

Cancer Genetics:

Understanding and Hope

What is Cancer?

- Uncontrolled Cell Division

AND

- The ability to spread (“metastasize”) from one place to another

What Causes Cancer?

Mutations or *epigenetic factors* that disrupt normal control of the cell cycle

The Cell Cycle

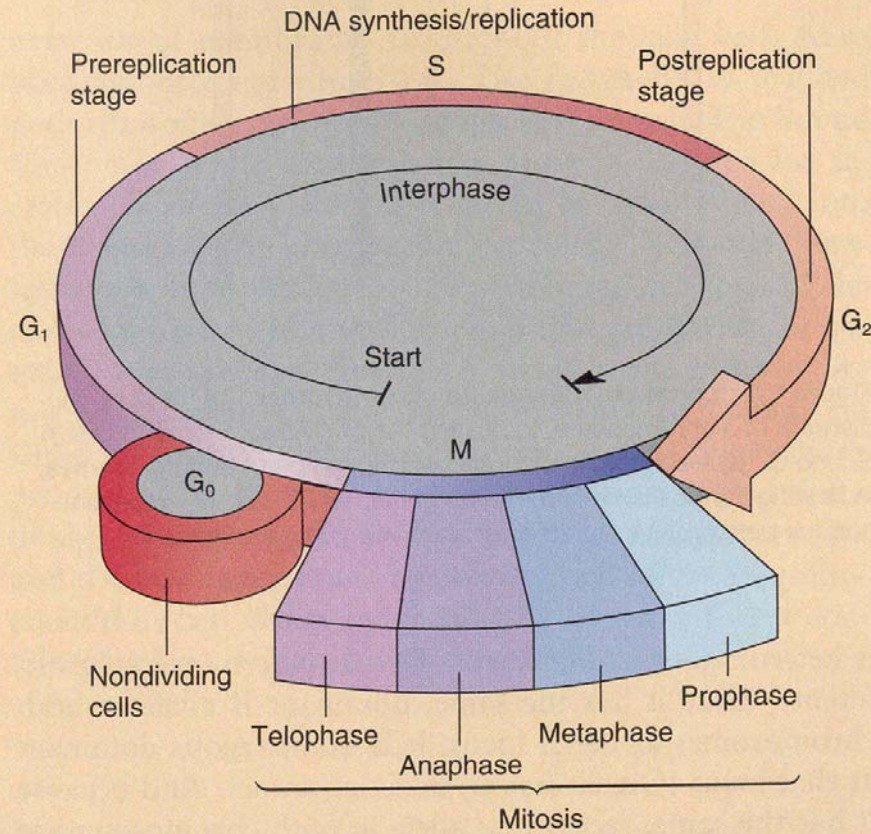


Figure B1.2a Cell cycle. Phases in the cell cycle of a typical eukaryotic cell. The events that occur from the start of one cell division (mitosis), when two daughter cells are produced, to the next cell division are collectively termed the **cell cycle**.

Control of the Cell Cycle in Multicellular Organisms is Critical!

- Cells must be able to divide both during development and as part of homeostasis
- Cell cycle progression must be tightly controlled!

Cell Cycle Progression is
Controlled Through Elaborate
Regulatory Circuitry

Two Broad Classes of Genes Are Involved

1. Protooncogenes

→ products promote cell division/survival

2. Tumor Suppressor Genes

→ products block cell division

→ products maintain genomic integrity

Protooncogenes Encode:

- Growth Factors (PDGF, EGF, VEGF, etc.)
- Growth Factor Receptors
- G proteins (Ras)
- Protein Kinases (Raf, ERK, cdks, etc.)
- Transcription Factors (Fos, Jun, Myc, etc.)
- “Cell Survival Proteins” (AKT, Bcl-2)

Protooncogene products are often
“on/off” switches, set up in a
series/pathway

- Growth factors bind to and activate receptors
- The activated receptor turns on a G protein
- The activated G protein turns on protein kinases
- The protein kinases activate transcription factors

