ILLINOIS CANCERCARE, P.C.

Specializing in Cancer and Blood Disorders

What is Cancer?

What is Cancer?

- NOT - What it does it do to people?
- NOT – How many die?
- NOT – What is the financial toll?

What is Cancer?

- Cells growing too fast (many normal cells grow faster)
- Cells spreading to new areas
- Cells causing clotting, fever & pain
- All characteristics of cancer (blind people feeling elephant)

How to kill cancer cells?

- Kill all rapidly growing cells (pediatric ALL)
- Basis of chemotherapy
- Chemotherapy works best in rapidly growing cancer
  - Testicular
  - Lymphoma
  - Leukemia
- Chemotherapy interferes with DNA replication & cell division and only target until recently.

Origins of Chemotherapy

- 1943
  - S.S. John Harvey sunk in WW2 Bari, Italy
- 1948
  - Sidney Farber use of MTX childhood ALL
- 1958
  - MTX cures Choriocarcinoma
- 1960's
  - POMP cures ALL in children
  - MOPP cures Hodgkins Disease

Origins of Chemotherapy

- ALL as model
  - Drugs very effective
  - Maintenance chemo helpful
  - Both exception – not the rule

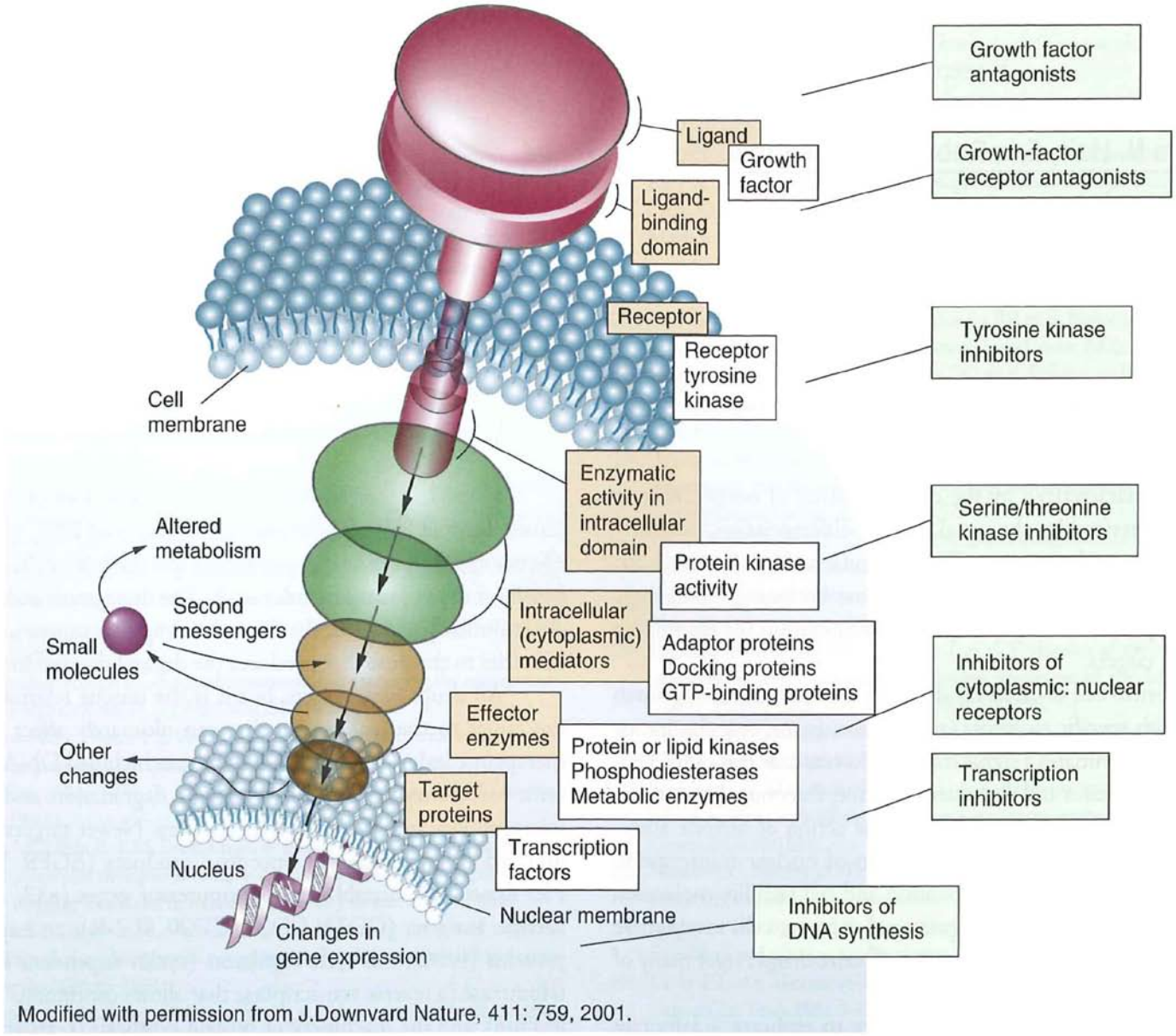


FIGURE 48-1 TARGETS FOR ANTICANCER DRUGS. Anticancer drugs work by interfering with the processes underlying normal cellular physiology. These include receptor activated signal transduction pathways culminating in transcriptional activation, DNA replication, protein synthesis and cell division. Reprinted by permission from Macmillan Publishers Ltd: J. Downward, *The ins and outs of signaling,* Nature 411:759, 2001.

Problems with chemotherapy

- Not all cancers growing that rapidly
- Kills rapidly growing normal cells
- Only a portion of cancer cells are growing
- Hard to kill slowly growing stem cells

How to kill cancer cells

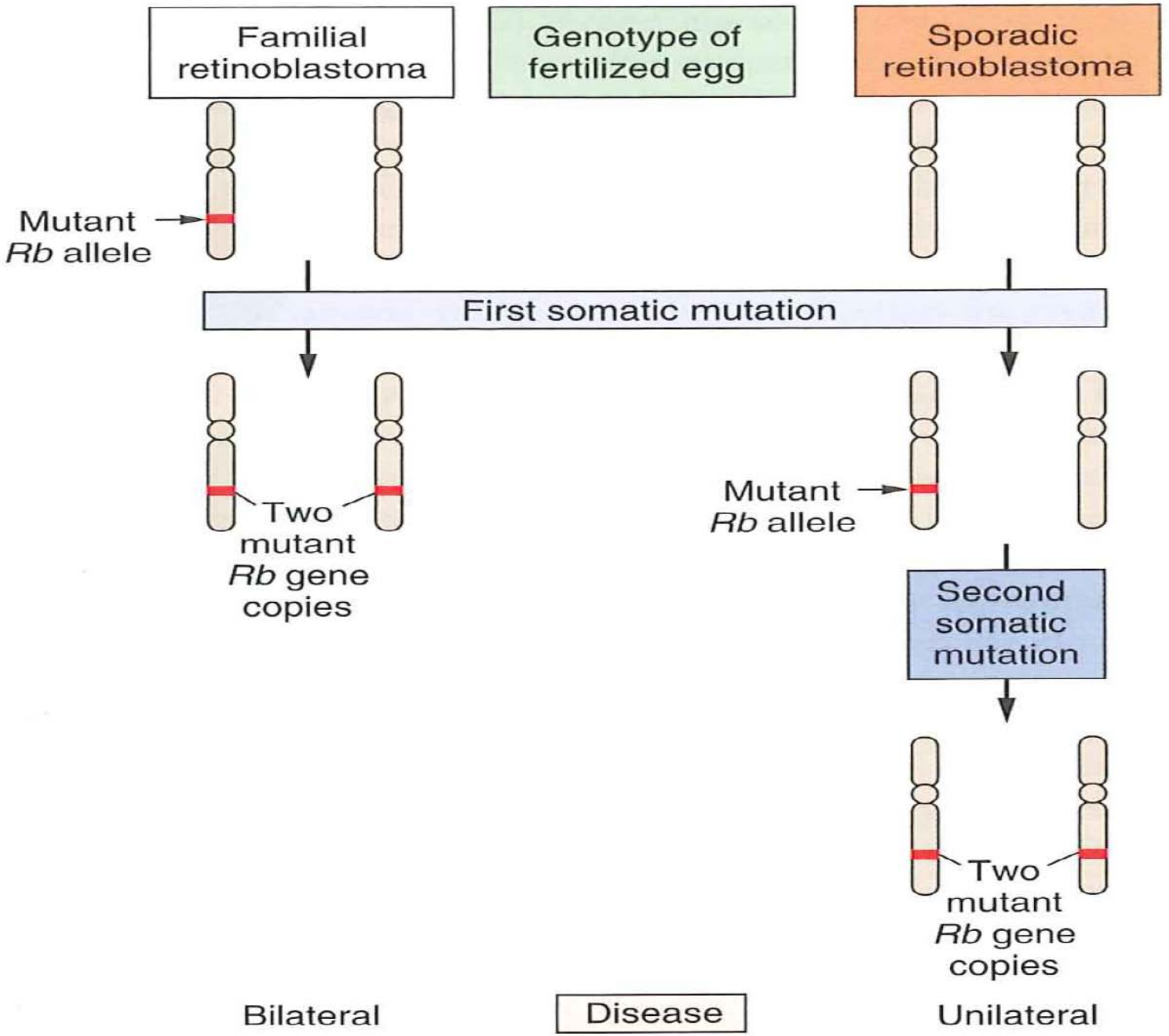
- Understand why they behave the way they do
- Attack the cancer cells strengths
- More specific target
- Less collateral damage to normal cells
- Estrogen positive breast cancer old

