Cancer genetics

Chapter 14

Facts

- Inherited genetic mutations play a major role in about 5 to 10 percent of all cancers
- Mutations in specific genes associated with more than 50 hereditary cancer syndromes

Examples of hereditary cancer syndromes

- Hereditary breast cancer and ovarian cancer syndrome
  - Genes: BRCA1, BRCA2
  - Related cancer types: Female breast, ovarian, and other cancers, including prostate, pancreatic, and male breast cancer
- Li-Fraumeni syndrome
  - Gene: TP53
  - Related cancer types: Breast cancer, soft tissue sarcoma, osteosarcoma (bone cancer), leukemia, brain tumors, adrenocortical carcinoma (cancer of the adrenal glands), and other cancers
- Cowden syndrome (PTEN hamartoma tumor syndrome)
  - Gene: PTEN
  - Related cancer types: Breast, thyroid, endometrial (uterine lining), and other cancers
- Lynch syndrome (hereditary nonpolyposis colorectal cancer)
  - Genes: MSH2, MLH1, MSH6, PMS2, EPCAM
  - Related cancer types: Colorectal, endometrial, ovarian, renal pelvis, pancreatic, small intestine, liver and biliary tract, stomach, brain, and breast cancers

Examples of hereditary cancer syndromes

- Familial adenomatous polyposis
  - Gene: APC
  - Related cancer types: Colorectal cancer, multiple non-malignant colon polyps, and both non-cancerous (benign) and cancerous tumors in the small intestine, brain, stomach, bone, skin, and other tissues
- Retinoblastoma
  - Gene: RB1
  - Related cancer types: Eye cancer (cancer of the retina), pinealoma (cancer of the pineal gland), osteosarcoma, melanoma, and soft tissue sarcoma
- Multiple endocrine neoplasia type 2
  - Gene: RET
  - Related cancer types: Medullary thyroid cancer and pheochromocytoma (benign adrenal gland tumor)
- Von Hippel-Lindau syndrome
  - Gene: VHL
  - Related cancer types: Kidney cancer and multiple noncancerous tumors, including pheochromocytoma

Features of hereditary cancer include the following:

- In the individual patient:
  - Multiple primary tumors in the same organ.
  - Multiple primary tumors in different organs.
  - Bilateral primary tumors in paired organs.
  - Multifocality within a single organ (e.g., multiple tumors in the same breast, all of which have risen from one original tumor).
  - Younger-than-usual age at tumor diagnosis.
  - Tumors with rare histology.
  - Tumors occurring in the sex not usually affected (e.g., breast cancer in men).
  - Tumors associated with other genetic traits.
  - Tumors associated with congenital defects.
  - Tumors associated with an inherited precursor lesion.
  - Tumors associated with another rare disease.

Features of hereditary cancer include the following:

- In the patient's family:
  - One first-degree relative with the same or a related tumor and one of the individual features listed.
  - Two or more first-degree relatives with tumors of the same site.
  - Two or more first-degree relatives with tumor types belonging to a known familial cancer syndrome.
  - Two or more first-degree relatives with rare tumors.
  - Three or more relatives in two generations with tumors of the same site or etiologically related sites.

