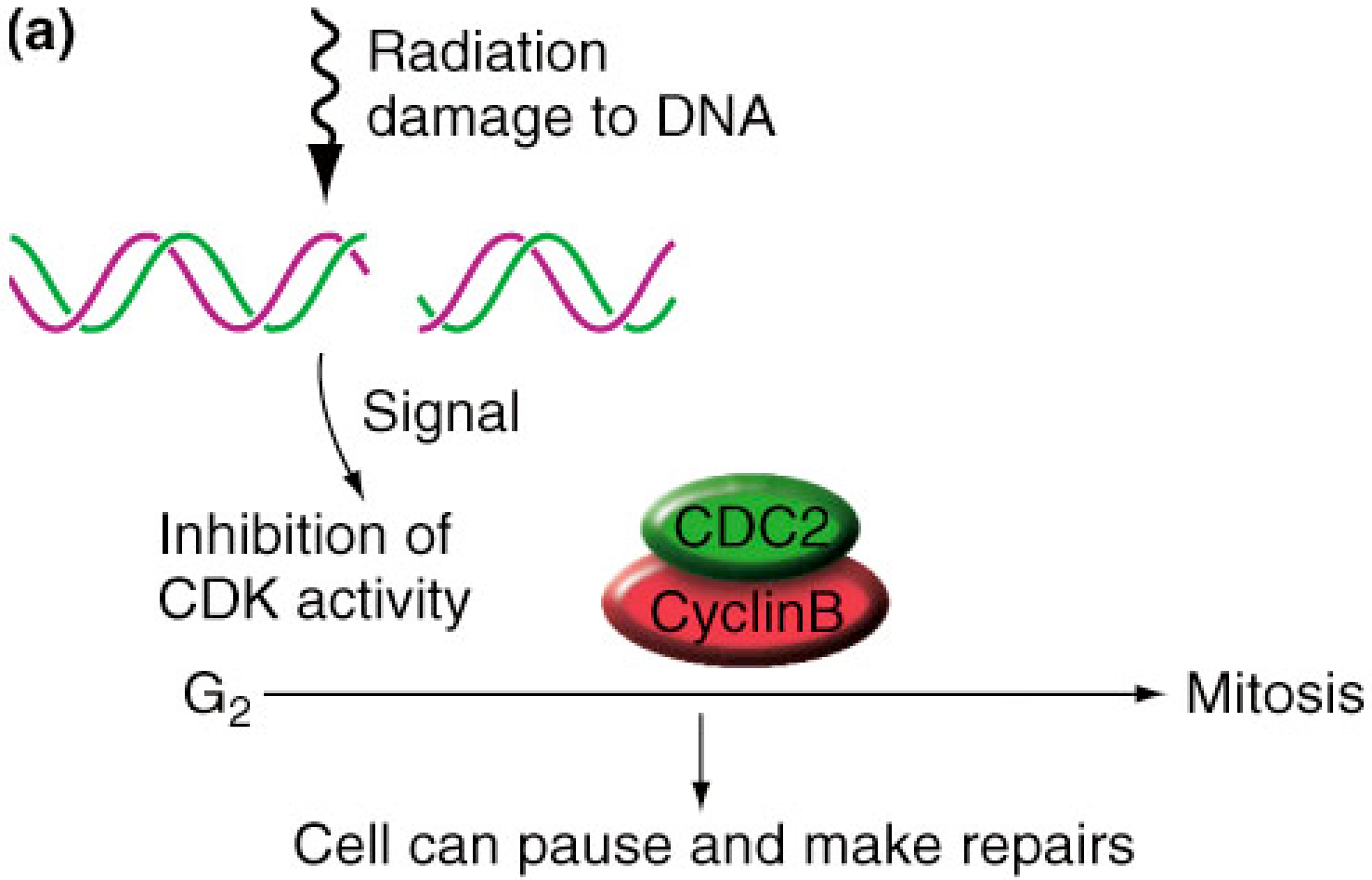


Fig. 18.12a

Metaphase to anaphase checkpoint

