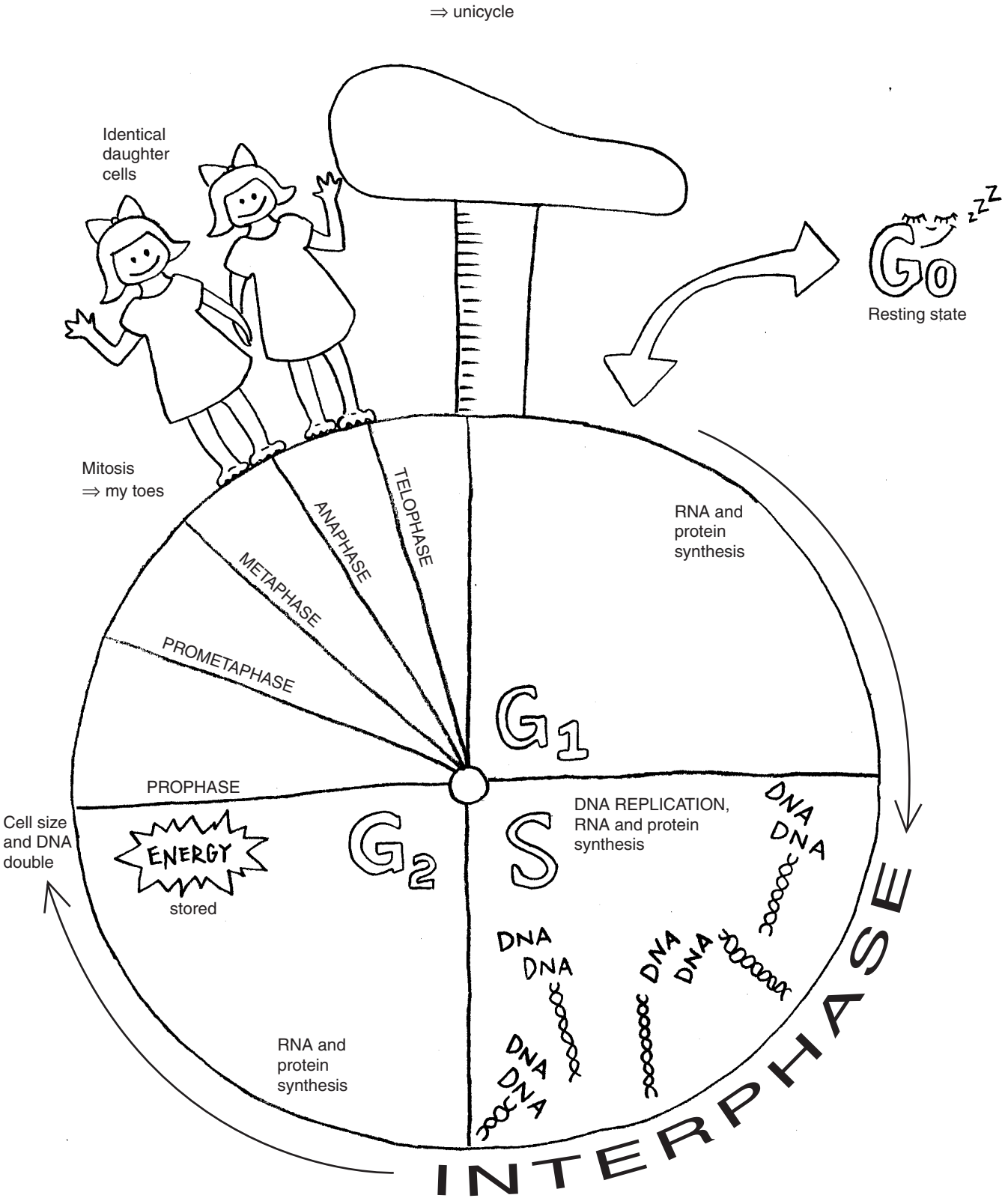
NOTES

CELL CYCLE

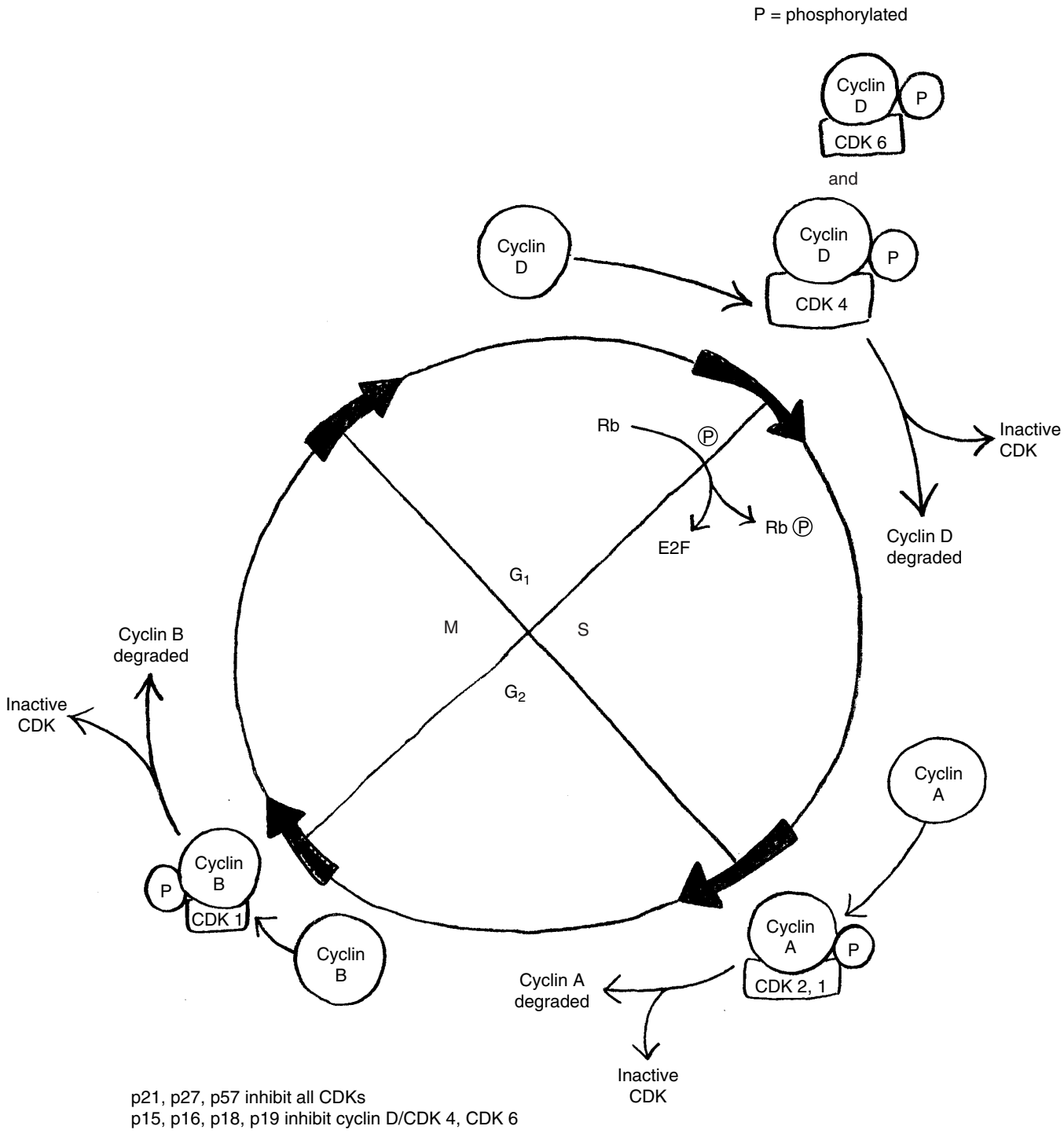
- G_0 state
  - Resting cells may re-enter the cell cycle
- Nondividing cells (skeletal and cardiac muscle, neurons)
  - Have left the cell cycle and cannot undergo mitosis
- The cell cycle is divided into two periods: **interphase** and **mitosis**
- During interphase, the cell size and amount of DNA double
- Interphase is the period between cell divisions and is divided into G_1, S, and G_2
- G_1 phase (gap one phase)
  - RNA and protein synthesis occur
  - Cells reach a restriction point and proceed to the S phase
  - Cells that fail to reach the restriction point enter the G_0 state
- S phase (synthetic phase)
  - DNA, RNA, and protein synthesis occur
  - 8–12 hours' duration
  - DNA replication occurs, resulting in chromosome duplication
  - S-phase activator initiates DNA synthesis
- G_2 phase (gap two phase)
  - RNA and protein synthesis occur
  - 2–4 hours' duration
  - During G_2, the cell prepares for mitosis; energy is stored and the centrioles mature
- Mitosis
  => my toes
  - Division of the nucleus and cytoplasm occurs
  - Results in two identical daughter cells
  - Five stages: prophase, prometaphase, metaphase, anaphase, telophase
  - 1–3 hours' duration
  - M-phase promoting factor allows the cell to enter mitosis
  - M-phase delaying factor inhibits synthesis of the M-phase promoting factor until all of the DNA is replicated