Oncogenes

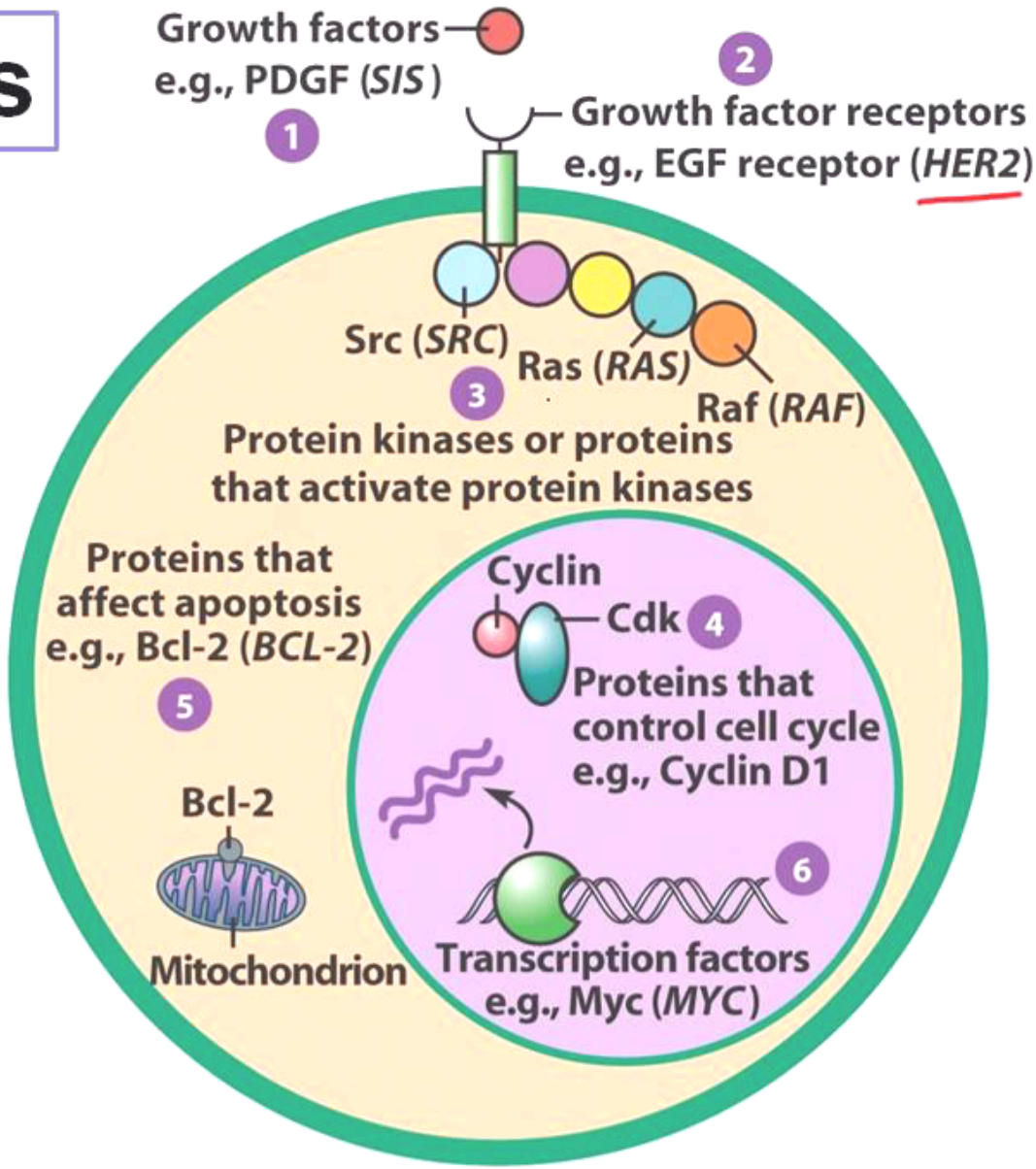


Figure 16-20 Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons)