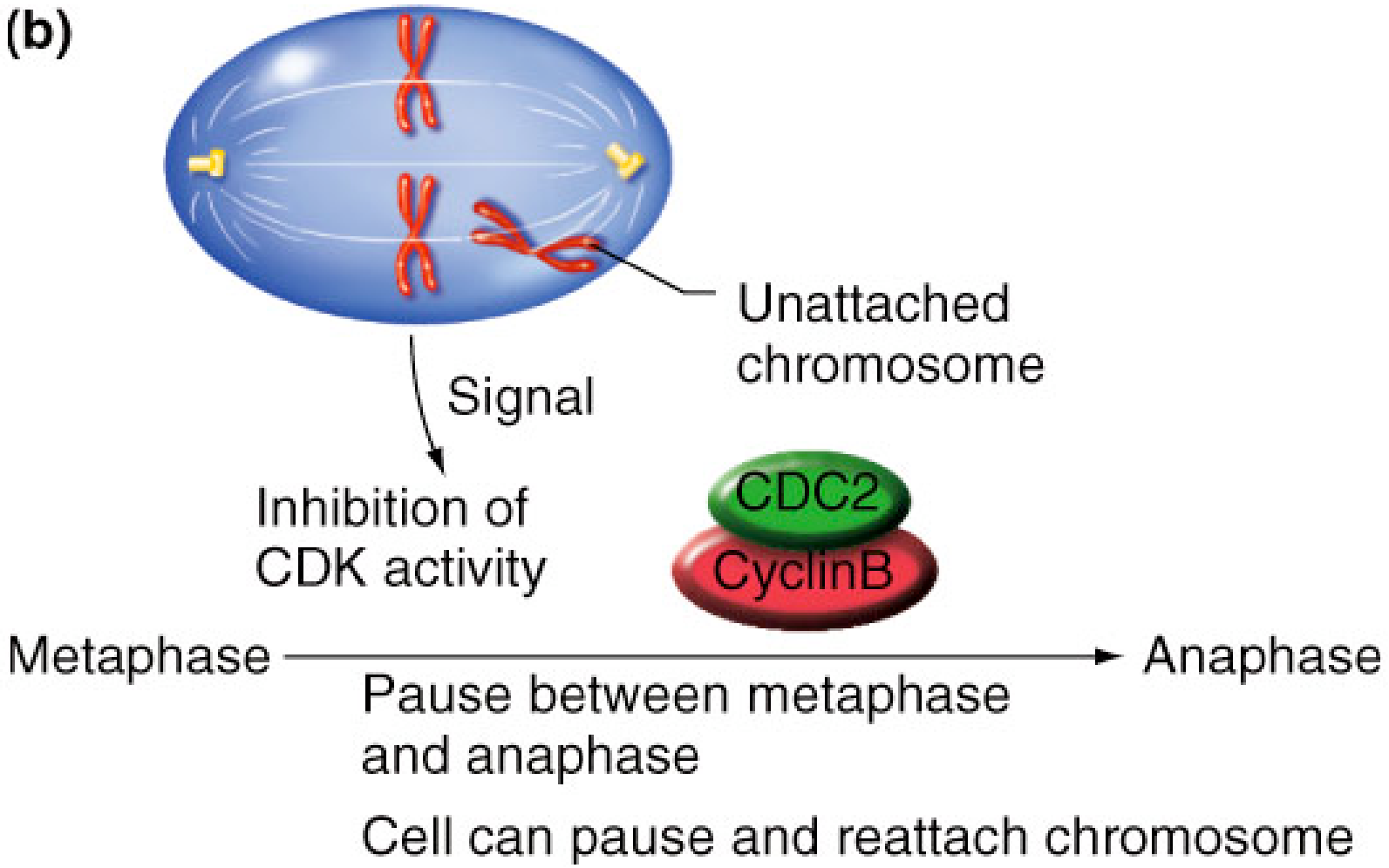
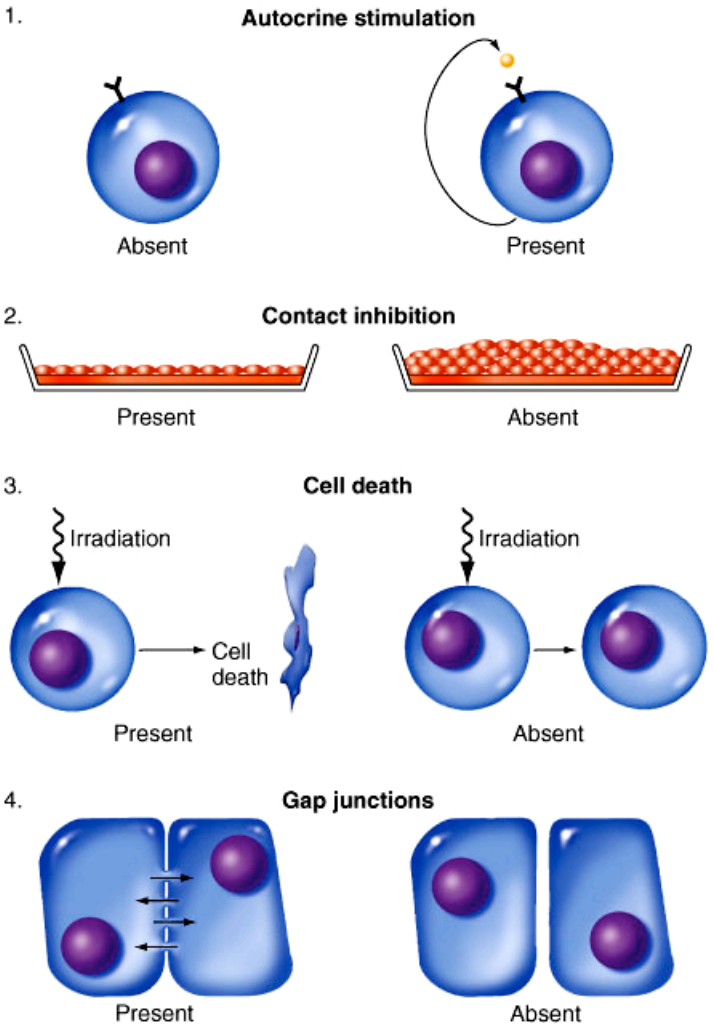