Example: Huge difference between UTI & bladder cancer

- targets very different
- difference allows massive dose of poison (i.e. Ampicillin)

What is Cancer?

- A genetic disease which can be inherited but which is usually acquired (can actually be both).


Familial retinoblastoma
Genotype of fertilized egg
Sporadic retinoblastoma
Mutant *Rb* allele
First somatic mutation
Two mutant *Rb* gene copies
Mutant *Rb* allele
Second somatic mutation
Two mutant *Rb* gene copies
Bilateral
Disease
Unilateral

What is Cancer?

- Cells with mutant (changed) genes which arise through somatic mutations of previously normal genes (at time of conception)

Human Genome

- 3 x 10 units of DNA
- 1 meter in length
- Contains 40,000 genes
- 1 gene codes for 1 protein
- DNA arranged 23 chromosomes (2) 46,xx 46,xy

COMPLEXITY AND PRECISION

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Types of Mutation

- Amplification – increased copies of a gene
- Deletion – loss of a gene
- Point mutation – single base pair change
- Translocation – switch to another chromosome

Mutations

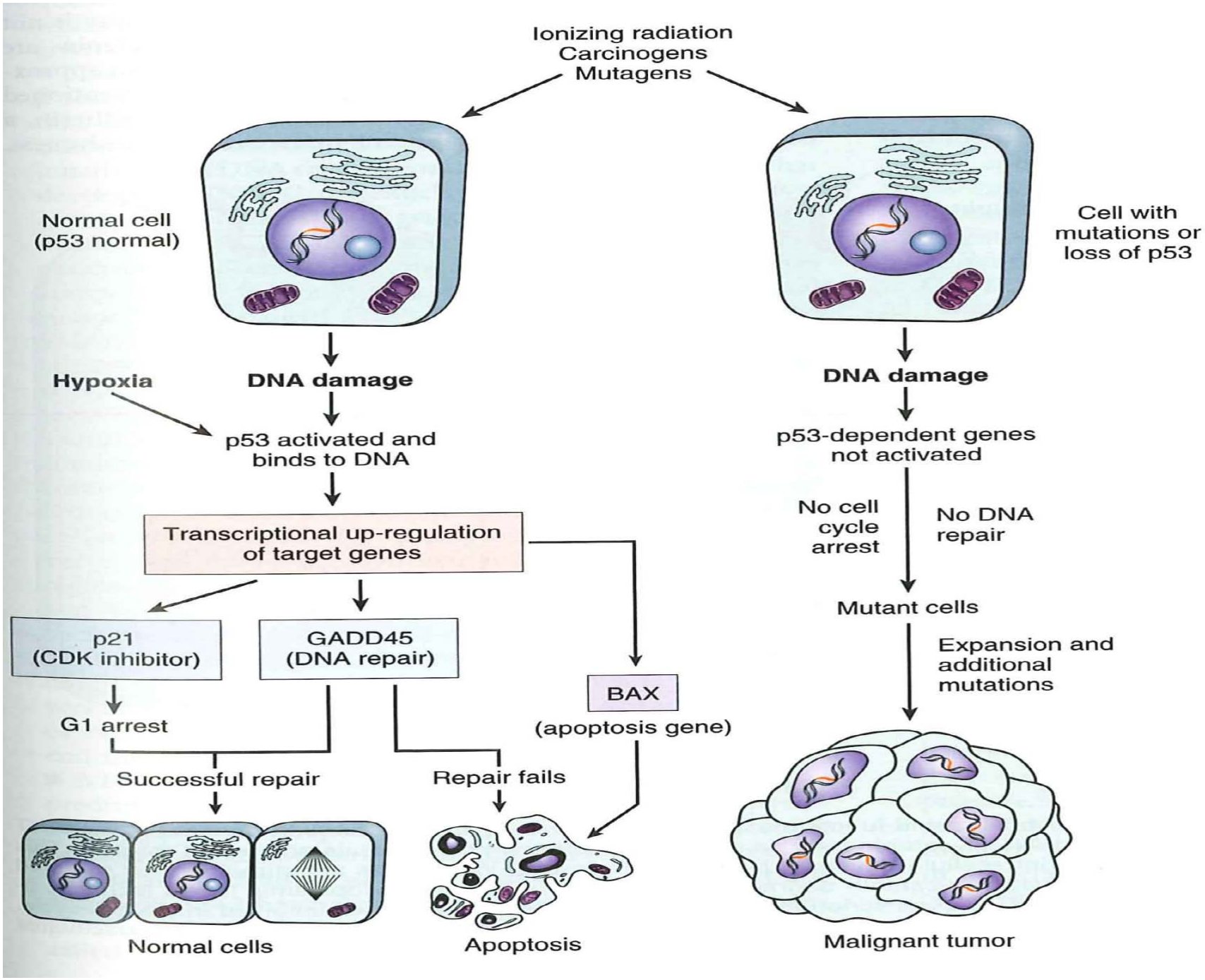
- Not all mutations cause cancer
- Mutated genes which cause cancer are oncogenes
- Proto-oncogene produces an additional protein
- Tumor suppressor genes stop the making of a protein

Table 3-1 Tumor Suppressor Genes

Gene	Protein Function	Familial Cancer Syndrome	Sporadic Cancers with Mutations
p53	Transcription factor	Li-Fraumeni syndrome	Many (over 50% of all tumors)
RB	Transcriptional regulation	Retinoblastoma, osteogenic sarcoma	Retinoblastoma; osteosarcoma; breast, lung, and bladder carcinoma
WT1	Transcriptional regulation	Wilms tumor	Pediatric kidney cancer
APC	Binds and degrades β-catenin, Wnt signaling	Familial adenomatous polyposis	Colon and stomach carcinoma
NF1	Ras-GAP activity	Neurofibromatosis type I	Astrocytoma, colon carcinoma
NF2	Membrane cytoskeletal attachment	Neurofibromatosis type II	Schwannoma, meningioma, ependymoma
