Phases of the Cell Cycle

- Prophase
- Metaphase
- Anaphase
- Telophase

Cell Cycle Progression:

Requirements:
- G2-M
- Are all chromosomes attached to the spindle?
- Is environment favorable?
- G2 TO M TRANSITION
- START TRANSITION
- ENTER CELL CYCLE AND PROCEED TO S PHASE
- ENVIRONMENT FAVORABLE?
- G1-S

Cell Cycle Control

- Cyclin:Cdk Complex
- Activated Protein Kinase
- Cyclin-dependent kinase (Cdk)
Expression Levels of Cyclins Oscillate

Various cell cycle phase-Cdns and Cyclins

Cdk Activation and Inactivation
Cdk's can be inhibited while in a complex with a Cyclin

**Control of Cyclin levels During the Cell Cycle**

Consequences: Decrease M-Cyclin, inactivate M-Cdk, and allow cytokinesis (cell division) to proceed.

**Control of CKI (p27, p21, p16) levels During the Cell Cycle**

Consequences: Decrease CKI, increase Cdk/Cyclin Activity, and allow cell cycle progression.
### Cell Cycle Checkpoints

<table>
<thead>
<tr>
<th>On/Off Switches</th>
<th>Sensitive extracellular environment</th>
<th>DNA damage</th>
<th>unreplicated DNA</th>
<th>DNA damage</th>
<th>chromosome misaligned to spindle</th>
</tr>
</thead>
<tbody>
<tr>
<td>On</td>
<td>G0/S-G1 checkpoint</td>
<td>On</td>
<td>Off</td>
<td>On</td>
<td>Off</td>
</tr>
<tr>
<td>Off</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

#### Table of the Major Cell Cycle Regulatory Proteins

<table>
<thead>
<tr>
<th>General name</th>
<th>Functions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cdk activity inhibitors (CKIs)</td>
<td>Phosphorylates or inactivates cyclin-dependent kinases (CDKs)</td>
</tr>
<tr>
<td>Brk’s homologs</td>
<td>Phosphorylates inhibitory site of Cdk2, primarily involved in regulating DNA activity before mitosis</td>
</tr>
<tr>
<td>Cdk 9/10 activation</td>
<td>Requires ubiquitination of cyclin B via the cyclin B ubiquitin ligase complex</td>
</tr>
<tr>
<td>Cdk 12/13 activity (CCIs)</td>
<td>Suppresses Cdk activity in S, phosphorylation by Cdk2 at the end of G2, and its degradation</td>
</tr>
<tr>
<td>p27 (inhibitor)</td>
<td>Suppresses G1/S and G2/M checkpoint proteins, inhibits DNA synthesis by Cdk</td>
</tr>
<tr>
<td>p16 (inhibitor)</td>
<td>Suppresses G1/S and G2/M checkpoint proteins, following DNA damage</td>
</tr>
<tr>
<td>p53 (inhibitor)</td>
<td>Suppresses Cdk activity in G2, frequently transcribed in cancer</td>
</tr>
<tr>
<td>APC/C</td>
<td>Catalyzes ubiquitination of regulatory proteins involved in cell cycle transitions, including cyclin B2, Cdk1, and Cdc20, to promote the cell cycle exit</td>
</tr>
<tr>
<td>Cdk3</td>
<td>APC/C activating protein in G1 and regulates cell cycle exit by APC/C at metaphase to anaphase transition inhibited by APC/C</td>
</tr>
<tr>
<td>Cdk1</td>
<td>APC/C activating protein in G1 and regulates cell cycle exit by APC/C at metaphase to anaphase transition inhibited by APC/C</td>
</tr>
<tr>
<td>SCP</td>
<td>Catalyzes ubiquitination of regulatory proteins involved in cell cycle transitions, including cyclin B2, Cdk1, and Cdc20, to promote the cell cycle exit</td>
</tr>
</tbody>
</table>

### Control of Chromosome Duplication

- **Helicases**: unwind DNA strands to allow for replication.
- **MCM (Minichromosome Maintenance) proteins**: recruit and activate the helicases.
- **PCNA (Processivity Factor)**: stabilizes the helicases and promotes their processivity.
- **CDC2/CDC5**: regulates the initiation of DNA replication.

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Activation of M-Cdk

The M to G1 Transition is Regulated by Stable Inhibition of M-Cdk

Mechanism of MAPK (ERK) activation and cell proliferation

Cell Cycle Genes are turned on/off (i.e. G1/S-Cyclins and S-Cyclins)
Mechanisms of ERK1/2-mediated cell growth

Due to a Mutation in Ras/Raf

Apoptosis → Cell Death

Degradation

Oncogenesis → Cell Cycle Progression

Cell Cycle Inhibitors
i.e. CDKI: p27

Mechanism of ERK1/2-mediated cell growth

Unphosphorylated Stabilized FOXO3a

phosphorylated Degraded

ERK1/2 → FOXO3a → CKI (p27) → Cdk/Cyclin

Cell Cycle Arrest

Regulation of Cell Death (Apoptosis)

Pro-Apoptotic

Bad and Bim

Apoptosis

Phosphorylated P-Bad and P-Bim

Sequestered (Bad) or Degraded (Bim)

Cell Cycle Progression

Anti-Apoptotic

Bcl-2, Bcl-XL

Apoptosis

Sequestered (Bad) or Degraded (Bim)
Cell Cycle Progression

Mechanism of ERK1/2-mediated cell cycle progression

Cell Death

- P-BIM is polyubiquitinated and degraded by the Proteasome
- Sequestered away from Bcl-2, Mcl-1, Bcl-XL

Cell Cycle Progression

Review: Favorable Environments for G1 Entry

- Mitogens: Growth Factors such as EGF, insulin, HRG, etc
- Receptor Tyrosine Kinase (RTK, i.e. EGFR)
- Mitogen Activated Protein Kinases (MAPKs, i.e. ERK)
- Transcription Factors (i.e. AP-1)
- Other Transcription Factors (i.e. Myc)
- Cyclin (G1 Cyclin)

Regulation of G1 to S Phase Transition

- Delayed response gene expression
- G1-Cyclin
- Positive feedback
- Active EGF protein
- Inactivated EGF protein
- Inactivated EGF protein
- Active EGF protein
- Inactivated EGF protein
- Active EGF protein
- G1-S phase transition
- S phase
- G2-S phase transition
- S phase
- G2-M phase transition
- M phase
- S phase
- G1 phase
- G1 phase
- G1 phase
- G1 phase
DNA Damage and Cell Cycle Arrest in G1

The Activation of p21 (CKI) by p53 results in inactivation of G1/S-Cdk Complex.

Consequence
G1/S Cell Cycle Arrest

The Mechanism by which p53 Arrests Cells in G1/S Phase

DNA Damage (radiation or chemotherapy)

DNA is not repaired

Cell Death (Apoptosis)

The gene name = WAF1
Cell Cycle Arrest or Apoptosis Caused by Excessive Mitogenic Stimulation

- excessive Myc production
- active Mdm2
- p53 degradation
- p53
- Art
- inactive Mdm2
- stable, active p53
- cell-cycle arrest
- OR apoptosis