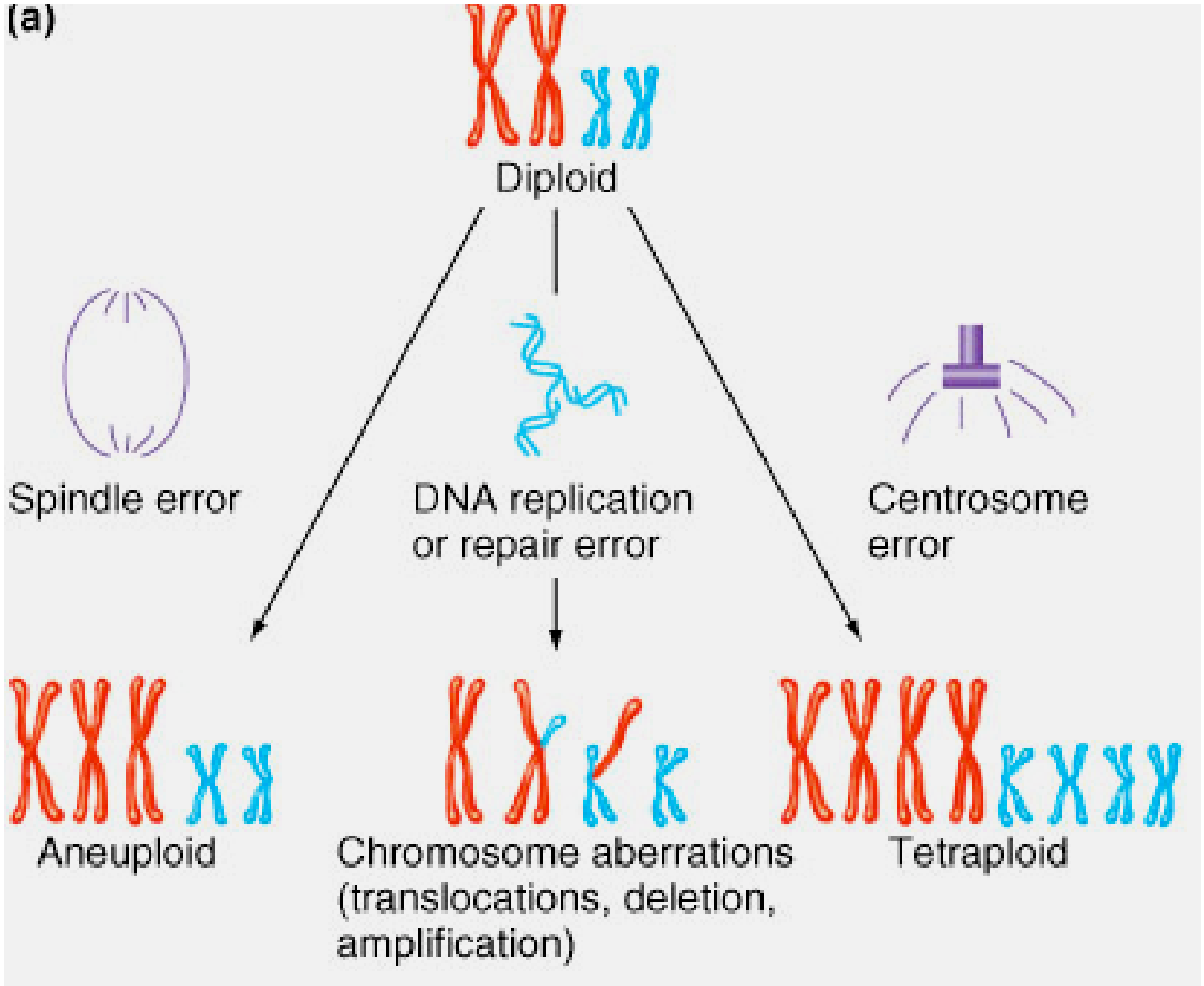
Fig. 18.12b

General cancer phenotype includes many types of cellular abnormalities

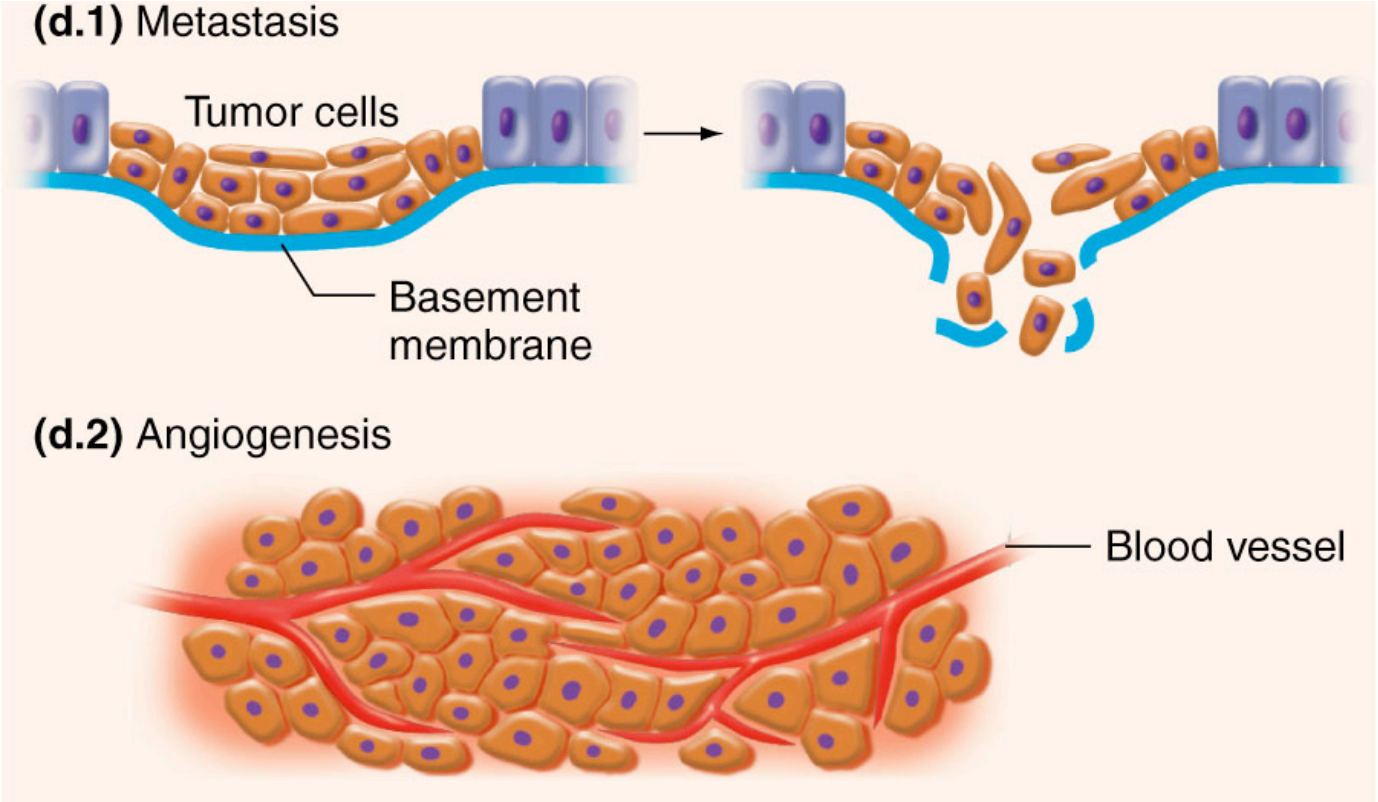


- Autocrine stimulation – tumor cells make their own signals to divide
- Loss of contact inhibition – lost property to stop dividing when contacted by another cell
- Loss of cell death – resistance to programmed cell death
- Loss of gap junctions – no channels for connecting to neighbor cell