⇒ unicycle
Identical daughter cells
Mitosis
⇒ my toes
PROPHASE
PROMETAPHASE
METAPHASE
ANAPHASE
TELOPHASE
RNA and protein synthesis
G1
S
DNA REPLICATION, RNA and protein synthesis
G2
ENERGY
stored
Cell size and DNA double
RNA and protein synthesis
G0
Resting state
INTERPHASE

NOTES

CYCLINS, CYCLIN-DEPENDENT KINASES (CDKs), AND THE REGULATION OF THE CELL CYCLE

- Cyclins control the progression of cells through the phases of the cell cycle by forming complexes with cyclin-dependent kinases (CDKs)
- Specific combinations of cyclins and CDKs are associated with the transitions in the cell cycle
- The complexes of cyclins and CDKs are activated by phosphorylation. The active kinase phosphorylates critical proteins in DNA replication, mitosis, and spindle formation for progression through the cell cycle
  - Cyclin D/CDK 4, 6 control $G_1 \rightarrow S$
  - Cyclin E/CDK 2 control $G_1 \rightarrow S$
  - Cyclin A/CDK 2, 1 control $S \rightarrow G_2$
  - Cyclin B/CDK 1 control $G_2 \rightarrow M$
- After a cell enters the next phase, the cyclin is degraded and the CDK returns to the inactive state
- The active CDK complexes are regulated by CDK inhibitors (p21, p27, p57; and p16, p15, p18, p19)
- CDK inhibitors p21, p27, and p57 inhibit all CDKs, while p16, p15, p18, and p19 selectively inhibit cyclin D/CDK 4, CDK 6
- The transition from G_1 to S is extremely important because the cells are committed to the S phase. Another critical step is the phosphorylation of the retinoblastoma protein (pRb) by cyclin D/CDK 4, CDK6
- Phosphorylation of pRb unbinds E2F transcription factors so they can transcribe genes whose products are required for S phase
- Amplification of cyclin D genes occurs in many cancers, including breast and liver
- Amplification of CDK 4 gene occurs in melanomas, sarcomas, and glioblastomas


P = phosphorylated
Cyclin D
P
CDK 6
and
Cyclin D
Cyclin D
P
CDK 4
Inactive CDK
Rb
Ⓟ
Rb Ⓟ
E2F
Cyclin D degraded
G1
M
S
G2
Cyclin B degraded
Inactive CDK
Cyclin A
Cyclin B
P
CDK 1
Cyclin B
Cyclin A
P
CDK 2, 1
Cyclin A degraded
Inactive CDK
p21, p27, p57 inhibit all CDKs
p15, p16, p18, p19 inhibit cyclin D/CDK 4, CDK 6