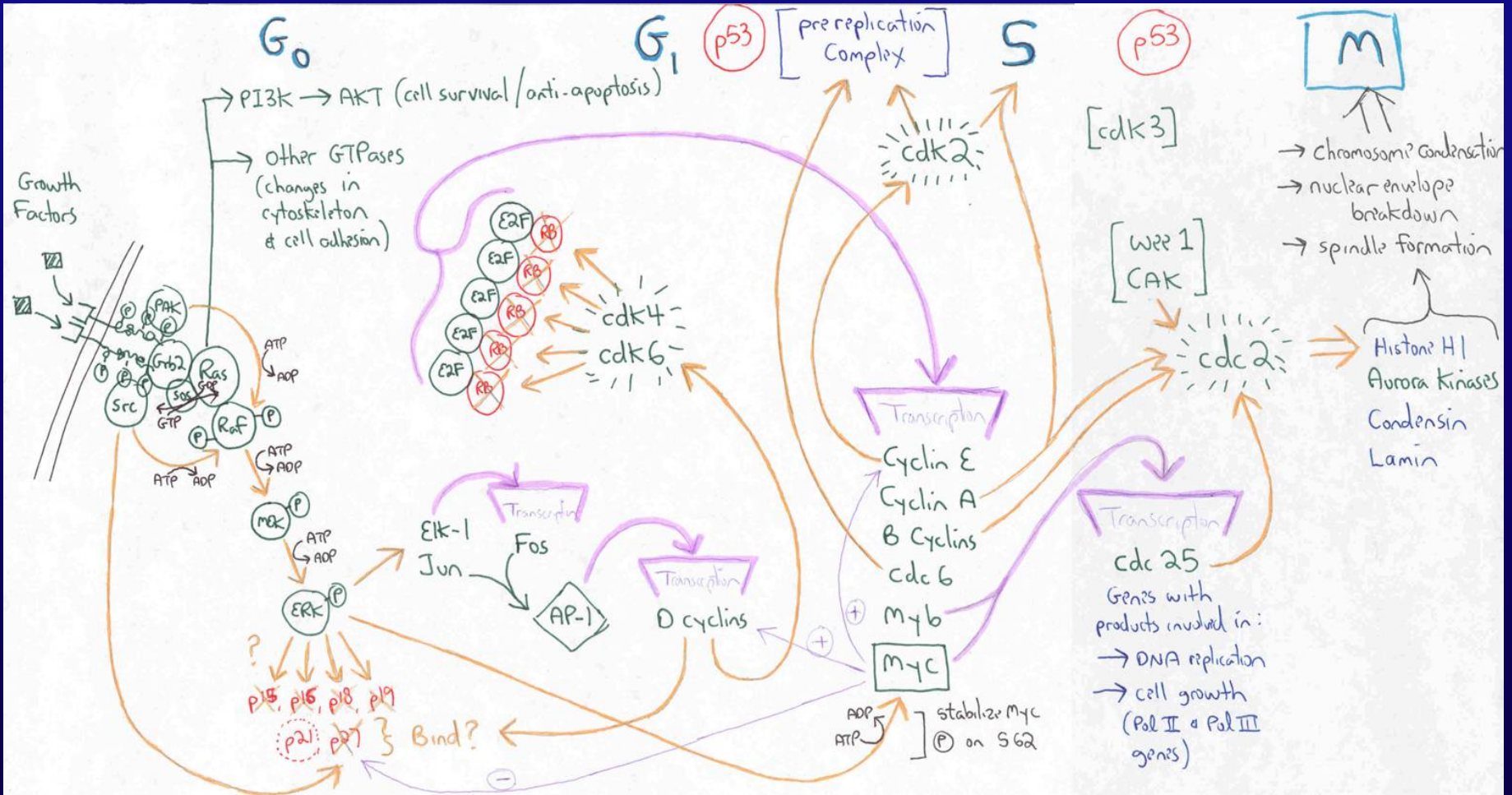
Genes are turned on (and off) sequentially:



Tumor Suppressor Products Include:

- Inhibitors of protein kinases (p16, p21, p27)
- Inhibitors of transcription factors (RB)
- Proteins involved in maintaining genomic integrity/
DNA repair:
 - p53
 - MSH2
 - BRCA1, BRCA2

Overview: Cell Cycle Regulatory Circuitry



* PKA and PKC can also regulate these events, perhaps via regulation of RAF and/or ERK (independent of Ras, PAK, & Src?)

* JAKs may also regulate this (i.e., response to prolactin in mammary gland cells).

How is Normal Control of the Cell Cycle Lost?

- Mutations that cause the inappropriate activation or expression of protooncogenes
- Mutations that abrogate the function of tumor suppressor proteins
- *Epigenetic silencing* of tumor suppressor genes

Cancer Cells Contain a Battery of Mutations and Epigenetic Events

Each tumor will have a different set of mutations!

Recent analysis of more than 13,000 genes in each of 22 breast tumors revealed 189 different mutations that contribute to the malignant phenotype.

The average tumor cell harbored 11 mutations!

This is what makes cancer so difficult to treat: *it is not a single disease!*

Advances in Understanding the Causes of Cancer Have Opened New Avenues for Diagnosis and Treatment

→ Genetic Testing for Predisposition

→ Genetic Profiles of Tumors to Establish Patient-specific Treatments

→ Rational Drug Design

Advances: Breast Cancer

- Genetic Testing for Predisposition:
Mutations in BRCA1 and BRCA2 genes
- Genetic Profiling of Tumors:
Analysis of Estrogen Receptor levels,
Cyclin-D levels, and Her2 levels.

Customized Treatment

- A drug called Herceptin can be used to treat Her2-positive breast tumors.
- Developed by Genentech.
- A **monoclonal antibody** that recognizes Her2 protein.
- Has greatly improved the prognosis for Her2-positive patients.

The Future?

- More Precise Genetic Profiling of Tumors and Customized Therapies
- Drug Design Targeting Specific Proteins
- Gene Therapy:
 - Traditional, combined with
 - RNA interference
 - “Customized” immune cells

Thank You!

Questions?