Three classes of error lead to aneuploidy in tumor cells



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



- 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

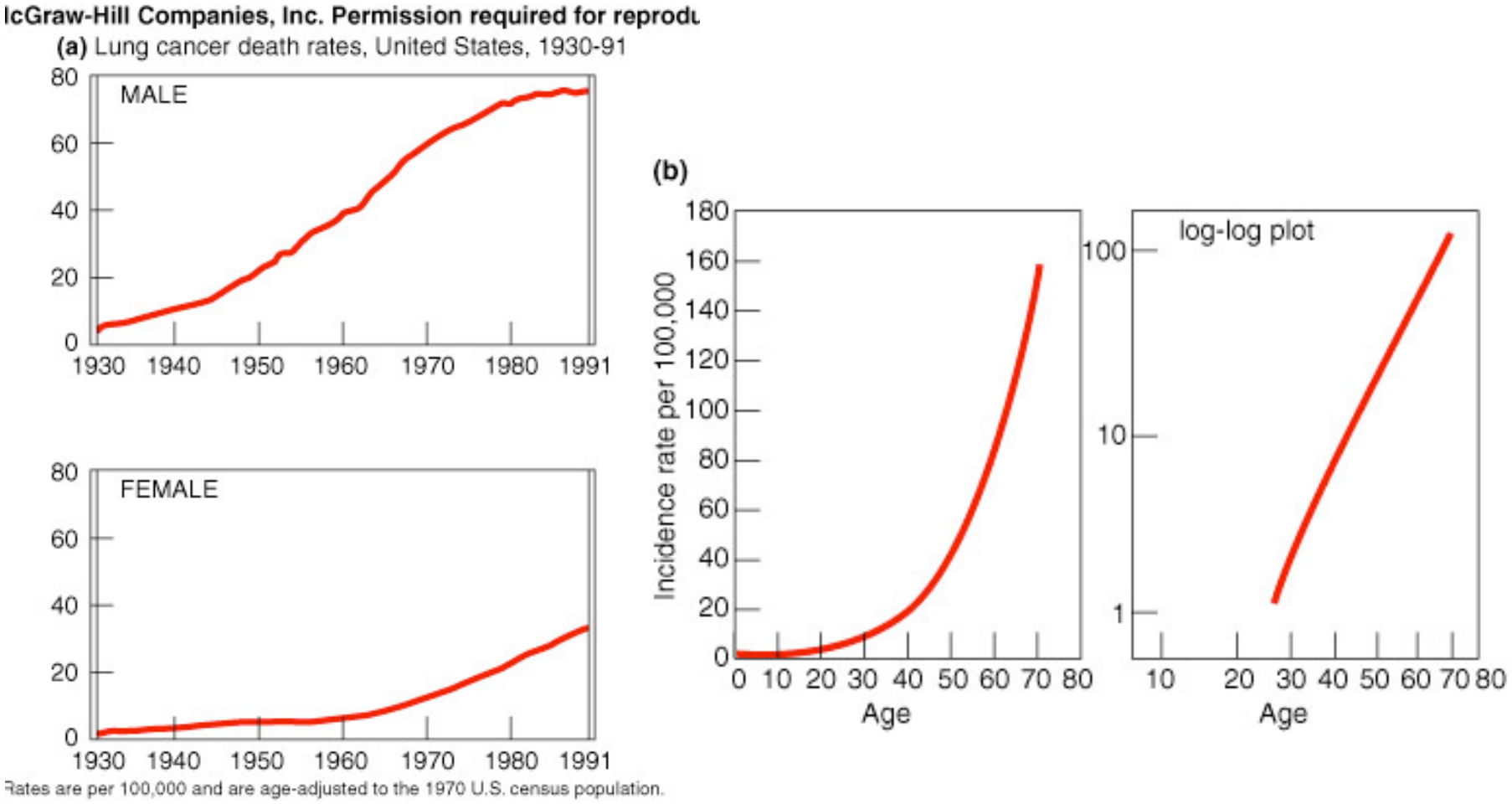