INK4A (p16)	Cdk inhibitor (RB inactivation)	Familial melanoma	Many
ARF	MDM2 antagonist (p53 activation)	Melanoma	Many
VHL	Hypoxia response	von Hippel-Lindau syndrome	Renal cell carcinoma, cerebellar hemangiosarcoma
LKB1	Phosphorylates and activates AMPK to inactivate mTOR	Peutz-Jeghers Syndrome	Lung adenocarcinomas
PTEN	Phosphoinositide-3-phosphatase protein	Cowden syndrome	Glioblastoma, endometrial, thyroid and prostate cancers
TSC1/2	GTPase activation, mTOR inhibition	Hamartoma Tuberous sclerosis	Unknown
BRCA1	DNA damage repair, cell cycle checkpoint control	Familial breast and ovarian cancer	Unknown
BRCA2	Regulation of genes involved in DNA repair and homologous recombination	Familial breast and ovarian cancer	Unknown
FHIT	Nucleoside metabolism	Prostate cancers	Esophageal, stomach, colon and lung carcinoma
DPC4 (Smad4)	Regulation of TGF-b/BMP signal transduction	Familial juvenile polyposis syndrome	Pancreatic carcinoma
PTCH	Transmembrane receptor for sonic hedgehog (shh), involved in early development through repression of action of smoothened	Basel cell nevus syndrome	Basel cell carcinoma
MEN1	Histone methylase	Multiple endocrine neoplasia type 1	Unknown
Beclin 1	Autophagy	Liver (rat and mouse)	Breast and ovarian cancers
ATM	DNA damage sensor (protein kinase)	Ataxia-telangiectasia (T-cell lymphoma)	T-prolymphocytic leukemia and mantle cell lymphoma
MSH2 and MLH1	DNA mismatch repair	Hereditary nonpolyposis colorectal cancer	Endometrial, gastric, ovarian, bladder cancer
E-cadherin (CDH1)	Cell–cell adhesion protein	Familial diffuse-type gastric cancer	Gastric cancer, lobular breast cancer
RASSF1	Cell cycle regulation, apoptosis, and microtubule stability	Unknown	Many
CHK2	Protein kinase (G_1 checkpoint control)	Li-Fraumeni syndrome	Unknown
FA genes	DNA repair, S-phase checkpoint	Franconi anemia	Acute myelogenous leukemia
NBS1	DNA repair, S-phase checkpoint	Nijmegen breakage syndrome (T-cell lymphoma)	Lymphoreticular malignancies
BIN1	Apoptosis, cell cycle control	Unknown	Breast and prostate cancers

