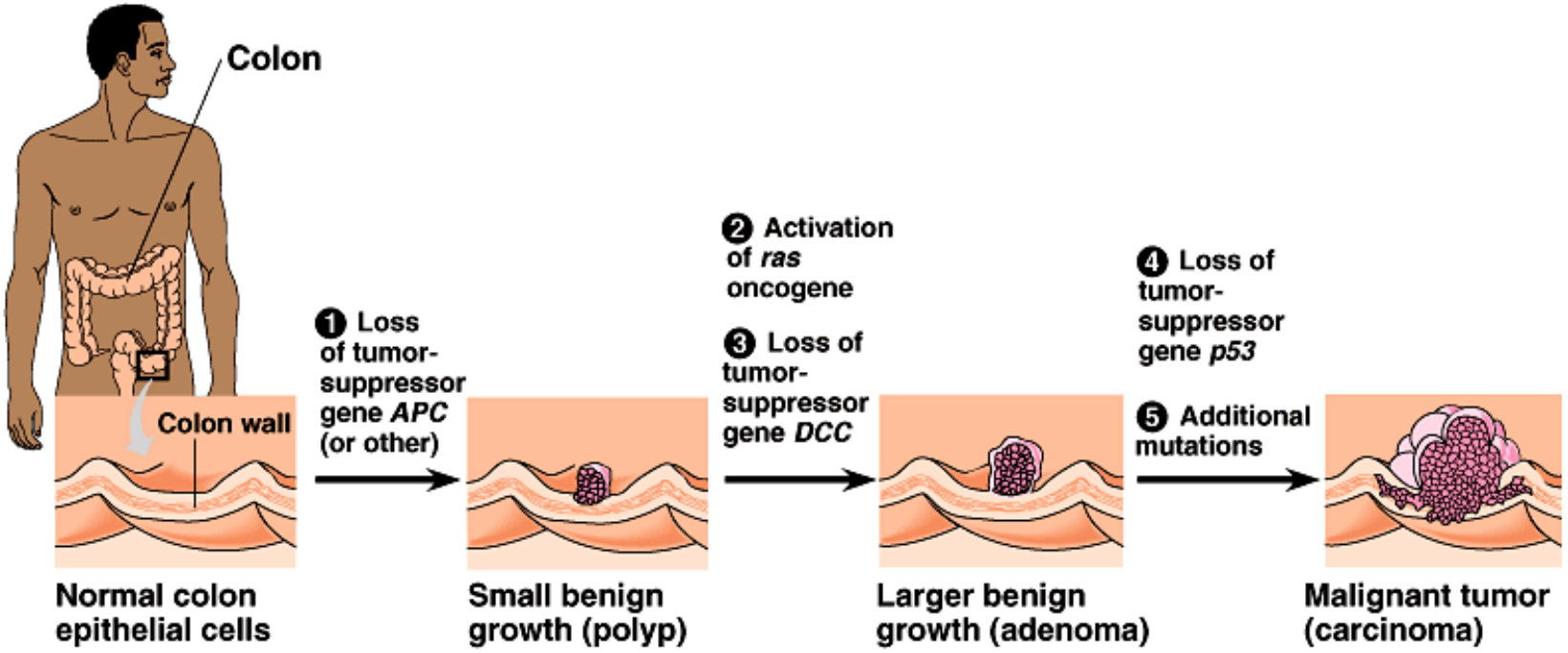
The Problem of Cancer

What are cancer cells ?

- **Cancerous growth involves unrestrained proliferation (malignancy) and spread (metastasis).**
- **Caused by: mutations that alter normal gene expression, exposure to carcinogens, infection from certain viruses (leukemia, liver cancer, cervical cancer)**
- **Viruses may add oncogenes, disrupt TSG (tumor-suppressor genes), or convert proto-oncogenes to oncogenes.**
- **Cells that do not demonstrate contact inhibition.**
- **Benign tumors – are not metastatic but continue to divide**
- **Cancer – no contact inhibition and continues to divide**

Characteristics of Cultured Cancer Cells

- Abnormal number of chromosomes
- Spherical and embryonic
- Anchorage independence
- Abnormal surfaces (fewer glycoproteins and glycolipids)
- Metastatic cancer cells produce laminin to bind to tissue cells and collagenase to break through and migrate.


Colon
Colon wall
1 Loss of tumor-suppressor gene *APC* (or other)
2 Activation of *ras* oncogene
3 Loss of tumor-suppressor gene *DCC*
4 Loss of tumor-suppressor gene *p53*
5 Additional mutations
Normal colon epithelial cells
Small benign growth (polyp)
Larger benign growth (adenoma)
Malignant tumor (carcinoma)

What is the multistep hypothesis ?