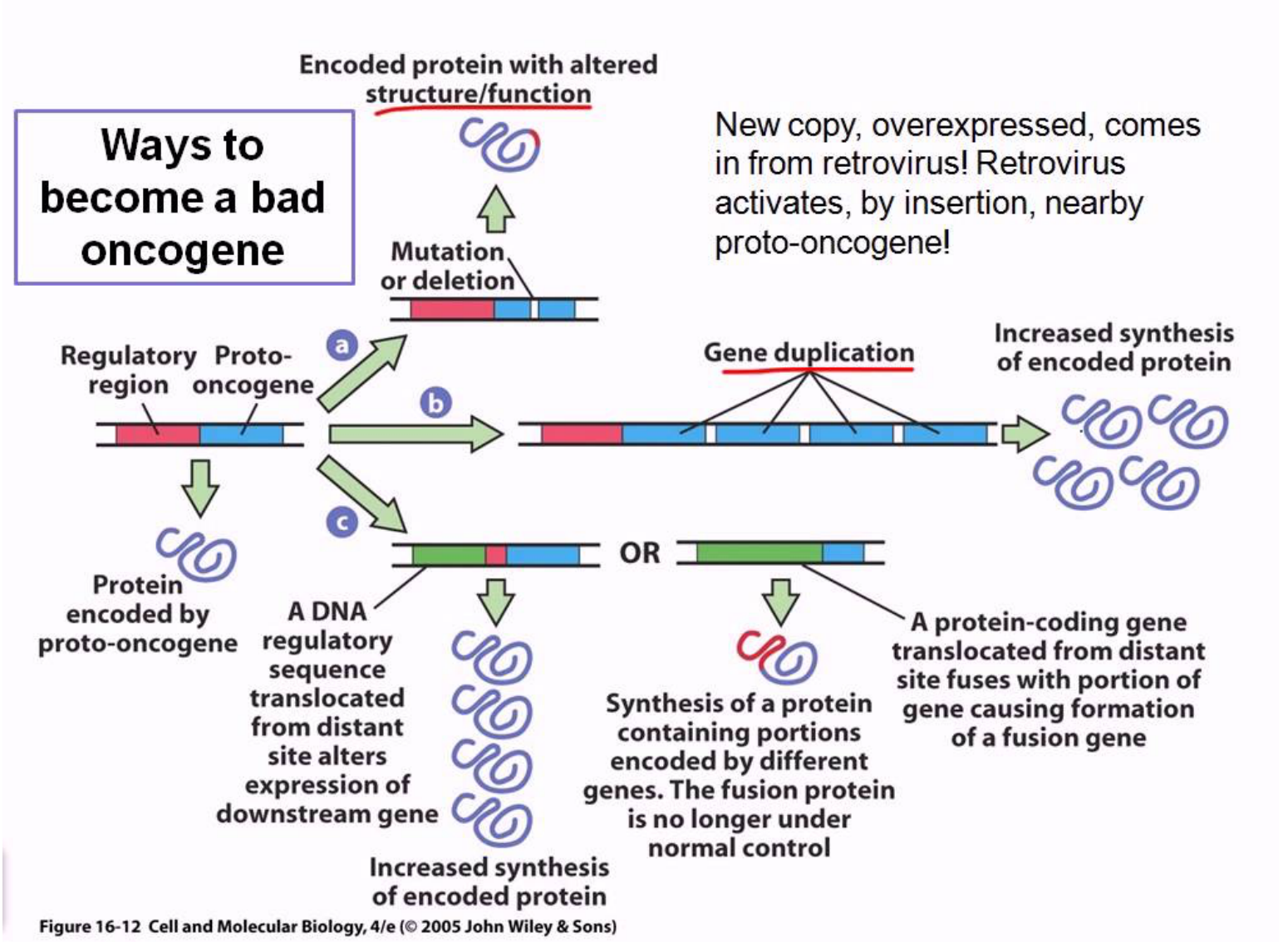
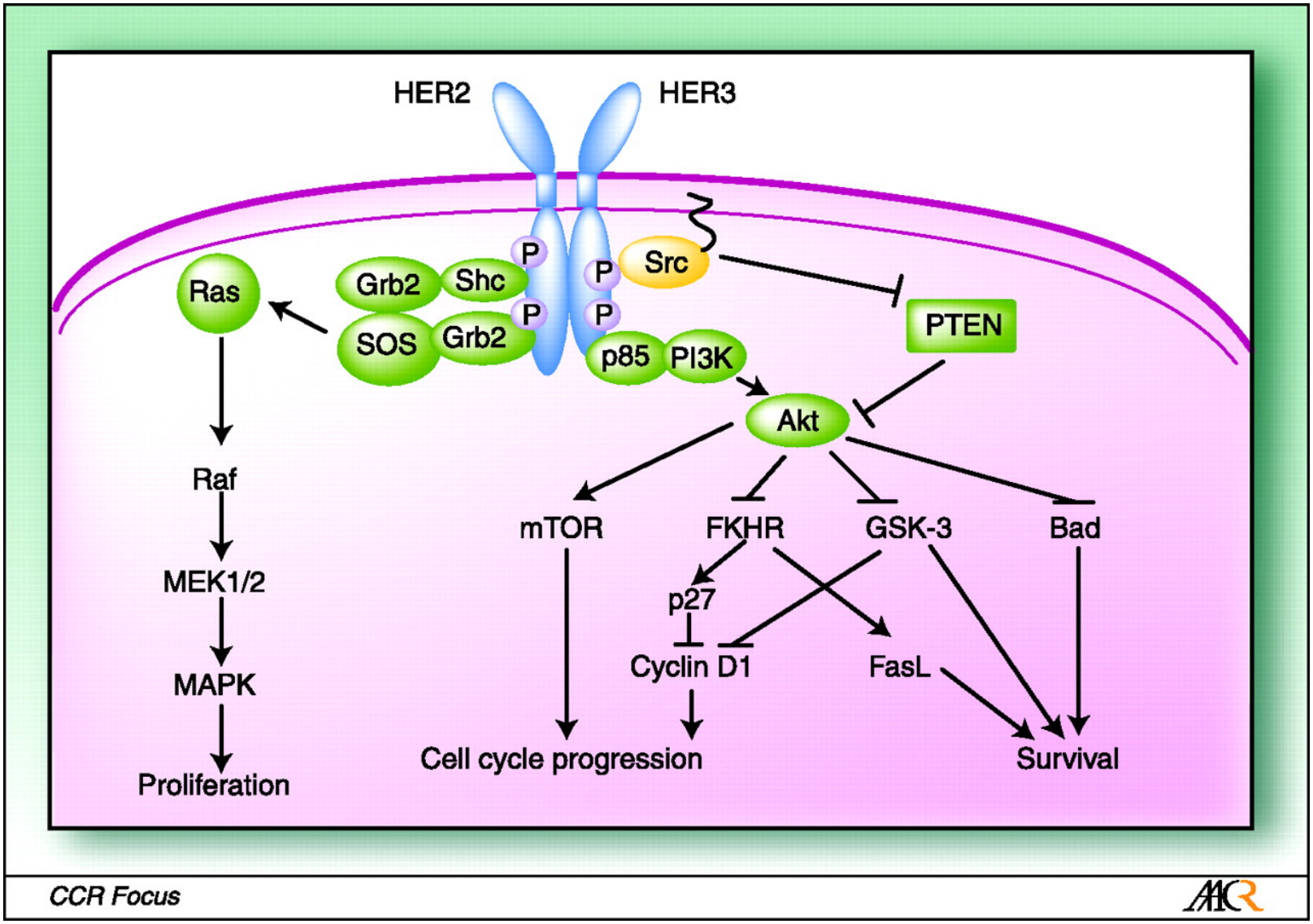
