

## SYSTEMS BIOMEDICINE

### The cell cycle and cancer

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#### Lecture Outline

Defects in cell cycle regulation contribute to oncogenesis in both direct and indirect ways:

- Loss of negative regulation in G1 causes cells to pass the restriction point and divide.
- Loss of checkpoint regulation results in genetic instability, which generates mutations and chromosomal rearrangements that affect the function and expression of growth control genes.

#### Loss of negative regulation in G1 phase

1. In G1 phase, Cdk4/6 with cyclin D and Cdk2 with cyclin E cause cells to pass the restriction point and undergo the G1/S transition.

Rb is phosphorylated by G1 Cdk/cyclins.

Phosphorylated Rb releases the transcription factor E2F, which transcribes S-phase genes.

2. Cyclin-dependent kinase inhibitors (CKIs) block the kinase activity of cdk/cyclin complexes.

INK4 family members inhibit Cdk4 (and its homologue Cdk6).

Loss of the regulatory circuit involving p16, Cdk4/cyclin D, Rb, and E2F is involved in oncogenesis.

CIP/KIP family members inhibit Cdk2/cyclin complexes.

INK4 and CIP/KIP family member CKIs are tumor suppressors.

#### Loss of checkpoint regulation

1. Checkpoints delay cell cycle transitions until the previous step is completed or damage is repaired. The principal checkpoints that act on the cell cycle are:

Arrest in G1 if DNA damage is present

Arrest in G2 if replication is not complete

Arrest in G2 if DNA damage is present

Arrest in metaphase if any chromosomes are not attached to the spindle

2. The final step that activates Cdk2/cyclin E to promote the G1/S transition and Cdk1/cyclin B to promote the G2/M transition is removal of the inhibitory phosphates on the cdk by a member of the Cdc25 phosphatase family. This step is blocked by the checkpoints for DNA damage.

3. The checkpoint kinases ATM and ATR are activated at sites of DNA damage.

ATM phosphorylates the downstream kinase Chk2.

ATR phosphorylates the downstream kinase Chk1.

Chk1 and Chk2 phosphorylate Cdc25 family members.

Phosphorylation of Cdc25A causes it to be targeted for degradation.

Phosphorylation of Cdc25B and Cdc25C causes them to be sequestered in the cytoplasm, where they do not have access to their substrate, Cdk1, which is in the nucleus.

4. The spindle assembly checkpoint causes cells to arrest in metaphase when kinetochores that are not attached to spindle are present.

Attachment of all kinetochores to the spindle causes activation of a protease that cleaves cohesin, the protein that holds sister chromatids together.

- Cleavage of cohesin allows sister chromatids to separate and anaphase to begin.
5. The tumor suppressor p53 is activated by DNA damage pathways and promotes cell cycle arrest and apoptosis.
    - In response to DNA damage, p53 is stabilized when it is phosphorylated by ATM, ATR, Chk1, and Chk2.
    - Activated p53 is a transcription factor that induces expression of the gene for the cyclin-dependent kinase inhibitor p21, which results in cell cycle arrest.
    - p53 also induces expression of genes involved in apoptosis.
  6. Apoptosis (also called programmed cell death) is required to remove unnecessary, damaged, or transformed cells during development and in adults.
    - During apoptosis, the cell shrinks and condenses, the cytoskeleton collapses, the nuclear envelope disassembles, and the nuclear DNA becomes fragmented.
    - Cells undergoing apoptosis remain contained within the cell membrane and are eventually engulfed by phagocytic cells.
  7. Proteases called caspases are required for apoptosis.
    - Caspases are synthesized as inactive procaspases, which are cleaved by other caspases to become active.
  8. p53 is involved in activation of apoptosis through the intrinsic pathway.
    - Pro-apoptotic proteins such as BAX induce apoptosis by promoting the formation of pores in the mitochondrial membrane, which causes the release of cytochrome c.
    - Cytochrome c binds to and aggregates the adaptor protein Apaf-1.
    - Aggregated Apaf-1 binds to and aggregates procaspase-9.
    - Aggregated procaspase-9 is cleaved and activated.
  9. Specificity of promoter activation by p53 may be determined by its pattern of acetylation.