NOTES

ONCOGENES

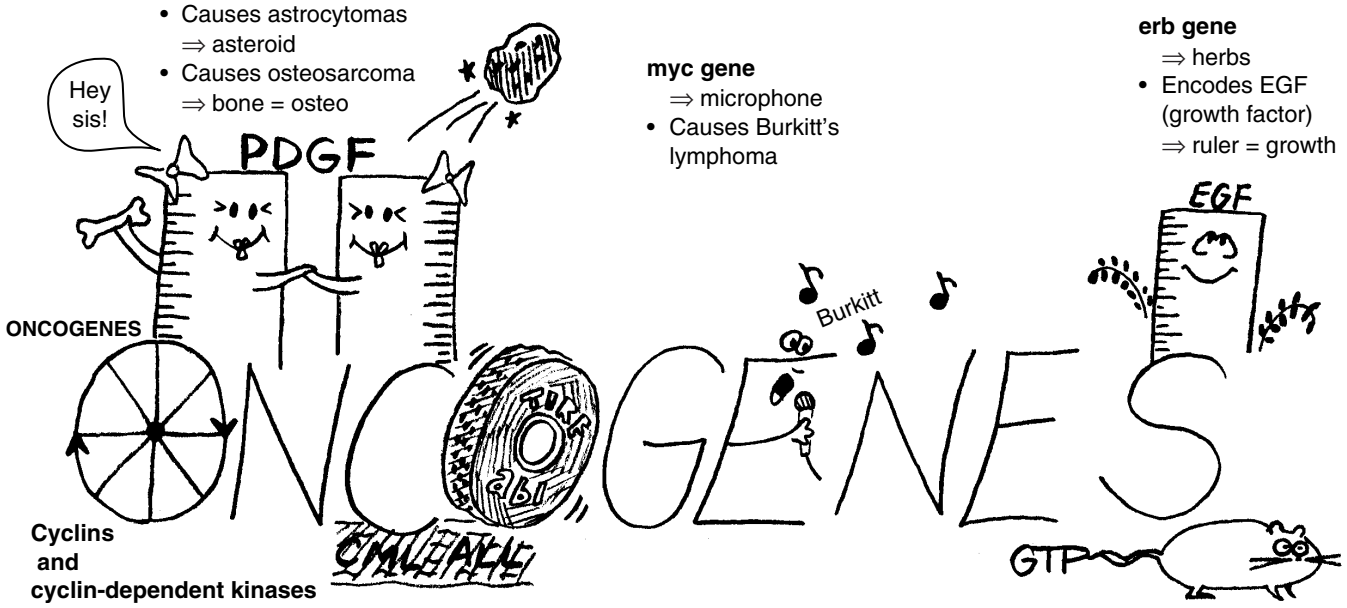
- Oncogenes are derived from mutations of proto-oncogenes and may induce a cell to become malignant
- Proto-oncogenes are involved with normal cellular growth and differentiation
- Retroviral transduction of proto-oncogenes by viral oncogenes (v-onc) induces tumorigenesis
- Genes with mutations that encode growth factor, growth factor receptors, signal-transducing proteins, transcription proteins, cyclins, and cyclin-dependent kinases may become oncogenic
- Proto-oncogenes are transformed into oncogenes by point mutations, chromosomal rearrangements (translocation), or overexpression

PROTEIN PRODUCTS	ONCOGENE	ACTIVATION	TUMORS
Cell cycle regulators			
Cyclins	Cyclin D	Overexpression	Breast, liver
Cyclin-dependent kinases (CDKs)	CDK 4	Overexpression	Melanoma, glioblastoma
Transcription protein	myc	Translocation	Burkitt's lymphoma
Signal-transducing proteins			
GTP-binding	ras	Point mutation	Many cancers
Tyrosine kinase	abl	Translocation	Acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML)
Growth factors			
Platelet-derived growth factor (PDGF)	sis	Overexpression	Astrocytoma, osteosarcoma
Growth factor receptor			
Epidermal growth factor (EGF)	erb	Overexpression	Squamous cell carcinoma of lung, breast, GI, ovarian

sis gene
⇒ sisters
- Encodes PDGF (growth factor)
  ⇒ rulers = growth
- Causes astrocytomas
  ⇒ asteroid
- Causes osteosarcoma
  ⇒ bone = osteo

myc gene
⇒ microphone
- Causes Burkitt's lymphoma

erb gene
⇒ herbs
- Encodes EGF (growth factor)
  ⇒ ruler = growth



Cyclins and cyclin-dependent kinases
⇒ cycle
- Regulate cell cycle

abl gene
- Encodes tyrosine kinase protein
  ⇒ tire = tyrosine
- Causes CML and ALL (leukemias)