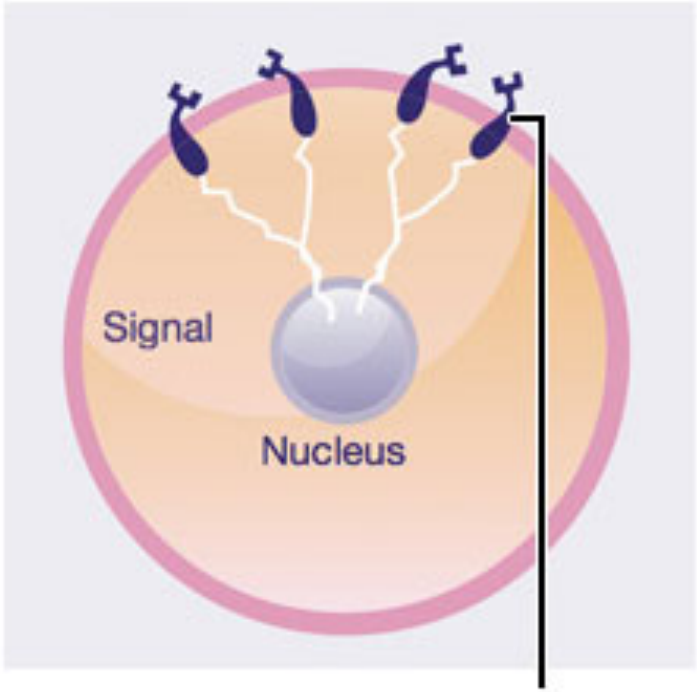