- More than one somatic mutation (usually 6) is probably needed to transform normal cells into cancerous cells.
- Conversion of normal cell to cancer cell involves many changes such as:

1) Unlimited cell divisions
2) Loss of contact inhibition
3) Loss of anchorage dependence
4) Vascularization (forming blood vessels)
5) Destruction of lamina and metastasis

What are oncogenes ?

Oncogenes are genes that cause cancer because they make the host cell proliferate abnormally.

Proto-oncogenes are genes that code for proteins that stimulate normal cell growth and division. They become oncogenes if the growth is uncontrollable.

How do oncogenes cause cancer ?

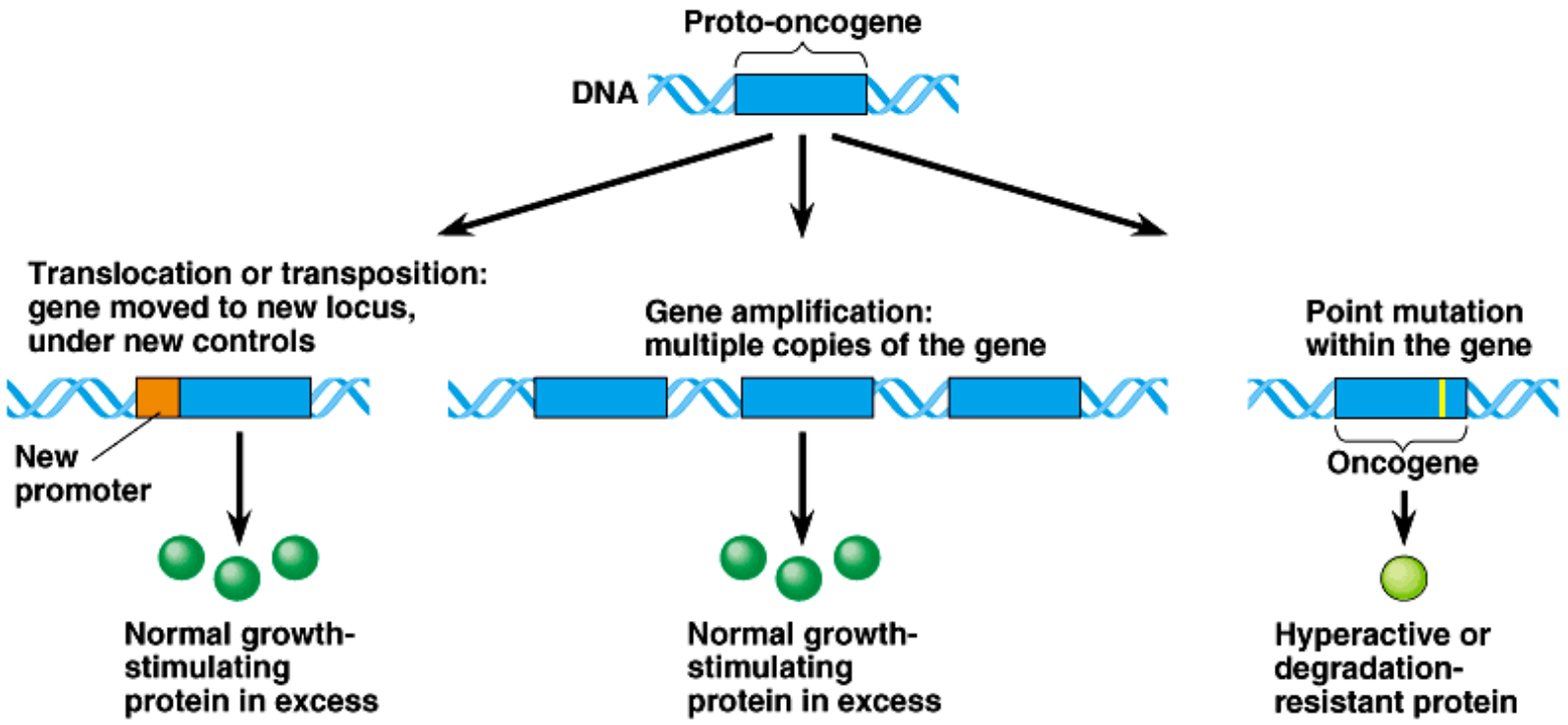
Oncogenes:

1) Produce too many growth factors or prevent tumor-suppressor genes from operating.
2) Affect the receptors of growth factors.
3) Produce products that prevent cells from adhering to one another.
4) Produce intracellular signals that turn cell division sites on.
5) Produce DNA-binding molecules which promote transcription of genes involved with DNA replication and cell division.

How do proto-oncogenes become oncogenes ?

Proto-oncogenes become oncogenes through mutations which:

1) Cause gene amplification (many copies of proto-oncogenes are made, increasing the possibility of further mutation and over-expression of growth factor.
2) Chromosome translocation near active promoter
3) Gene transposition near active promoter
4) Point mutations making growth factor more active or resistant to protein degradation.