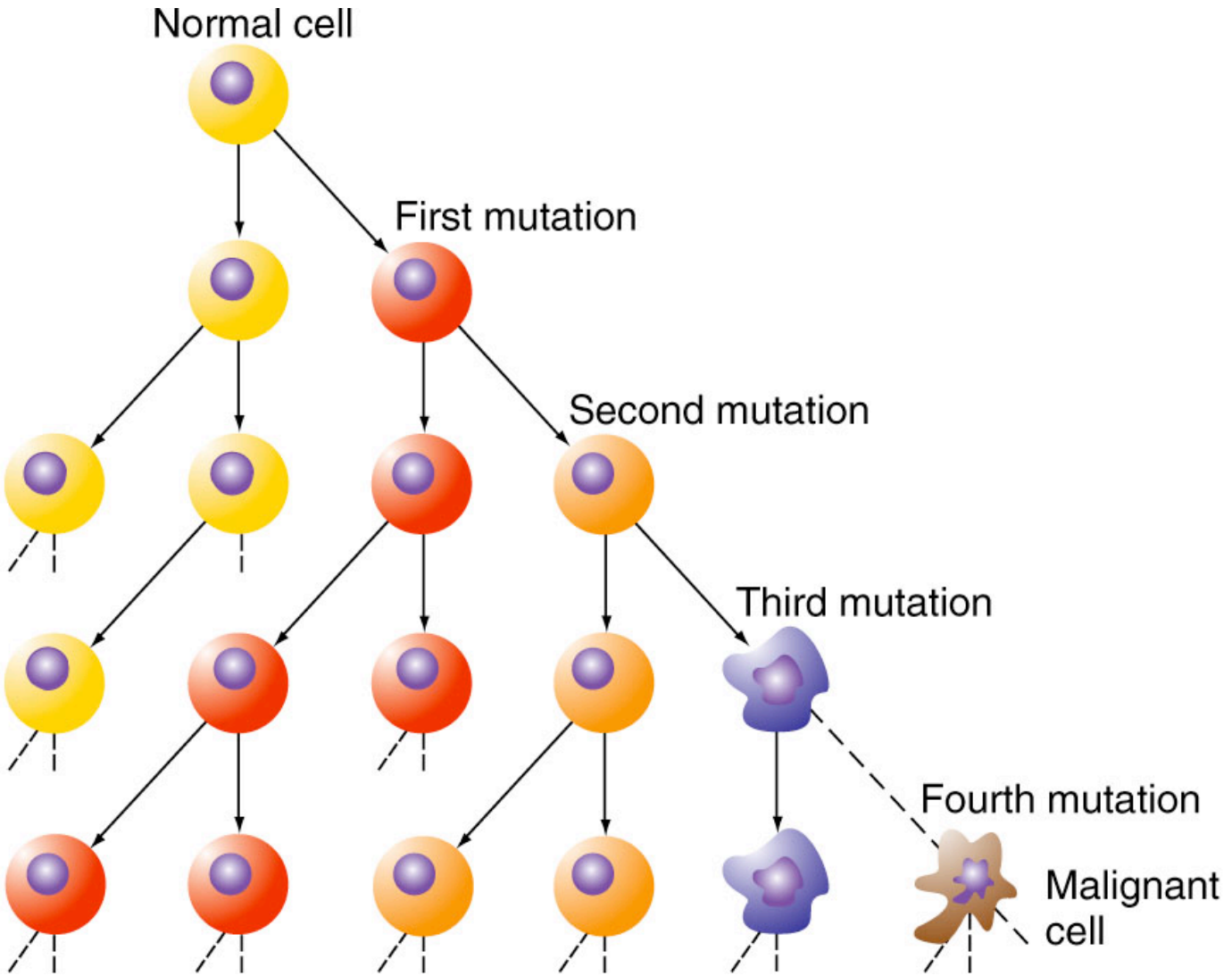
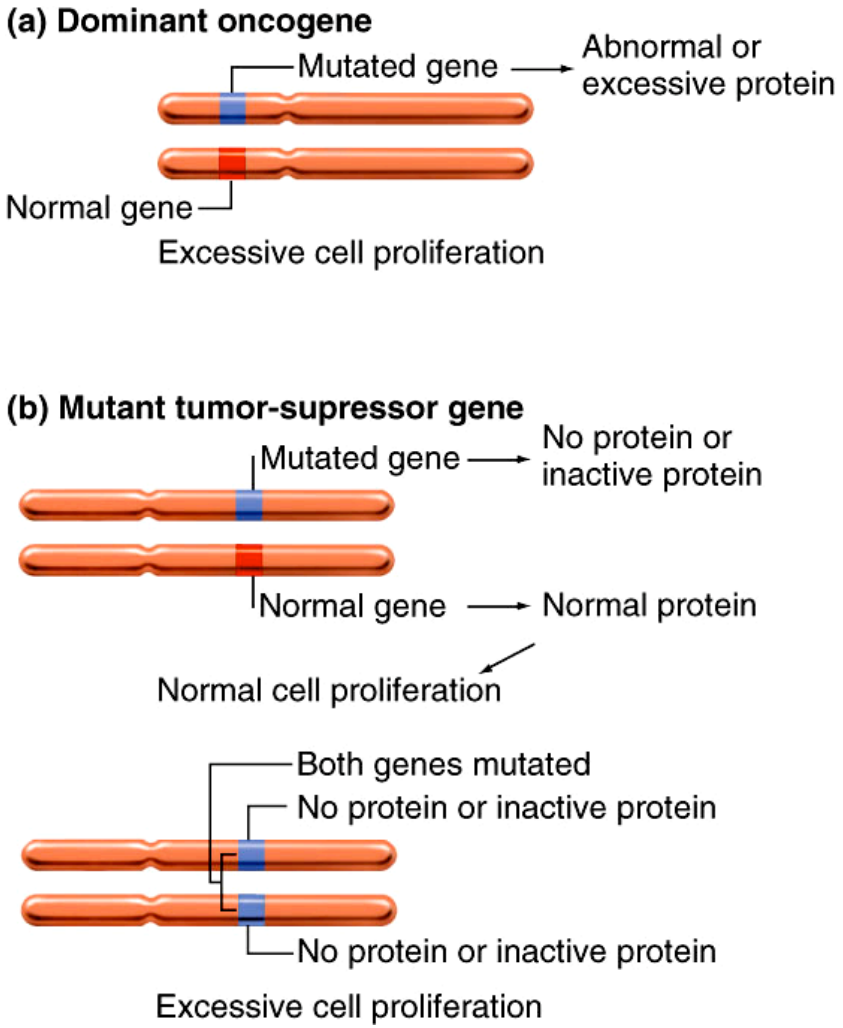