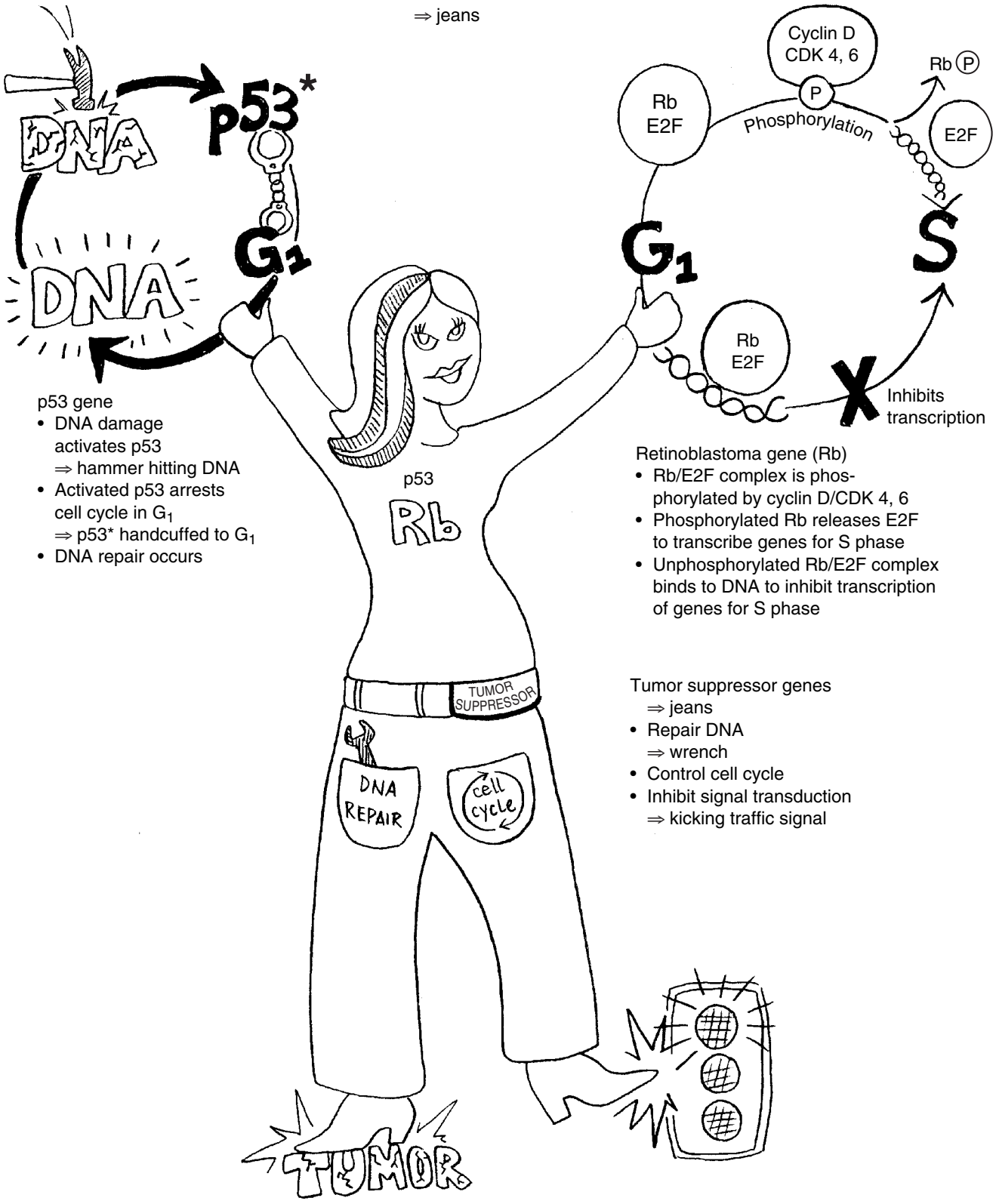
ras gene
⇒ rat
- Encodes GTP-binding protein

NOTES

TUMOR SUPPRESSOR GENES

=> jeans

- Tumor suppressor genes regulate cell growth
- Tumor suppressor genes encode proteins that control the cell cycle and transcription, repair DNA, inhibit signal transduction, and inhibit growth
  Repair DNA = wrench
  Inhibit signal transduction = kicking traffic signal
- Retinoblastoma gene (Rb)
  - Regulates $G_1 \rightarrow S$ of cell cycle
  - Underphosphorylated Rb protein complexes with E2F transcription factors and binds to DNA to inhibit transcription of genes essential for S phase
  - Rb protein is phosphorylated by cyclin D/CDK 4, 6 and Rb releases E2F. The E2F transcription factor then transcribes genes for S phase. Cells are then committed to divide
- p53 gene
  - p53 is activated by DNA damage and arrests the cell cycle in G_1 to induce DNA repair
    p53 activated by DNA damage = hammer hitting DNA
    Activated p53 arrests cell cycle = p53 handcuffed to G_1
  - If DNA repair is unsuccessful, then p53 activates the bax gene to induce apoptosis
  - Mutations or loss of p53 allows DNA-damaged cells to proliferate, leading to malignant tumors



p53 gene
- DNA damage activates p53
  ⇒ hammer hitting DNA
- Activated p53 arrests cell cycle in G_1
  ⇒ p53* handcuffed to G_1
- DNA repair occurs

Retinoblastoma gene (Rb)
- Rb/E2F complex is phosphorylated by cyclin D/CDK 4, 6
- Phosphorylated Rb releases E2F to transcribe genes for S phase
- Unphosphorylated Rb/E2F complex binds to DNA to inhibit transcription of genes for S phase

Tumor suppressor genes
  ⇒ jeans
- Repair DNA
  ⇒ wrench
- Control cell cycle
- Inhibit signal transduction
  ⇒ kicking traffic signal