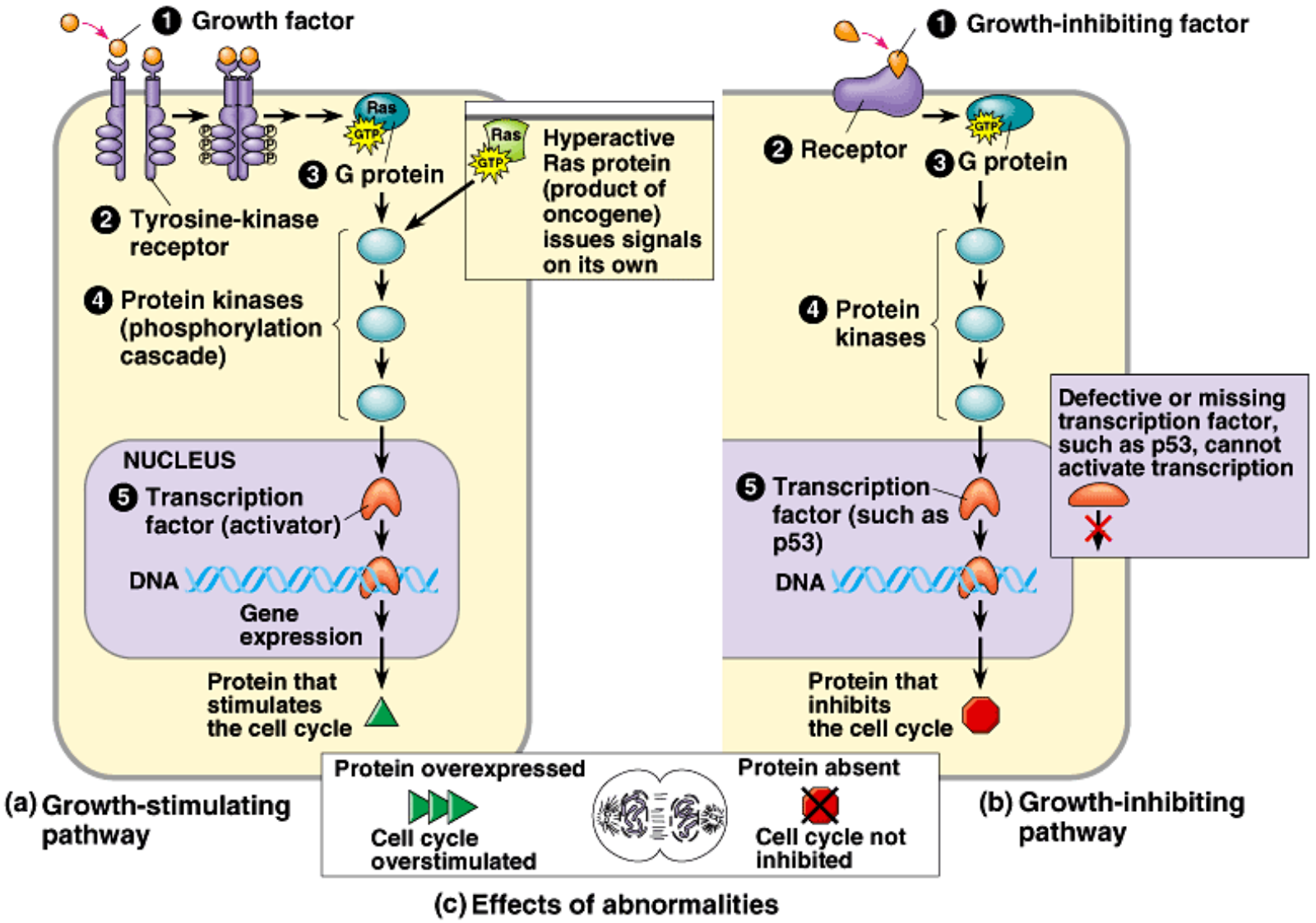

Proto-oncogene
DNA
Translocation or transposition:
gene moved to new locus,
under new controls
New
promoter
Normal growth-
stimulating
protein in excess
Gene amplification:
multiple copies of the gene
Normal growth-
stimulating
protein in excess
Point mutation
within the gene
Oncogene
Hyperactive or
degradation-
resistant protein

What are anti-oncogenes ?

- Anti-oncogenes are genes that encode for proteins that deactivate oncogene products.
- If these anti-oncogenes fail, oncogene products can function and initiate cancer process.

What is the Ras proto-oncogene ?