Figure 16-12 Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons)

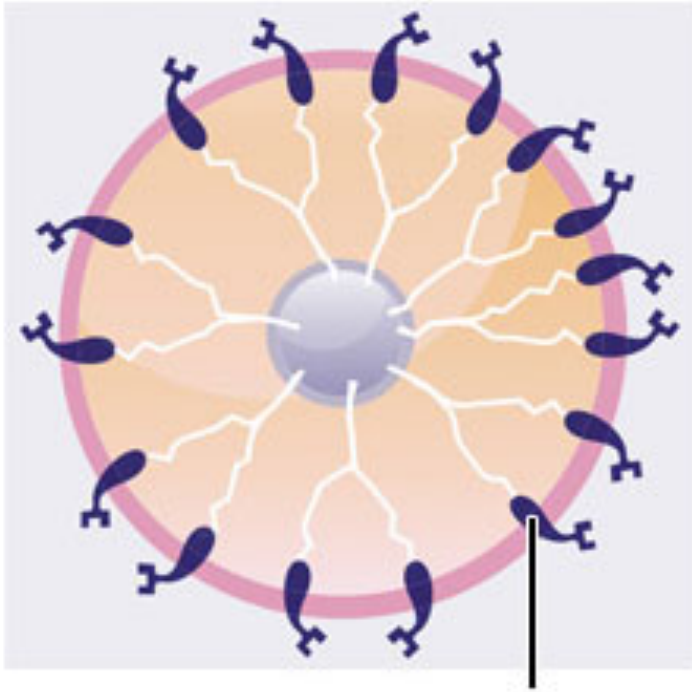

HER2
HER3
P
P
P
P
Src
Grb2
Shc
SOS
Grb2
Ras
PTEN
p85
PI3K
Akt
Raf
MEK1/2
MAPK
Proliferation
mTOR
FKHR
GSK-3
Bad
p27
Cyclin D1
FasL
Cell cycle progression
Survival