Fig. 18.19

Cancer arises by successive mutations in a clone of proliferating cells



Cancer mutations occur in two forms

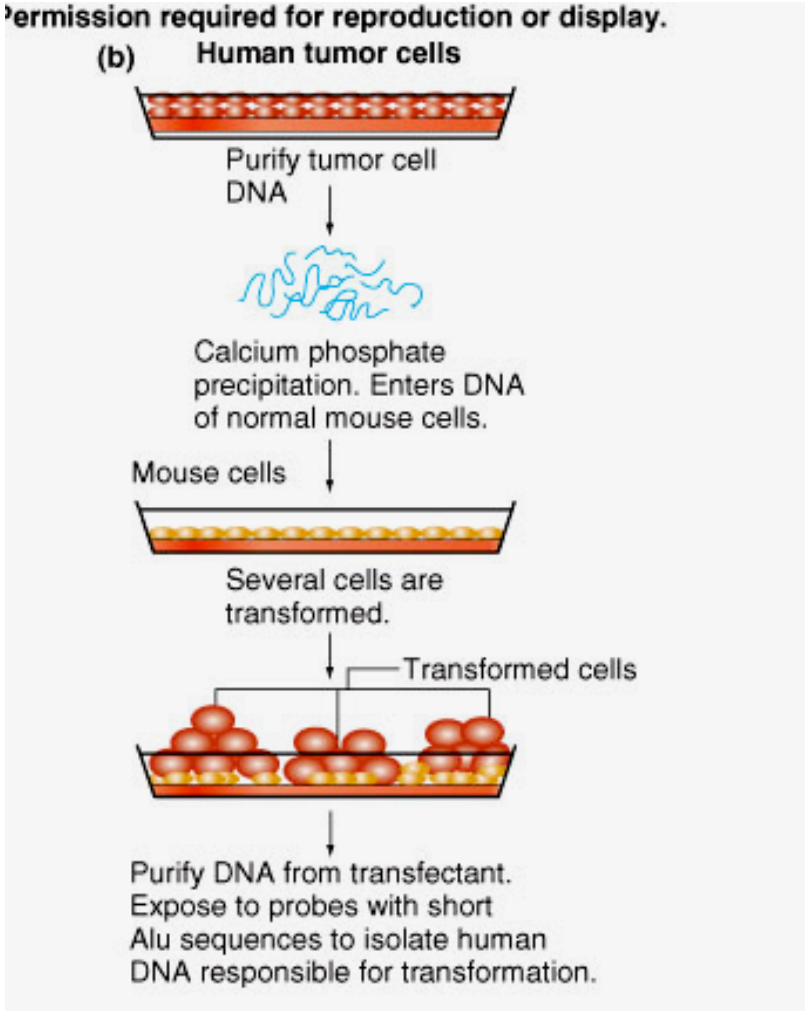


- Oncogenes
  - dominant mutations
- Mutant tumor-suppressor genes
  - recessive mutations

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*



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

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

Some cancers run in families such as retinoblastoma