- This proto-oncogene usually responds to a growth factor and stimulates the production of proteins that stimulate the cell cycle.
- Ras oncogene is caused by a point mutation. It works by issuing signals for further cell division on its own without growth factors (30% of all human cancers)


1 Growth factor
Ras
GTP
3 G protein
2 Tyrosine-kinase receptor
Ras
GTP
Hyperactive Ras protein (product of oncogene) issues signals on its own
4 Protein kinases (phosphorylation cascade)
NUCLEUS
5 Transcription factor (activator)
DNA
Gene expression
Protein that stimulates the cell cycle
(a) Growth-stimulating pathway
1 Growth-inhibiting factor
2 Receptor
GTP
3 G protein
4 Protein kinases
Defective or missing transcription factor, such as p53, cannot activate transcription
5 Transcription factor (such as p53)
DNA
Protein that inhibits the cell cycle
(b) Growth-inhibiting pathway
Protein overexpressed
Cell cycle overstimulated
Protein absent
Cell cycle not inhibited
(c) Effects of abnormalities

What is the p53 tumor suppressor gene ?

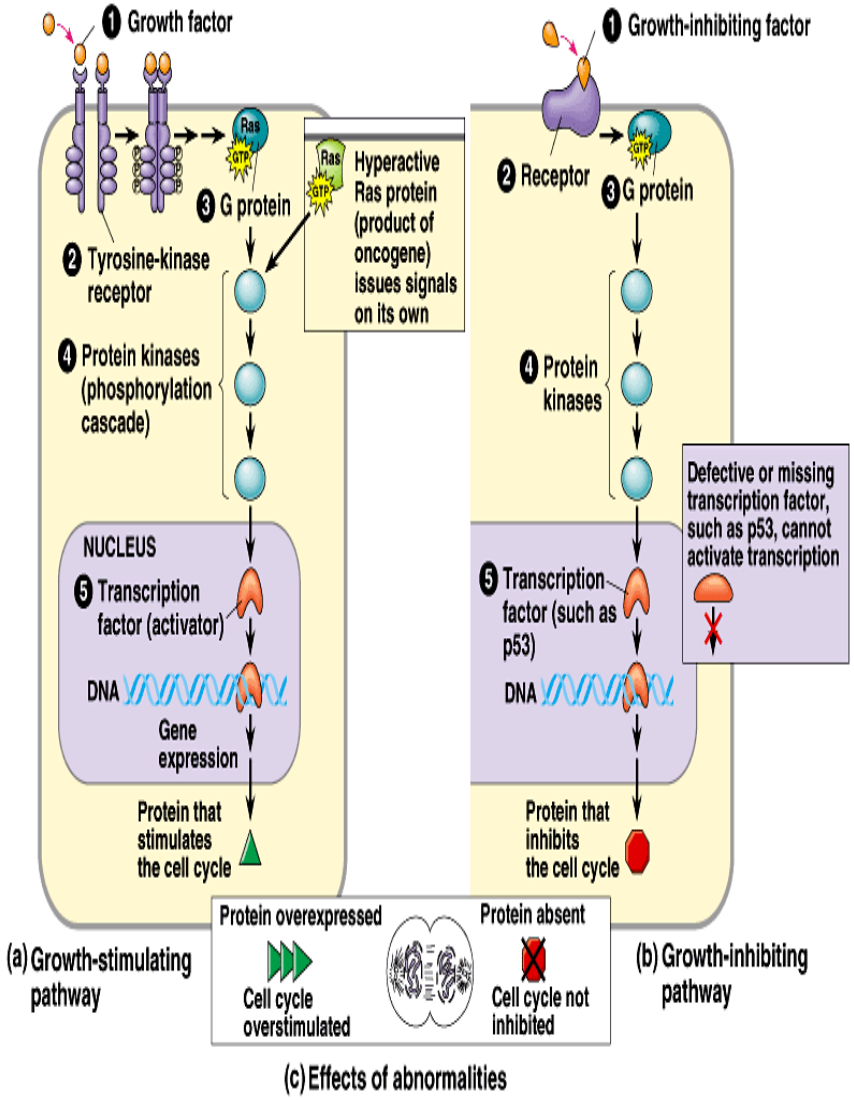
- Tumor-suppressor genes create products that inhibit cell division by:
  1) Repairing mutated DNA
  2) Controlling adhesion (cancer cells do not adhere to other cells, normal cells do)
  3) Components of cell-signaling pathways

If TSG's mutate, cancerous effects increase.

p53 tumor suppressor gene

- Normal p53 TSG produce transcription factors that help turn on genes that inhibit cell growth. (50 % human cancers occur when these genes mutate). They:

1) Activate p21 gene which produces a product that binds to cyclin-dependen kinases, slowing cell growth.
2) Turn on genes that help in DNA repair
3) Turn on suicide genes that destroy cells with irreparable damage.



What affects breast cancer ?

- Breast cancer is associated with somatic mutations to tumor-suppressor genes.
- Inherited cancer (5-15%)
- Mutations in either the BRCA1 or BRCA2 gene