Normal breast cancer cell

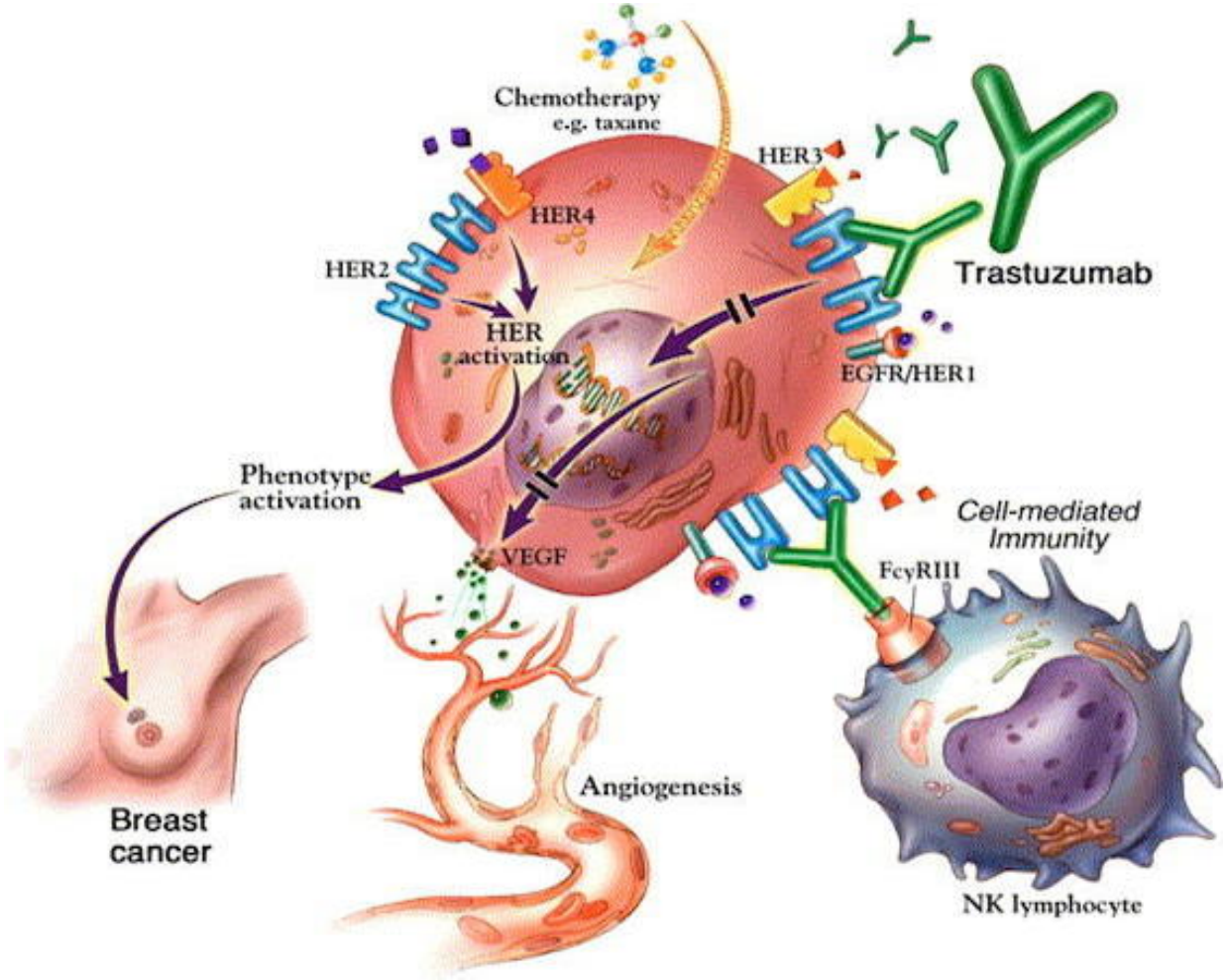


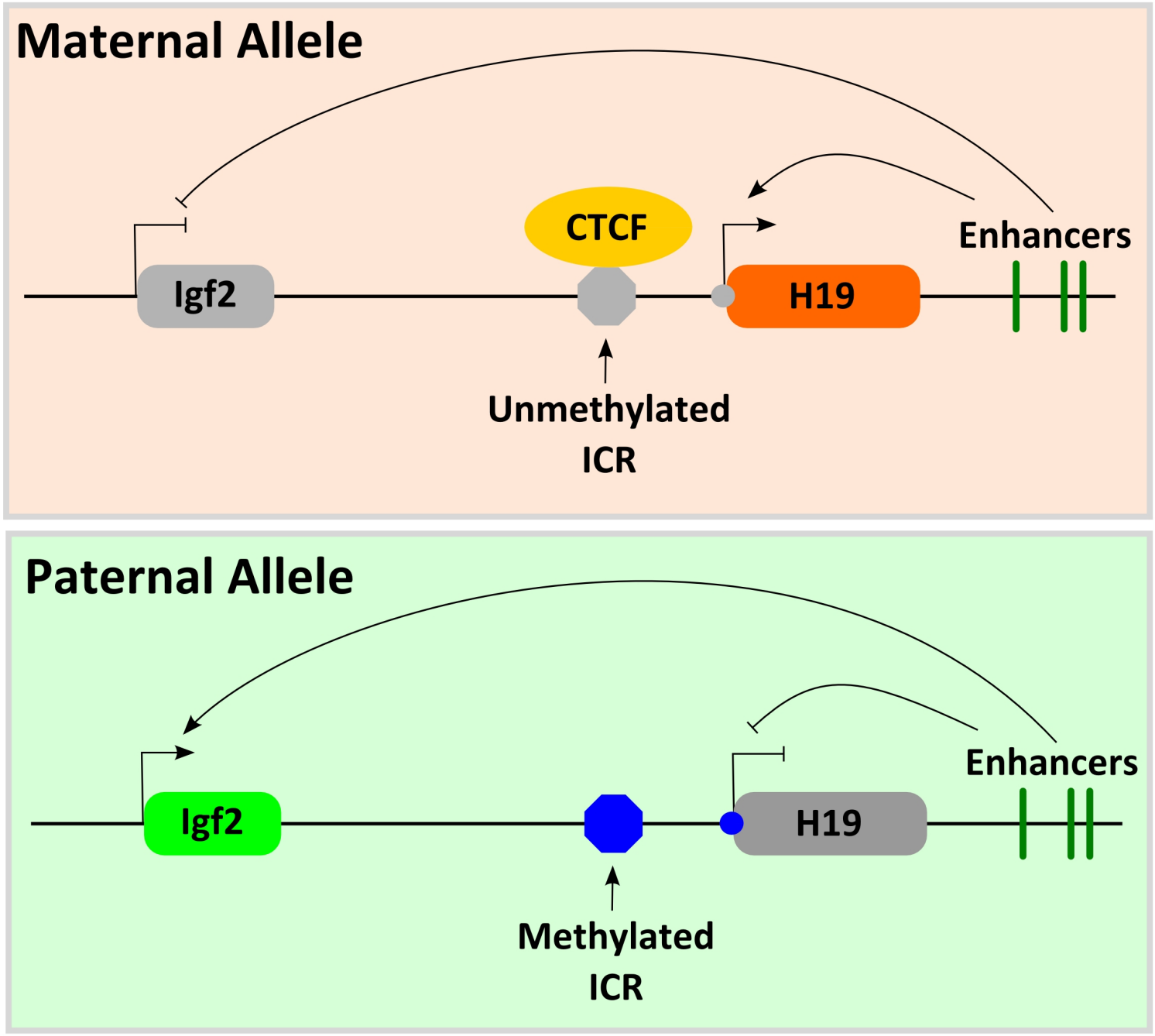
Normal amount of HER2 receptors send signals telling cells to grow and divide.[1]

Abnormal HER2+ breast cancer cell



Too many HER2 receptors send more signals, causing cells to grow too quickly.[1]


Chemotherapy
e.g. taxane
HER3
HER4
HER2
Trastuzumab
HER
activation
EGFR/HER1
Phenotype
activation
Cell-mediated
Immunity
VEGF
FcγRIII
Angiogenesis
Breast
cancer
NK lymphocyte


Maternal Allele
CTCF
Enhancers
Igf2
H19
Unmethylated
ICR
Paternal Allele
Enhancers
Igf2
H19
Methylated
ICR