p53

- 50% of tumors contain mutations of this gene lung, colon, breast
- Usually both copies inactivated somatically
- Li-Fraumeni syndrome – person inherited 1 mutant copy – increased risk of cancer by 25 fold
- A tumor supressor gene


Ionizing radiation
Carcinogens
Mutagens
Normal cell
(p53 normal)
Cell with
mutations or
loss of p53
Hypoxia
DNA damage
DNA damage
p53 activated and
binds to DNA
p53-dependent genes
not activated
No cell
cycle
arrest
No DNA
repair
Transcriptional up-regulation
of target genes
Mutant cells
p21
(CDK inhibitor)
GADD45
(DNA repair)
Expansion and
additional
mutations
BAX
(apoptosis gene)
G1 arrest
Successful repair
Repair fails
Normal cells
Apoptosis
Malignant tumor

Treatment Metastatic Breast Cancer

- ER+ (40-80%) (Luminal A&B)
- Antiestrogen therapies – 5
- Chemotherapy – 10
- HER2+ (20%) increased growth factor receptors
  - Trastuzumab (herceptin), lapatinib (tykerb) with chemotherapy
  - Herceptin and lapatinib with antiestrogens
- Triple negative (20%)
  - Chemotherapy only
  - PARP inhibitors

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Treatment Metastatic Breast Cancer

Chemotherapy

- Multiple drugs available
- No regimen is curative
- Two together better response rate
- Two together more toxicities
- All work by inhibiting cell division
- None exclusively attack breast cancer cells

Chemotherapy Breast Cancer

- Taxanes
  - Paclitaxol
  - Docetaxel
- Anthracycles
  - Doxorubicin
- Gemcitabine
- Platinum
  - Cisplatin
  - Carboplatin
- Vinorelbine
- Ixabepilone

Chemotherapy Breast Cancer Benefits

- Response rate

1st line	**60%**
2nd line	40%
3rd line	20-30%
4th line	<20%
5th line	<10%

- Survival benefit not well defined.
- Quality of life harder to measure.

Chemotherapy Breast Cancer

Timing can matter

- Paclitaxol weekly vs. q3 weeks
  - Response rate - 42% vs. 29%
  - Time to progression - 9 months vs. 5 months
  - Survival - 24 months vs. 12 months
  - Toxicity – overall less

Chemotherapy Breast Cancer

- Ixabepilone
  - Studied as 3rd or 4th line Rx
  - Response duration 5.7 months
  - Response rate 19%
  - Survival 8.6 months
  - G 3-4 toxicities 60%

Chemotherapy Breast Cancer

- Type & behavior of disease
- Responses to previous treatment
- Tolerance to previous treatments

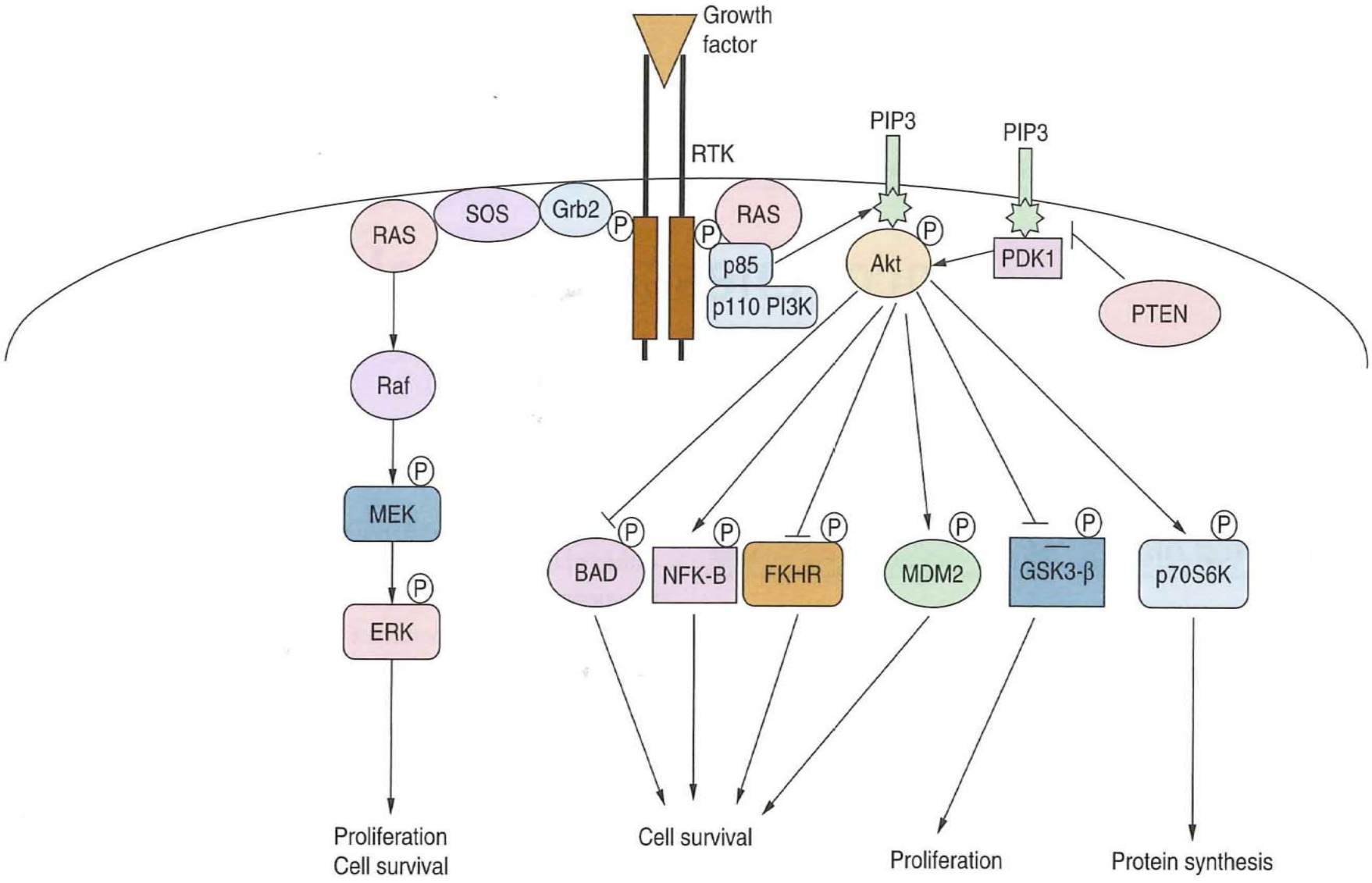

FIGURE 2-1 Receptor tyrosine kinase signaling in cancer. Scheme for growth factors signaling through receptor tyrosine kinases.